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# Antimicrobial consumption and bacterial resistance pattern in patients admitted in I.C.U at a tertiary care center

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ABSTRACT

*Background:* Throughout the world multi drug resistant nosocomial infections are one of the leading causes of death and morbidity among hospitalized patients. Antimicrobial resistance [AMR] has become a major problem in treatment of such infections. High consumption of antimicrobials particularly in ICUs is often described as the most important factor leading to AMR.
*Objective:* The aim of the study was to study the magnitude of antimicrobial resistance amongst nosocomial pathogens and the antimicrobial prescription patterns of patients admitted in intensive care unit.
*Methods:* The study was conducted in I.C.U of a tertiary care government hospital in Delhi over a period of 4 months, on 100 patients admitted in I.C.U. Depending on clinical suspicion laboratory samples were collected and subjected to antimicrobial sensitivity testing. Antimicrobial prescription of these patients were collected from I.C.U records and analyzed.
*Observations: Staphylococcus aureus* and *Klebsiella* species were the most common organism [23%]. Among patients where causative organism was isolated, two or more organisms were isolated from 50% of the samples. Most of the *Klebsiella* species and *Acinetobacter* species were resistant to beta lactam group of antibiotics such as cephalosporins and piperacillin-tazobactam. 60% of isolates of *S. aureus* were found to be MRSA while none of the *S. aureus* were resistant to linezolid and vancomycin. All patients were prescribed two or more antimicrobials while 66% patients were prescribed 3–5 antimicrobials. Commonest combination was beta lactam with metronidazole followed by levofloxacin with metronidazole with addition of aminoglycosides or linezolid as third drug. Total 20 antimicrobial agents were used in the treatment of the patients. Among these consumption [in DDD/100bed days] of metronidazole was highest [100.9] followed by fluconazole [76.6] and levofloxacin [62.7].
*Conclusion:* High usage of antimicrobial consumption has been noted in this study, prompting institution of measures to formulate and adherence to antimicrobial policy strictly.



## Introduction

Throughout the world multi-drug resistant nosocomial infections are one of the leading causes of morbidity and mortality among hospitalized patients, and account for a major burden on patients and the public health system of any country. Compared to a ward patient, a critically ill patient has 5–7 times higher risk of nosocomial infection. Intensive care unit [ICU] infections contribute to 20%–25% of all nosocomial infections in a hospital. Factors like increasing use of invasive devices, immunosuppressive drugs and irrational use of antimicrobial therapy in ICUs contribute to the same [1].

Development of antimicrobial resistance is a major stumbling block in the treatment of such infections. This growing menace has left fewer options for treatment of these infections. This is due to high consumption of antimicrobials particularly in ICUs [2]. The patterns of organisms causing infections and their antimicrobial resistance patterns vary widely from one country to another; as well as from one hospital to other and even among different ICUs within one hospital. Keeping this overview in mind this study was

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initiated to study the pattern of organisms and their resistance pattern along with consumption of antimicrobials in our ICU.

## Material and methods

### *Demographic profiling*

A Prospective Observational Cohort study was conducted in a 4 bedded surgical I.C.U, in collaboration with Department of Microbiology and Department of Anaesthesia at a tertiary care government hospital in New Delhi. The institutional ethics committee's approval was obtained prior for the study of 100 consecutive patients admitted to the surgical ICU during six month period. Patients were identified by daily visit by the investigators to the intensive care units [ICU]. Once patients were identified, they were enrolled in the study according to study criteria. All patients readmitted to ICU and those on anti-tubercular therapy were excluded from the study. Informed consent was obtained from patients/relatives before enrolling into the study. Patients were followed from the day of admission in the surgical I.C.U till the day of discharge/recovery/death.

Patient data like demography [age, sex], the antimicrobial prescribed and its usage details total number of antimicrobials prescribed, generic name, dose, grams per unit dosage, number of doses per package, number of packages consumed, duration, and route of administration of the antimicrobial, length of hospital stay and clinical outcome were recorded in case record forms (CRF). The antimicrobials were classified using the "Anatomical Therapeutic Chemical [ATC] Classification System" [3]. At the same time all microbiological investigations sent to the microbiological departments were analyzed for growth. The isolates were identified by standard techniques [4]. The identification methods used were based on colony morphology, motility and biochemical identification for bacterial isolates. Fungal isolates were identified by colony morphology, germ tube and growth on chrome agar. The antimicrobial resistance profile was determined by Kirby Bauer disc diffusion method using different antimicrobial agents according to CLSI guidelines recommended by Clinical and Laboratory Standard Institute. Brain Heart Infusion agar with vancomycin 6 μg/ml was used to detect susceptibility to vancomycin [5]. For calculating antimicrobial resistance data WHONET 5.6$^{TM}$ was used using date and site specific criteria in data analysis tool. Multidrug-resistant (MDR) isolates were defined as those with acquired non-susceptibility to at least one agent in three or more antimicrobial categories [6]

### *Antimicrobial prescription analysis*

The antimicrobial prescriptions of these 100 patients were noted from the case records available in the ICU. The doses of antimicrobial treatment were estimated by calculating Defined Daily Dose or DDD. It is the assumed average maintenance dose per day for a drug used for its main indications in adults. It acts as a technical measurement of antimicrobial usage that allows comparisons [3].

$$\text{DDD} = \frac{\text{No. of packages used} \times \text{No.of tablets per package} \times \text{No. g per tablet}}{\text{WHO DDD of antimicrobials [g/MU]}}$$

Total use of antimicrobials in ICU patients was calculated as DDD/100 bed days using WHO ABC Calc v3.1. The occupancy index of ICU was calculated during this period. For calculating the DDD/100 bed days WHO DDD Units of each antimicrobial was collected from WHO ATC DDD guidelines 31 [3]. The following formula was used to calculate DDD/100 bed days.

$$\text{DDD/100 bed days} = \frac{\text{DDD} \times 100}{\text{No. of bed days}}$$

$$\text{No.ofbed-days} = \text{No.ofbedsinthehospital} \times \text{Occupancyindex} \times \text{No.ofdays[duringthestudyperiod]}$$

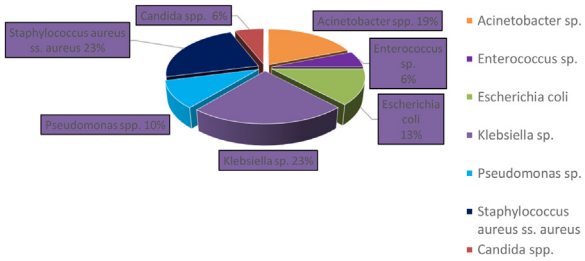


**Fig. 1.** Microorganisms isolated from patients in I.C.U (N = 64).
Note: *60% of the Staphylococcus aureus isolated were MRSA.

## Results

The occupancy index of the surgical ICU during the study period was 0.63. The study population comprised of predominantly females [64%]. The mean age of study population was 39.5 years and maximum patients were in the age group 20–39 years [48%]. The mean patient days of admission during study period were 5 days. Overall mortality in the study population was 28%. However, only 4 patients died of infective cause, while remaining 24 died due to other complications.

Out of 100 patients admitted in the surgical ICU during the course of study, culture sensitivity was done for only 24% of the patients. A total of 128 samples [tracheal aspirate, blood culture, urine culture] were received in the microbiology laboratory for these 24 patients. No samples for screening were included in sensitivity testing. Pathogenic organisms were isolated from 64 (50%) of these samples. For each surveillance period, only one result was included for each patient per surveyed specimen type and surveyed pathogen. The isolation rates of various organisms are illustrated in Fig. 1. *Staphylococcus aureus* and *Klebsiella* species were the most common organism [23%]. Polymicrobial flora was observed in 50% of cases. Candida species were isolated from three blood samples using automated culture system (BactAlert$^{TM}$). Antimicrobial sensitivity was not performed for these isolates.

Antimicrobial sensitivity pattern of various organisms is shown in Tables 1 and 2. Most of the *Klebsiella* species were resistant to beta lactam group of antimicrobials such as cephalosporins and piperacillin-tazobactam. Most *Acinetobacter* species were multidrug resistant, leaving fewer options for clinicians. 60% of *S. aureus* were found to be MRSA. None of the *S. aureus* were resistant to linezolid and vancomycin.

Prescription analysis: A total of 318 antimicrobial prescriptions were made for 100 patients. Seventy two patients continued to receive antimicrobials prescribed by their operating surgeon in ICU. Commonest antimicrobial prescribed in ICU belonged to beta lactam group and metronidazole. Table 3 lists the common antimicrobial prescribed to these patients. All patients were prescribed two or more antimicrobials while 66% patients were prescribed 3–5 antimicrobials. Commonest combination was beta lactam with metronidazole followed by levofloxacin with metronidazole. Aminoglycosides or linezolid were added as third drug.

Antimicrobial utilization pattern were analyzed by WHO DDD method. Total 20 antimicrobial agents were used in the treatment of the patients. Among these consumption [in DDD/100bed days] of metronidazole was highest [100.9] followed by fluconazole [76.6] and levofloxacin [62.7]. Consumption of Vancomycin was least [0.9]. Antimicrobial consumption pattern has been demonstrated in Table 4.

**Table 1**
Antibiotic resistance pattern of Gram negative isolates.

| Antibiotic | Acinetobacter species (%)(n = 12) | *Klebsiella* spp. (%) (n = 15) | *E. coli* (%) (n = 8) | *Pseudomonas aeruginosa* (%) (n = 6) |
|---|---|---|---|---|
| Piperacillin/tazobactam | 75 | 70 | 70 | 30 |
| Ceftazidime | 87.5 | 83 | 60 | 50 |
| Cefotaxime | – | 83 | 60 | – |
| Imipenem | 87.5 | 66 | 40 | 60 |
| Meropenem | 81 | 61 | 40 | 40 |
| Amikacin | 75 | 65 | 50 | 20 |
| Gentamicin | 75 | 74 | 60 | 20 |
| Ciprofloxacin | 75 | 74 | 60 | 70 |
| ESBL | – | 83 | 70 | – |

**Table 2**
Antibiotic resistance pattern of *Staphylococcus aureus*.

| Antibiotic | % resistance (n = 15) |
|---|---|
| Cefoxitin | 60 |
| Amikacin | 26 |
| Gentamicin | 58 |
| Ciprofloxacin | 58 |
| Trimethoprim/sulfamethoxazole | 37 |
| Clindamycin | 40 |
| Erythromycin | 42 |
| Tetracycline | 16 |
| Chloramphenicol | 10 |

None of the isolates were resistant to vancomycin and linezolid.

**Table 3**
Antibiotic prescription pattern in ICU.

| S. no. | Antibiotic prescribed | Number of patients |
|---|---|---|
| | Beta Lactam* | 88 |
| | Ceftriaxone | 50 |
| | Amoxiclavulanate | 28 |
| | Pipiracillin-tazobactum | 10 |
| | Carbepenems (meropenem & imipenem) | 42 |
| | Metronidazole | 80 |
| | Aminoglycosides | 56 |
| | Fluoroquinolones (levofloxacin & ciprofloxacin) | 20 |
| | Linezolid | 14 |
| | Colistin | 10 |

**Table 4**
Antibiotic consumption analysis.

| Antimicrobial agent | ATC code | WHO DDD | DDD/100 patient days |
|---|---|---|---|
| Ampicillin | J01CA01 | 2 | 6.6 |
| Amoxicillin-Clavulanate | J01CR02 | 3 | 37.75 |
| Piperacillin Tazobactam | J01CR05 | 14 | 2.5 |
| Ceftriaxone | J01DD04 | 2 | 44.8 |
| Cefotaxime | J01DD01 | 4 | 2.3 |
| Imipenem | J01DH51 | 2 | 31.7 |
| Meropenem | J01DH02 | 2 | 49.5 |
| Ciprofloxacin | J01MA02 | 0.5 | 5.3 |
| Levofloxacin | J01MA12 | 0.5 | 62.7 |
| Vancomycin | J01XA01 | 2 | 0.9 |
| Teicoplanin | J01XA02 | 0.4 | 4.6 |
| Gentamicin | J01GB03 | 0.24 | 22.7 |
| Amikacin | J01GB06 | 1 | 39.1 |
| Metronidazole | J01XD01 | 1.5 | 100.9 |
| Linezolid | J01XX08 | 1.2 | 12.9 |
| Clindamycin | J01FF01 | 1.8 | 2.6 |
| Azithromycin | J01FA10 | 0.5 | 10.56 |
| Fluconazole | J02AC01 | 0.2 | 76.6 |
| Colistin | J01XB01 | 3MU | 44.2 |
| Tetracycline | J01AA | 1 | 1.9 |
| | | Total | 560.11 |

## Discussion

Patients in ICU are often prescribed antimicrobial therapy empirically as these patients are critically ill and no time is available to wait for the culture reports [7]. According to WHO, irrational antimicrobial use is a major contributor to rising trends in antimicrobial resistance worldwide [8]. This study was conducted at an ICU of a tertiary care center, where postoperative patients who require intensive care and monitoring are admitted, to analyze the antimicrobial utilization patterns and to assess any correlation between rising trends of antimicrobial resistance and antimicrobial utilization. Our study included antimicrobial sensitivity pattern of bacterial organisms isolated from different samples of critically ill patients and analysis of the antimicrobial consumption pattern in the ICU.

*S. aureus* and *Klebsiella* species were the most common organisms [23%]. More than 2 organisms were isolated from different samples in 50% of patients. Most isolates of *Acinetobacter* and *Klebsiella* species were multi-drug resistant. In a study on bacteriological profile and drug sensitivity pattern in an ICU in a tertiary care hospital in Ahmedabad the most common organism isolated was *Acinetobacter* spp.[30.9%] followed by *Klebsiella* spp.[29.7%] and then *Pseudomonas aeruginosa* [22.9%] [9]. Another study from an ICU at Birdem also showed that with major isolate was *Pseudomonas* spp. [29.1%], and *Acinetobacter* spp. [27.5%] [10]. As most gut infections arise from intra-abdominal flora and are often poly-microbial in etiology, it appears justified to use combination antimicrobial chemotherapy especially with metronidazole. But double coverage can be avoided as many beta lactams such as piperacillin tazobactum and meropenem have excellent anaerobic activity. Almost three fourth of the patients were prescribed antimicrobial as surgical prophylaxis and the same prescription was continued thereafter. Only in 24% cases specific therapy was modified after culture report. However, continuation of this prophylaxis beyond 24 h of surgery is worrisome and unjustified. Surgical prophylaxis cannot be an alternative to infection control practices. A total of 20 antimicrobial agents were used in the treatment of the patients. Among these, highest consumption was seen for metronidazole (100.9) followed by fluconazole (76.6), levofloxacin (62.7) and meropenem (49.5). Least consumption was seen for vancomycin (0.9). This data indicates that the empirical therapy for anaerobic organisms in the form of metronidazole was started for almost all patients and continued for a long time. Longer duration of prophylaxis or therapy and use of multiple antimicrobial agents can also predispose to *Clostridium diffcile*-associated colitis [11,12].

Prescription analysis showed a staggering 78% of patients were prescribed beta lactam while aminoglycosides were given in 56% followed by carbapenems in 42%. Ceftriaxone was the most common prescribed beta lactam drug (50%). Similar observations have been made by other researchers across India and other develop-

ing countries [13–16]. Cephalosporins continue to be used as the most commonly used antimicrobial in ICU. High margin of safety and broad spectrum activity could be a reason for this. As per hospital policy surgical prophylaxis should not continue 24 h post-surgery. As the antimicrobials in this ICU are prescribed by clinician under whose care the patient is admitted this distinction often gets blurred. Only in some cases antimicrobials are prescribed by ICU in charge and even they are ratified by concerned clinician. This could be one of the reasons for overuse of antimicrobials in ICU.

Analysis of pathogens isolated from ICU shows that Candida was isolated from 6% of the total isolates. This indicates the need to prescribe fluconazole therapy empirically. Higher isolation rates have been reported from elsewhere in India also [18]. Earlier *Candida albicans* used to be the predominant pathogen in ICU but now non albicans candida isolations have increased [17]. Increased use of fluconazole therapy is often responsible for change in epidemiology of Candida species causing infections in ICU patients [19]. High consumption of fluconazole in our ICU also could predispose to non-Candida albicans infections.

Very high level of Extended Spectrum Beta lactamases (ESBL) isolates were seen amongst Gram negative bacilli. Still the consumption of this beta lactams was very high in the ICU. This would result in treatment failures. The use of this drug must be restricted to cases where sensitive organisms were isolated. Carbapenems are known to be strong inducers of class C beta lactamases. This could have contributed to high resistance to beta lactams. Also, in our study resistance to aminoglycosides and fluoroquinolones was also above 50%. This could be due to high utilization of this drug leading to selective pressure in our ICU. Similar observations have been made by Al-Lawati et al. from Oman [20].

We have used ATC/DDD calculations to study the antimicrobial consumption in our ICU, which is a good method for comparison of drug usage in different hospitals. Our ICU showed a very high usage of antimicrobial at 560.11 DDD/100 patient days. Most studies from India and outside have reported lower utilization [21,22]. Most patients are referred to our center after receiving treatment from other hospitals. This coupled with high number of life threatening conditions encountered at our tertiary care center and lack of strictly enforced antimicrobial policy could be a reason for such high usage of antimicrobials.

Highest consumption was seen for metronidazole, levofloxacin, meropenem, ceftriaxone and colistin. Beta lactams, carbapenems and metrionidazole have predominantly been used in other studies as well [13,14,22]. In a study in Nepal most common antimicrobials used were ampicillin, amoxicillin, metronidazole [23]. In another study conducted by Adiga et al., beta-lactams, nitroimidazoles and fluoroquinolones were commonly prescribed groups of antimicrobials [24].

An alarming fact seen in this study was the very high utilization of colistin. Colistin is often used as last resort antimicrobial in case of multidrug resistant bacteria. This clearly indicates need for strict monitoring of its usage. Disk diffusion cannot be used for susceptibility testing of colistin as it does not discriminate between susceptible and resistant isolates [25]. Also, resistance is now being increasingly reported indicating caution and awareness regarding its use needs emphasis [26].

For antimicrobials effective against Gram positive organisms, it was noticed that the consumption of linezolid was highest. The reason for this is its excellent activity against MRSA. Teicoplanin was used more commonly than vancomycin. This could probably because of its availability in hospital formulary. Very low resistance was observed to cotrimoxazole probably due to its non-usage in the hospital. Resistance to gentamicin was higher than amikacin.

## Conclusion

To conclude, very high usage of antimicrobial consumption has been noted in this study. As the study was carried out on a small number of patients, it would have affected our statistics to some extent. However, institution and ICU specific antimicrobial policy are needed to control this issue. Regular audits with monitoring of adherence to these guidelines are required. Antimicrobial stewardship program with educational intervention and sensitization of medical students in rational antimicrobial prescription is the need of the hour to control the menace on antimicrobial resistance.

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## Competing interests

None declared.

## Ethical approval

Not required.

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