Prescription pattern, safety and prevalence of resistance of antimicrobial drugs in MICU of IGIMS, Patna: An observational and prospective study

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Abstract
Objective: Due to limited availability of newer antibiotics to treat emerging multidrug-resistant species of pathogens, there is an urgent need for highlighting the misuse of antibiotics and taking appropriate measures to promote rational antibiotic prescription. This study was designed to know the antibiotic prescription patterns in MICU, the prevalence of antibiotic resistance, the effectiveness of empirical antibiotic therapy and safety and tolerability of the antibiotics prescribed.

Materials and Methods: This study was an observational and prospective study. 100 consecutive prescriptions were collected from MICU, IGIMS, Patna from January 2019 to June 2019. All antibiotics listed on first prescription slip was noted and their dosage schedule, route of administration, date of discontinuation, generic name and related laboratory investigations were also recorded.

Result: 723 drugs were prescribed out of which 244 were antibiotics. 3rd generation cephalosporins (118 prescriptions/48.36 %) were most frequently prescribed followed by Amoxicillin + Clavulanate (40 prescriptions/16.39%). Prevalence of resistance was most in cephalosporins (6%) followed by Amoxicillin + Clavulanate (5%). Approx. 27.5% failure of treatment was found in patients receiving empirical antibiotic therapy. Percentage of suspected ADRs was mostly found in linezolid (33.33%) followed by Ceftriaxone (16.66%).

Conclusion: Antibiotics are overprescribed in our ICUs and this is increasing the burden of unnecessary adverse effect, resistance and treatment costs. At the time of admission, patients with poor prognosis and older age are prescribed more antibiotics. Antibiotics stewardship programs should be promoted and regulation of antibiotic utilization, proper use of guidelines and proper surveillance should be ensured by responsible authorities.

Keywords: Antibiotics, ICU, Prescriptions, Resistance, Safety & tolerability.

Introduction
Discovery of antibiotics has brought a drastic change in treatment of infectious diseases. But in present era; misuse, overuse and emerging resistance continue to be threat for the management of infection. In intensive care unit, mostly empirical therapy is given. In ICU setting before obtaining culture & sensitivity reports, patients are frequently treated with more than one antibiotic. And most of these are broad spectrum antibiotics. As compared to patients of general wards, patients of ICU are in serious condition and undergo more invasive procedures. So, they have high risk of multidrug resistant pathogenic infection. The prescriptions of ICUs are generally more empirical leading to misuse and overuse of antibiotics. Besides increasing treatment cost, overuse of antibiotics exposes patients to unnecessary side effects and also increases the burden of antibiotic resistance.1–3 Due to limited availability of newer antibiotics to treat emerging multidrug-resistant species of pathogens4, there is an urgent need for highlighting the misuse of antibiotics and taking appropriate measures to promote rational antibiotic prescription.1,2 Some of the previous studies suggest that reducing the use of antibiotics may be associated with similar or improved outcomes and reduced adverse effects.5–8

Hence, in this study we aimed to observe the antibiotic prescription patterns in MICU, the prevalence of antibiotics prescribed and antibiotic resistance, the effectiveness of empirical antibiotic therapy, safety and tolerability through prospectively observing the prescription given in MICU.

Materials and Methods
Study Site/Place
Medical Intensive Care Unit (MICU) of Indira Gandhi Institute of Medical Sciences, Patna

Study duration
6 Months from January 2019 to June 2019

Study design
Observational and prospective study

Inclusion criteria
1. Age ≥ 18 years and all gender
2. At least one antibiotic in prescription

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Exclusion criteria
Pregnant and Breastfeeding women

100 Prescriptions of the patients admitted in medical ICU were collected. They were followed up and their IPD files were observed. Demographic variables on patients such as name, sex, age, clinical diagnosis and the APACHE II score (Acute Physiology And Chronic Health Evaluation score to assess the severity of illness) were recorded. APACHE II score was calculated from the calculator provided in Medscape website.

All antibiotics listed on first prescription slip was noted and their dosage schedule, route of administration, date of discontinuation, generic name and related laboratory investigations were also recorded.

Culture reports of patients were collected, and sensitivity and resistance patterns of Antimicrobials were recorded. Suspected Adverse Drug Reactions (ADRs) were also noted.

Results

Table 1: Demographic data and patient characteristics

| Variable            | Number (n=100) | Percentage |
|---------------------|----------------|------------|
| Gender              |                |            |
| Male                | 65             | 65         |
| Female              | 35             | 35         |
| Age Distribution    |                |            |
| 15-30               | 25             | 25         |
| 31-45               | 14             | 14         |
| 46-60               | 33             | 33         |
| 61-75               | 20             | 20         |
| >75                 | 8              | 8          |
| Apache II Score     |                |            |
| 0-9                 | 22             | 22         |
| 10-19               | 46             | 46         |
| 20-29               | 24             | 24         |
| >29                 | 8              | 8          |
| Drugs Prescribed    |                |            |
| 1-5                 | 45             | 45         |
| 6-10                | 48             | 48         |
| >10                 | 7              | 7          |
| Antibiotics Prescribed |            |            |
| 0                   | 5              | 5          |
| 1-2                 | 70             | 70         |
| 3-4                 | 21             | 21         |
| >5                  | 4              | 4          |
| Length of ICU Stay  |                |            |
| 1-5                 | 58             | 58         |
| 6-10                | 32             | 32         |
| 11-15               | 8              | 8          |
| >15                 | 2              | 2          |
| Outcome from ICU    |                |            |
| Discharged          | 60             | 60         |
| Expired             | 40             | 40         |

Table 2: Pattern of antibiotic prescribed

| Diagnosis                                           | Patients (n) | Total Drugs | Total Antibiotics |
|-----------------------------------------------------|--------------|-------------|-------------------|
| Sepsis/SIRS (Systemic Inflammatory Response Syndrome)| 30           | 223         | 103               |
| Surgical                                            | 15           | 76          | 35                |
| Dengue/DHS (Dengue Haemorrhagic Syndrome)           | 11           | 75          | 18                |
| Trauma/Poisoning                                    | 11           | 61          | 19                |
| Burns                                               | 2            | 8           | 4                 |
| Others                                              | 31           | 280         | 65                |
Table 3: Univariate analysis of the factors affecting the number of antibiotics prescribed

| Variables                  | 1-2 Antibiotics (n= 70) | >/=3 Antibiotics (n=30) |
|----------------------------|-------------------------|-------------------------|
| Age (Years)                |                         |                         |
| ≤45/>45                    | 24/46                   | 12/14                   |
| Gender                     |                         |                         |
| Male/Female                | 48/22                   | 14/12                   |
| Total ICU Days             |                         |                         |
| ≤5days/>5 Days             | 42/28                   | 13/12                   |
| Mortality (Overall)        | 24                      | 13                      |
| Mortality Based on Apache Id |                        |                         |
| 1-14                       | 6                       | 4                       |
| 15-30                      | 16                      | 07                      |
| ≥31                        | 2                       | 2                       |

Table 4: Most frequently used antibiotics and prevalence of their resistance

| Name                        | Number of prescriptions | Treatment failure| Death | Number of culture reports showing resistance |
|-----------------------------|-------------------------|------------------|-------|----------------------------------------------|
| Ceftriaxone                 | 60                      | 15               | 3     | 06                                           |
| Cefotaxime                  | 58                      | 12               | 2     | 06                                           |
| Amoxycillin/Clavulanate     | 40                      | 8                | 2     | 05                                           |
| Levofloxacin                | 30                      | 5                | 1     | 04                                           |
| Metronidazole               | 28                      | 6                | 3     | 02                                           |
| Amikacin                    | 27                      | 3                | 2     | 03                                           |
| Gentamicin                  | 20                      | 2                | 1     | 03                                           |
| Imipenem                    | 06                      | 0                | 0     | 01                                           |
| Meropenem                   | 04                      | 1                | 1     | 01                                           |
| Linezolid                   | 03                      | 1                | 1     | 01                                           |
| Clindamycin                 | 02                      | 1                | 1     | 01                                           |
Table 5: Effectiveness of empirical therapy

| Name of antibiotic          | Number of Prescriptions In Which the Antibiotic Was Given Before Culture Reports | Treatment Failure | Number of Prescriptions In Which the Antibiotic Was Given After Culture Reports | Treatment Failure |
|----------------------------|---------------------------------------------------------------------------------|-------------------|---------------------------------------------------------------------------------|-------------------|
| Ceftriaxone                | 51                                                                              | 14                | 09                                                                              | 01                |
| Cefotaxime                 | 49                                                                              | 11                | 09                                                                              | 01                |
| Amoxyccillin/Clavulanate   | 34                                                                              | 7                 | 06                                                                              | 01                |
| Levofloxacine              | 26                                                                              | 5                 | 04                                                                              | 00                |
| Metronidazole              | 24                                                                              | 5                 | 04                                                                              | 01                |
| Ampicillin                 | 23                                                                              | 3                 | 04                                                                              | 00                |
| Gentamicin                 | 17                                                                              | 2                 | 03                                                                              | 00                |
| Imipenem                   | 05                                                                              | 0                 | 01                                                                              | 00                |
| Meropenem                  | 02                                                                              | 1                 | 02                                                                              | 00                |
| Linezolid                  | 02                                                                              | 1                 | 01                                                                              | 00                |
| Clindamycin                | 02                                                                              | 1                 | 00                                                                              | 00                |

Table 6: Safety & Tolerability

| Name             | Total Number of Prescriptions | Number of Suspected ADRs | Percentage of Suspected ADR |
|------------------|------------------------------|--------------------------|----------------------------|
| Ceftriaxone      | 60                           | 10                       | 16.66                      |
| Cefotaxime       | 58                           | 08                       | 13.8                       |
| Amoxyccillin/Clavulanate | 40                        | 02                       | 05                         |
| Levofloxacine    | 30                           | 03                       | 10                         |
| Metronidazole    | 28                           | 02                       | 7.14                       |
| Amikacin         | 27                           | 03                       | 11.11                      |
| Gentamicin       | 20                           | 02                       | 10                         |
| Imipenem         | 06                           | 00                       | 0                           |
| Meropenem        | 04                           | 00                       | 0                           |
| Linezolid        | 03                           | 01                       | 33.33                      |
| Clindamycin      | 02                           | 00                       | 0                           |

Discussion
A total of 100 prescriptions was collected over 6 months from MICU of IGIMS, Patna. Most of the patients admitted were middle aged (46-60 years). Median APACHE II score of our sample was 14. Most of the patients were from medical speciality and most of them were having sepsis syndrome (30 Patients). The demographic data and patients’ characteristics are given in Table 1.

723 drugs were prescribed of which 244 were antibiotics. It means 33.74 of the total drug prescribed were antibiotics. 85 patients were prescribed antibiotic at the time of admission into ICU. Distribution of patients according to number of patients is shown in figure 1.

Various clinical factors influencing number of drugs and antibiotics prescribed such as diagnosis at time of admission and APACHE II score were studied. Most number of antibiotics were prescribed to patients with sepsis syndrome [Table 2]. More number of drugs were prescribed to patients having higher APACHE II score (>15) but the average number of antibiotics prescribed were similar. Poor outcomes were seen more in patients prescribed more antibiotics. Patients who were prescribed more than 3 antibiotics and had APACHE II scores between 15 and 30 had significantly more risk of mortality (P=0.0289).

Ceftriaxone was most prescribed followed by cefotaxime. However, in culture reports of most of the patients showed resistant to ceftriaxone and cefotaxime.

Most of the patients in our study were discharged from the ICU after recovery (60 patients) while 40 patients expired.

In Iran, a study on ICU drug use pattern, the mean age of patients was 50 years and mean period of stay was 6 days and the mean period of stay in surgical patients was higher. A similar study was carried out by Bergmans et al, the mean period of stay was 7 days and the diagnosis most frequent found was skin and soft tissue infections. Their APACHE II scores were also like our study.

The average number of drugs prescribed to patients is an important factor for a prescription audit. To decrease the burden of bacterial resistance, hospital costs, adverse effects and risk of drug interactions number of drugs should be kept as low as possible. A mean of 6.19 drugs were prescribed per patient in our study and it is comparable to other studies in which we can find the range of drugs prescribed between 5.1 to 12 varying on the basis of type of patient population and the geographical location studied.

It was found in this study that many of the patients were prescribed antibiotics at the time of admission.
(approximately 95%). Biswal et al found that approximately 62% patients were prescribed antibiotics in ICU of tertiary care hospital of northern India while shrikala et al found 64% prescriptions containing antibiotics in ICU. 58%-61% use of antibiotics were reported from studies in Europe and from other countries it was found to be 60-75% . In a survey done in Australia and New Zealand on prescribing pattern of antibiotics in ICUs, it was found that 656 antibiotics were prescribed in 120 days study period.  

Antibiotics were chosen at the first hour of treatment in patients of severe sepsis and this is identified as an important factor for clinical outcomes. Capp et al has done a study on 1400 patients of ICU and found that 82% patients received appropriate antibiotic therapy. They also found that following set guidelines for community and healthcare associated infection was 100% sensitive tool for selecting patients having infections caused by more resistant organisms.

In our study 3rd generation cephalosporins (118 prescription) were most frequently prescribed followed by Amoxicillin/Clavulinate (40 prescriptions). In other studies, conducted in India, cefaperazone and piperacillin were the most prescribed antibiotics.

We found that patients with poor prognosis were prescribed more number of antibiotics and this could be the reason for overuse of antibiotics in ICU. Our study was done prospectively and the relation between prescription of antibiotics and age, sex, gender, prognosis of the patients was studied. The data on utilization of antimicrobial in ICU is limited and this data is important in health care system of India because most of the people hardly bear the cost of treatment and there is lack of health insurance and government fund. So, more studies are required to add up to this data.

The result of this study shows that there are many areas that need our attention. Strict antibiotic restriction policy and implantation of protocol for rational use of antimicrobials are needed to ensure appropriate use of antimicrobials. Other studies have also shown that better health care services can be provided to patients at affordable cost by implementing policies for rational use of antibiotics. Similarly decrease in consumption of antibiotics has been observed with restricted authorization to prescribe antibiotics, consultation with infectious disease specialist and implementation of local antibiotic management programs.

National and state government should have their antibiotic utilisation policies to ensure appropriate use of antibiotics. Every hospital should have their own antibiotic utilisation policies based on disease present in their localities. It must be ensured that every prescriber know recent guidelines and clinical pathways. Promoting antibiotic stewardship program will aid in resolving the emerging problems of overprescribing and developing resistance.

**Conclusion**

Antibiotics are overprescribed in our ICUs and this is increasing the burden of unnecessary adverse effect, resistance and treatment costs. At the time of admission, patients with poor prognosis and older age are prescribed more antibiotics. Antibiotics stewardship programs should be promoted. And regulation of antibiotic utilization, proper use of guidelines and proper surveillance should be ensured by responsible authorities.

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**Conflict of Interest**

None.

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