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Original Article

Recent Prescribing Trends of Anti-Microbial Agents and their Sensitivity Pattern in an Intensive Care Unit of a Tertiary Care Teaching Hospital

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ABSTRACT

Background: *Due to the injudicious and indiscriminate use of Anti-Microbial Agents (AMAs) among hospitalized patients especially in ICUs, it is extremely imperative to monitor and refine the prescribing pattern of antibiotics regularly. Hence an effective surveillance team consisting of a physician, a pharmacologist and a microbiologist should develop and implement an antimicrobial stewardship program based on the local antibiogam to increase the therapeutic benefits and curb the menace of Anti-Microbial Resistance (AMR).* ***Aims****:-To study the prescribing pattern of Anti-Microbial Agents and to evaluate the antimicrobial sensitivity pattern of common bacterial isolates in Medical ICU (MICU) of a tertiary care hospital.* ***Methods****: After taking approval from the Institutional ethical committee, this prospective observational study was conducted in the department of Pharmacology and Microbiology over a period of six months. Patient records were reviewed and analyzed to assess the prescribing pattern of antibiotics and Culture-sensitivity reports of various specimen from MICU were collected to determine the antibiotic sensitivity pattern.* ***Results****: Ceftriaxone (26%) was the most commonly prescribed drug followed by Metronidazole (16%). Fixed drug combinations such as Piperacillin+Tazobactam (14%), Amoxicillin + clavulanic acid (10%) and Cefoperazone + Sulbactam (8%) were also frequently used. The most predominant organism isolated was Klebseilla species (25%) followed by Acenitobacter species (19.4%). Colistin /Imipenem and Vancomycin/Linezolid depicted100% sensitivity for Gram-Negative (GNIs) and Gram-Positive Isolates (GPIs) respectively.* ***Conclusions****: The need of the hour is to preserve the power of the almost exhausted antimicrobial armamentarium against the rampantly emerging multidrug resistant organisms.*

Key words: *prescribing pattern, antimicrobial agents, antibiotic sensitivity, multidrug resistance.*

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INTRODUCTION

Antimicrobial Agents (AMAs) are one of the most commonly prescribed drugs to patients in the Intensive Care Units (ICUs). The total antimicrobial consumption is approximately tenfold greater in ICUs than in a general hospital wards.[1] the paradox remains where the antibiotics are needed the most (ICU), there resistance is the highest.

Since the discovery of the very first antibiotics in the 1930s and 1940s, these medicines have played a revolutionary role by fighting against various lethal infectious diseases and have saved countless lives.[2,3] However, still the menace of infectious diseases account for 20% of deaths worldwide; equating to 11 million deaths yearly.[4] This is due to the development of Anti-Microbial Resistance (AMR), a threat that was first observed in 1947, when Staphylococcus showed resistance against penicillin.[5] The rapidly emerging Drug Resistant microbial species make the treatment options very meager and costlier.

Although a number of factors are thought to contribute to the increasing prevalence of AMR, but a large number of studies support the claim that inappropriate use of antibiotics is the main determinant of AMR. [6, 7, 8] Indiscriminate prescribing of AMAs leads to unsafe treatment, exacerbation of adverse drug reactions and increase the length of hospital stay and health care expenditures.

Prevalent pathogens and their antimicrobial resistance pattern may differ amongst various hospitals depending upon the antibiotic pressure in that region. Hence the knowledge

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of a particular ICU's most common bacterial isolates and their antibiotic susceptibility patterns facilitates in choosing the most appropriate and effective empirical antibiotic therapy.[9] Such knowledge is important not only for the clinicians but also for the health policy-makers for improving the quality of care, availability of effective drugs and cost containment.

So it is extremely important to audit, monitor and refine the prescribing pattern of antimicrobials from time to time to enable judicious and rational use of AMAs.[10] However, very limited data is available from North India about the antimicrobial prescribing patterns and their sensitivity for the emerging bacterial isolates, so we planned our study with the following objectives.

1. To evaluate the prescribing pattern of antimicrobial agents in the Medical Intensive Care Unit of RMCH Bareilly
2. To analyze the sensitivity pattern of culture isolates to antimicrobial agents.
3. To suggest necessary modifications in prescribing drugs to achieve better outcomes.

METHODS

A prospective, observational study was conducted by the department of Pharmacology in collaboration with the department of Microbiology of a tertiary care teaching Hospital. The study material comprised of the 250 eligible case records of patients admitted in the Medical Intensive Care Unit over a period of six months (from January 2017 to June 2017). Case records of patients who got transferred to other Specialty Intensive Care Units or another ward or discharged within 24 hours of admission were excluded from the study. The demographic and the prescribing pattern data of patients admitted in MICU was collected in the following format:

- Age & Sex of the patient
- Diagnosis of patients
- Average no. of drugs prescribed per patient
- Percentage and type of AMAs prescribed in order of preference
- Culture of isolates and Sensitivity pattern of AMAs

Culture & Sensitivity Testing

Bacterial isolates from clinical specimens such as urine, pus, blood, sputum etc. were detected. The antibiotic susceptibility testing was performed under the guidelines of Clinical and Laboratory Standard Institute (CLSI) in the Microbiology Department. The following antibiotics were tested for sensitivity. Ceftriaxone, Levofloxacin, Norfloxacin, Nitrofurantoin, Amikacin, Amoxycillin + Clavulanic acid Cefoperazone + Sulbactum, Piperacillin + Tazobactum, Imipenem, Colistin, Erythromycin, Ciprofloxacin, Clindamycin, Vancomycin and Linezolid.

Ethics

Approval for the study was sought from the Institutional Ethics Committee (IEC) before the initiation of study and informed consent was taken from the patients.

Statistical Analysis

The entire data was then recorded in the proforma and analysed using Microsoft Excel. Descriptive statistics was applied to the data using SPSS version 22. Prescribing trend of AMAs and their susceptibility pattern were analysed and expressed as percentage.

RESULTS

A total of 250 eligible case records were analyzed over a period of six months. The demographic data reveals that there were more male patients (61) as compared to females (39). Age of the patients was ranging between 16-80 years with the mean age around 58 years. The most common diagnosis which warranted admission to Medical ICU was Respiratory infections (32%) followed by cardio-vascular disorders (27%) like ischemic heart disease and congestive heart failure, GI and metabolic ailments (16%), diseases of the central nervous system (14%), pyrexia of unknown origin (11%) and others (2%), as shown in Figure 1.

The mean number of drugs received by patients in the present study was 6.8±2. Table 1 shows that in ICU ceftriaxone was the most commonly used AMA for 26% patients, followed by metronidazole 16% patients, and levofloxacin by 6.8% patients. Fixed drug combinations such as Piperacillin +Tazobactam (14%), Amoxicillin + clavulanic acid (10%) and Cefoperazone + Sulbactam (8%), were considered as a single type of AMAs and were the frequently prescribed group of AMAs in the MICU. Other commonly utilized antibiotics were Ciprofloxacin, Imipenem, Amikacin, Vancomycin, Linezolid etc. Figure2 shows that in this study 73.2% (102+81) patients were prescribed 1- 2 AMAs, while 26.8% (45+22) patients were given 3-4 AMAs.

Table 1: Prescribing frequency of AMAs in MICU

AMAs	Number	(%)
Ceftriaxone	65	26
Metronidazole	40	16
Piperacillin-Tazobactum	35	14
Amoxycillin-Clavulunate	25	10
Cefoperazone-Sulbactum	20	8
Levofloxacin	17	6.8
Ciprofloxacin	13	5.2
Amikacin	10	4
Imipenem	10	4
Vancomycin	4	1.6
Linezolid	4	1.6
Nitrofurantoin	3	1.2
Clindamycin	1	0.4
Colistin	1	0.4
Others	2	0.8

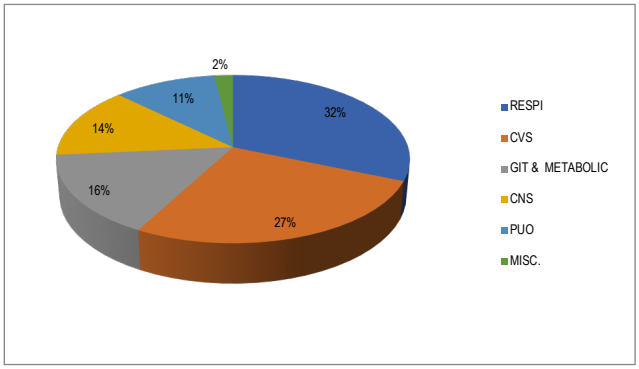

Fig 1: Distribution of diseases in admitted patients of MICU

Culture & Sensitivity testing results

Out of the 250 prescriptions analyzed, it was found that 75 samples were sent for culture and sensitivity. Out of these, organisms were isolated from 26 samples. A total of 36 organisms were detected, of which 26 were Gram-negative (72.3%), 10 were Gram-positive (27.7%). Figure 3 shows the isolation pattern of organisms obtained from different

specimens. Amongst the gram-negative organisms, Klebseilla was obtained in highest numbers 9(25%) followed by Acinetobacter 7(19.4%), Pseudomonas aeruginosa 6(16.6%) and E. Coli 4(11.1%). Staphylococcus 6(16.6%) and Enterococcus 4(11.2%) were the only organisms isolated in the gram positive category.

The sensitivity pattern of AMAs agents for Gram-negative (GNIs) and Gram-positive (GPIs) isolates are presented in Table 3&4, respectively. The evidence generated from the antibiogram indicates Imipenem (100%), Colistin (100%) to be the most effective drugs against gram negative isolates. Piperacillin-Tazobactum showed a good sensitivity of 77.78%/66.67%/85.71/75% for Klebseilla, Pseudomonas, Acinetobacter species and E. coli respectively. The frequently used 3rd generation Cephalosporin i.e. Ceftriaxone showed a poor sensitivity towards these organisms.

It is clear from the sensitivity pattern of Gram positive isolates that antibiotics like Amoxycillin-Clavulanic acid and Erythromycin are least sensitive against them, while drugs like Vancomycin and Linezolid are 100% effective, followed by Clindamycin, Amikacin and Ciprofloxacin which showed a sensitivity of 83.34%, 83.34% and 66.67% respectively for Staphylococcus aureus.

Table 2: Sensitivity Pattern of Gram-Negative Isolates expressed as number (%)

Antibiotics	Klebseilla	Pseudomonas	Acinetobacter	E. coli
Ceftriaxone	2 (22.23%)	2 (33.34%)	4 (57.14%)	1 (25%)
Piperacillin-Tazobactum	7 (77.78%)	4 (66.67%)	6 (85.71%)	3 (75%)
Cefoperazone-Sulbactum	6 (66.67%)	3 (50%)	5 (71.42%)	3 (75%)
Amoxycillin-clavulanic acid	1 (11.12%)	NT*	2 (28.57%)	1 (25%)
Levofloxacin	7 (77.78%)	4 (66.67%)	4 (57.14%)	3 (75%)
Norfloxacin	5 (55.56%)	1 (16.67%)	NT*	2 (50%)
Nitrofurantoin	8 (88.89%)	3 (50%)	NT*	3 (75%)
Amikacin	7 (77.78%)	3 (50%)	4 (57.14%)	3 (75%)
Imipenem	9 (100%)	9 (100%)	7 (100%)	4(100%)
Colistin	9 (100%)	9 (100%)	7 (100%)	4 (100%)

*NT- Not Tested

Table 3: Sensitivity pattern of Gram-positive Isolates expressed as number (%)

Antibiotics	Staphylococcus Number (%)	Enterococcus Number (%)
Amoxycillin-clavulanic acid	3 (50%)	1 (25%)
Erythromycin	2 (33.34%)	NT*
Ciprofloxacin	4 (66.67%)	2 (50%)
Clindamycin	5 (83.34%)	NT*
Amikacin	5 (83.34%)	NT*
Vancomycin	6 (100%)	4 (100%)
Linezolid	6 (100%)	4 (100%)

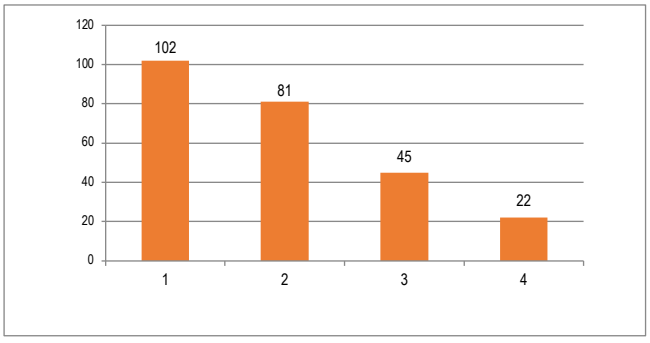

Fig 2: Number of Antibiotics per patient

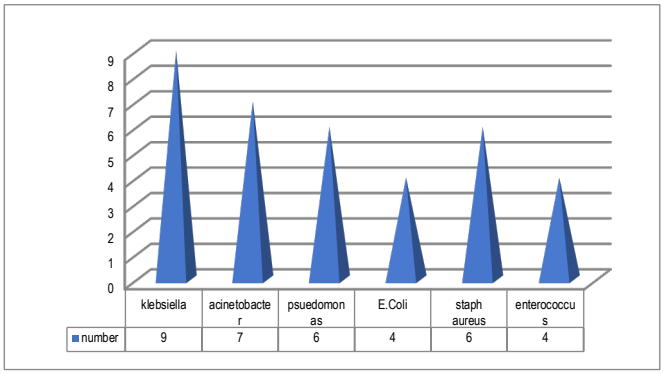

Fig 3: Isolation pattern of microorganisms

DISCUSSION

Infections continue to play a significant role in the overall global mortality and disability and have plagued the developing countries ferociously.[11]The presence of extremely vulnerable patients with diminished host defenses and reduced immune responses, undergoing multiple procedures, and use of invasive devices distorting the anatomical integrity and protective barriers of patients, render the ICUs as a hub for antimicrobial resistance.[12] Hence seriously monitoring the appropriate utilization of antibiotics in ICUs is crucial to preserve the power of almost exhausted anti-microbial armamentarium to fight against fatal infections.

The demographic results of patients admitted to the medical ICU in our study revealed male preponderance (1.56:1) with a mean age of around 58 years, similar to a study done by Pandiaminian J et al.[13] The reason for more male admissions in our study may be attributed to the fact that in the Indian scenario it is noticed that female populations are reluctant to utilize health care facilities even if they are critically ill.

The mean number of drugs received by patients in the present study (6.8±2 drugs) was comparable to Vandana etal.[14] who reported the average number of drugs in their study to be 7.5. Other authors in the field like Drupad etal.[15] and Shankar et al.[16] have reported a higher mean of number of drugs prescribed per prescription. Average number of drugs per person is an important index of prescription audit. It is desirable to keep the mean number of drugs per prescription as low as possible, since higher figures are inclined to increased risk of drug interaction, emergence of bacterial resistance and inflate the expenditure as well.

A variety of critical cases are admitted in a medical ICU. In the present study, majority (32%) of the patients were admitted with respiratory infection. Similar result were seen in other study done by Choudhary et al.[17]and Drupad et al.[15] Antibiotics are the most powerful weapons used in a Medical ICU to combat against the debilitating infectious diseases. Amongst the total number of AMAs prescribed, Ceftriaxone (26%) ranked the highest in our study followed by Metronidazole (16%). The results of our study are in agreement with the findings of a latest study published in BioMed Central by Atif et al.[18] who also reported Ceftriaxone and Metronidazole to be the most commonly prescribed first line antibiotic in the ICU. Vandana et al[14] and Pandiamunian J et al13also observed Cephalosporins like Ceftriaxone(23%) and Cefotaxime(32%) respectively, to be the most frequently utilized group of AMAs in ICU, which is in accordance with our study results.

Studies done a decade back on prescription pattern of AMAs in ICU revealed penicillins and aminoglycosides as the most commonly used AMAs. But recent studies conducted on the similar topic, documented that third generation Cephalosporins are the most frequently prescribed AMAs in the ICUs as well as in the out-patient clinics in India.[19,20] The reason for such extensive use of Cephalosporins may be their broad anti-microbial spectrum effective against majority of bacteria, better patient tolerability and compliance.

Drupad et al.[15] have found Metronidazole was prescribed along with Cephalosporins in majority of the prescription (22.4%) as the first line drug. The rationale behind prescribing metronidazole is that it covers the anaerobic infection which is quite common in a hospital setting and are usually treated empirically without susceptibility testing, Earlier studies have also showed similar use of metronidazole given along with the Cephalosporins.[14]

The results of the current study depict that most frequently prescribed antimicrobial fixed dose combinations were Piperacillin + Tazobactam (14%), Amoxicillin + clavulanic acid (10%) and Cefoperazone + Sulbactam(8%). Our results are in line with Beg MA[21] who in his study reported that most frequently prescribed antimicrobials combinations were Piperacillin + Tazobactum in 73 (6.06 %), followed by Amoxicillin + Clavulanic acid in 71 (5.89 %) and Cefoperazone + Sulbactam in 54 (4.48%) patients. A similar trend of prescription pattern of antimicrobial combinations was noted by Sireesha GBN et al.[22]

Our study shows that 73.2% patients were prescribed 1- 2 AMAs, while 26.8 % patients were given 3-4 AMAs. Our findings are in concurrence with other authors.[14,22] in the field who observed that 77% patients were prescribed between 1-3 AMAs while 23% patients were given 4-8 AMAs in the ICU.

The present study also provides information on the distribution of bacterial pathogens in patients admitted in a Medical ICU. In the present study also, Gram-negative isolates (72.3%) were predominant over Gram-positive isolates (27.7%) as observed in various other studies.[23,24]

Amongst the gram negative isolates, Klebseilla was the most common organism (25%) followed by Acinetobacter (19.4%), Pseudomonas aeruginosa (16.6%) and E.Coli (11.1%). Similar findings were reported by Ghanshani R et al[25] who documented in their study that Gram-negative bacteria were the most common and included A. baumannii (20.9%), K. pneumoniae (19.7%), E. coli (18.3%), and Pseudomonas aeruginosa (14.0%). Chand Wattal et al.[26] also found that among GNIs, Klebsiella species was the commonest followed by Acinetobacter spp. Our results are in contrast to the study conducted by Singh AA et al.[27] who reported Pseudomonas aeruginosa as the most frequently (38.17%) isolated bacteria .

The most common Gram-positive bacterium isolated in the present study were Staphylococcus aureus (16.6%) and Enterococcus (11.2%). Our results are in concordance with Gupta and Kashyap[28] and other authors.[25,26]

There is no doubt that antibiotics have revolutionized the healthcare services worldwide. As by the famous saying “Every coin has two sides”, the mutant bacteria are becoming recalcitrant and troublemaker by developing resistance to these antibiotics. During the past decades, a global shift in the AMR scenario has been noted from Gram-positive to Gram-negative.

According to our data, all the GNIs were 100% sensitive to Imipenem and Colistin. Similar trends of susceptibility pattern have also been observed by Gupta and Kashyap[28] and C.M. Divyashanthi.[29] Acinetobacter is a new emerging organism in nosocomial infection that has been reported in many studies to be widely resistant. We, however, found comparatively good sensitivity of Acinetobacter species, as seen in Table 2. Our results are in line with Sheth et al.[30] Non-isolation of carbapenem-resistant Gram-negative bacteria (GNB) in our study may be due to its restricted use as a reserve drug in our ICU. Other antibiotics which have retained their usefulness against GNIs are Piperacillin-Tazobactum, Cefoperazone-sulbactum, Levofloxacin and Amikacin. However, the frequently used Ceftriaxone and a combination of Amoxycillin-Clavulanic acid revealed a disturbing trend, as they showed a poor sensitivity towards these organisms. Similar findings have been reported by Gupta and Kashyap.[28] who found that majority of Enterobacteriaceae were sensitive to imipenem (98.77%), amikacin (90.76%), and cefoperazone/sulbactam combination (81.14%). They also noted a high degree of resistance to amoxicillin/ clavulanic acid combination and cephalosporins. The indiscriminate and excessive use of cephalosporins could be the reason for such high level of resistance being observed all across the country. The mechanism of resistance of Enterobacteriaceae to cephalosporin is usually due to breakdown of the drug by extended spectrum beta-lactamases (ESBL). Infection with ESBL organisms is associated with increased hospital stay and increased cost of management. In our study also, 28% of pathogens out of Klebseilla and E. coli together were ESBL-producers. Nitrofurantoin showed high rate of sensitivity towards Klebseilla (88.89%) and E. coli (75%) which were the predominant isolates in urine samples.

Among GPIs, the pharmacological sensitivity profile shows Vancomycin and Linezolid to be the most effective antibiotics (100% sensitive) for Staphylococcus aureus and Enterococcus both. In our study, 33% MRSA were detected, which is almost similar to the finding observed by Ahmadey and Mohammed et al.[31] Ciprofloxacin, Clindamycin and Amikacin showed good sensitivity for GPIs. But these organisms showed varying level of resistance for drugs like Amoxycillin-clavulanic acid and Erythromycin, which were once considered the drug of choice for Gram positive infections. Several studies[27,28,29,32,33] are available across the globe which have documented similar findings with respect to susceptibility pattern of GPIs.

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CONCLUSION

Based on the results we recommend that the prescribing pattern could be improved by adhering to the WHO prescribing indicators. Moreover, an Antibiogram specific to the institute, based on the local profile of the prevalent strains of microorganisms, needs to be framed and followed to promote the rational use of antimicrobials and for the containment of Antimicrobial Resistance.

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