Utilization pattern of antimicrobial agents and its culture sensitivity pattern in intensive care units in a tertiary care center in eastern Nepal

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ABSTRACT

A retrospective study was conducted to find out drug utilization pattern of antimicrobial agents (AMA) and its sensitivity pattern in the intensive care units (ICU). This study was done at B.P. Koirala Institute of Health Sciences, Dharan, Nepal by analyzing the case sheet records of the patients admitted to the ICUs over a period of three months (April to June, 2014). Piperacilin (16.6%) was the most commonly prescribed AMA followed by Amikacin (15.5%), Vancomycin (14.4%), Ceftriaxone (13.3%) and Ampicillin (12.2%). 17.7% patients were prescribed more than two antibiotics.None of the drugs were prescribed by the generic names. Of the various pathogenic organisms isolated, *Staphylococcus aureus* constituted for 31.8% followed by *Escheria coli* (20.5%), *Pseudomonas* (18.2%) and others. *S. aureus* was found to be most sensitive toCarbenicilin, Imipenem, Vancomycin and Amoxyclav and least sensitive to Cefotaxime and Ceftriaxone. *E. coli* was found to be most sensitive to Gentamicin, Imipenem and Chloramphenicol and least sensitive to most commonly used drugs like Ciprofloxacin, Cefotaxime and Amoxyclav. Pseudomonas was found to be most sensitive to Ceftazidime, Carbenicilin and Imipenem and least sensitive to Amoxyclav, Ceftriaxone, Vancomycin and Ciprofloxacin. . There is a considerable scope for improving the prescribing habits through rational prescription and providing feedback to the hospital authorities.

Keywords: AMA, ICU, sensitivity, Nepal

INTRODUCTION

Infection is a major cause of morbidity and mortality in intensive care units (ICUs).[1] A large number of drugs are administered to patients admitted in ICUs and the costs of hospitalization and drug treatment are also high in the ICUs.[2] Antibiotics are among the most common drugs prescribed in the hospitals that may lead to the emergence of and promote the spread of antimicrobial resistance.[3] An alarming increase in infections caused by antibiotic-resistant pathogens, including methicillin-resistant *Staphylococcus aureus*, Vancomycin-resistant *Enterococcus* species, Carbapenem-resistant *Pseudomonas aeruginosa*, extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella*spp., and multidrug-resistant *Acinetobacter* spp., has been observed particularly in the ICUs.[4] Widespread and excessive use of broad-spectrum antibiotics, invasive medical devices, critically ill and immunosuppressed patients in the ICUs favor the spread of resistant organisms. Infection with antibiotic resistant organisms can cause increased length of hospital stay, mortality, and costs to the patient.[5]

Prevalent flora and antimicrobial resistance pattern may vary from region to region depending upon the antibiotic utilization in that locality. Hence, evaluation of drug utilization pattern in the ICUs along with information on the sensitivity pattern of microorganisms from time-to-time is very crucial. Drug utilization research can also provide useful information to health care providers and policy makers. It offers the prospect of improving the quality of pharmacotherapy. It also contributes to rational drug use by describing drug use patterns, detecting early signs of irrational drug use and identifying interventions to improve drug use and follow-up. Information on drug utilization in ICUs are lacking in eastern Nepal. Hence the present study was carried out to obtain information on the basic demographic pattern of the admitted patients, utilization pattern of antimicrobial agents (AMAs), and the antibiotic sensitivity patterns of isolated microorganisms in ICUs.

MATERIAL AND METHODS

This was a retrospective study carried out by department of Clinical Pharmacology and Therapeutics in ICUs at B.P. Koirala Institute of Health Sciences (BPKIHS) from April 2014 to June 2014. BPKIHS is a 733 bedded hospital situated in Dharan, Nepal. The hospital has 28 bedded ICUs where critically ill patients are admitted. Ethical clearance was taken from the Internal Review Board, BPKIHS. After obtaining the necessary permission from the concerned authorities for data

collection, the record case sheets of the patients admitted in the ICUs during the three month period were analyzed for demographic data, different drugs prescribed, specimens sent for culture and report of the antibiotic sensitivity test. All the relevant data were collected with the help of standard proforma. WHO drug use indicators like average numbers of drugs prescribed, the percentage of drugs prescribed by the generic name and the percentage of encounters with an antibiotic were calculated.[6] The data was subjected to descriptive analysis using Microsoft Excel 2013 and the data were expressed as mean and percentage.

RESULTS

A total of 62 patients were admitted in the different ICUs during the three months of the study period. Majority of the patients (68%) were male. More than half (56.5%) of the patients were above 50 years of age. Results showed that 67.9% of the patients were from Nepal and the remaining (32.1%) were from India. Diagnosis could not be made at the time of admission in ten patients. Pattern of diseases is given in **Table 1.** Most common diagnosis at the time of admission was septicemia (19.23%) followed by meningitis and ischemic heart disease. The empirical AMAs were given in 52 (83.9%) patients at the time of admission.

Table 1: Pattern of diseases in the ICUs (n=52)

S.N.	Diseases	No. (%)
1	Septicemia	10 (19.23)
2	Meningitis	8 (15.38)
3	Ischemic Heart Disease	8 (15.38)
4	Chronic Obstructive Pulmonary Disease	5 (9.62)
5	Pneumonia	5 (9.62)
6	Others*	16 (30.77)

*Others include organophosphorus poisoning, renal calculus with hydronephrosis, cholilithiasis with periampullary carcinoma, acute large bowel obstruction, gangrenous appendicitis, traumatic quadriplegia, traumatic hollow viscus perforation.

General prescription data is given in **Table 2.** All of the patients (n=62) were prescribed a total of 199 drugs with 3.2mean drugs per patient. None of the drugs were prescribed by the generic name. Very few drugs (9.04%) were prescribed as fixed dose combination (FDC) with 0.3 FDC per patient. Pattern of drugs utilization in the ICUs is given in **Table 3.** AMAs (56%) were the most commonly prescribed drugs followed by cardiovascular drugs (13.5%) and central nervous system drugs (12.6%). Pattern of utilization of AMAs is given in **Table 4.** Total of 112 AMAs were prescribed to 62 patients with 1.8 mean number of AMAs per patient. Among the AMAs, Penicillins (29.5%) were the most commonly prescribed group, followed by Cephalosporin (17.8%), Aminoglycosides (12.5%), Glycopeptides (12.5%), Fluroquinolones (8.0%), Lincosamide (4.5%), Nitroimidazoles (4.5%) and others (10.7%). Pattern of utilization of top ten AMAs is given in**Table 5**. Among all the antibiotics prescribed, Piperacillin/Tazobactam (16.7%) was the most commonly prescribed, followed by Amikacin (15.6%), Vancomycin (14.4%), Ceftriaxone (13.3%), Ampicillin (12.2%), Levofloxacin (8.9%) and others (13.3.%).

Table 2: General prescription data

Total number of patients	62
Total numbers of drugs	199
Mean number of drugs per patient	3.2
Total numbers of AMAsprescribed	112
Mean number of AMAs per patient	1.8
Total number of drugs prescribed by generic name	Nil
Total number of Fixed dose combinations (FDC) prescribed	18 (9.04%)
Mean no. of FDC per patient	0.3

Table 3: Pattern of total drugs utilization in ICUs (n=199)

S.N.	Drug classes	Frequency (%)
1	Antimicrobial agents	112 (56.3)
2	Cardiovascular system	27 (13.6)
3	Central nervous system	24 (12.1)
4	Gastrointestinal system	18 (9.0)
5	Minerals and vitamins	6 (3.0)
6	Endocrine system	5 (2.5)
7	Respiratory system	4 (2.0)
8	Musculoskeletal system	3 (1.5)
Total		199 (100)

Table 4: Pattern of AMAs utilization in ICUs (n=112)

S.N.	Groups of antibiotics	Frequency (%)
1	Penicillins	33 (29.5)
2	Cephalosporins	20 (17.8)
3	Aminoglycosides	14 (12.5)
4	Glycopeptides	14 (12.5)
5	Flouroquinolones	9 (8.0)
6	Lincosamides	5 (4.5)
7	Nitroimidazoles	5 (4.5)
8	Others*	12 (10.7)
Total		112 (100)

*Others include Macrolides, Tetracyclines, Sulfonamides, antimalarial drugs, antiviral drugs.

Table 5: Pattern of utilization of top ten AMAs

S.N.	Individual Antimicrobial agents	Number of prescription (n=90)	%
1	Piperacilin/Tazobactam	15	16.7
2	Amikacin	14	15.6
3	Vancomycin	13	14.4
4	Ceftriaxone	12	13.3
5	Ampicillin	11	12.2
6	Levofloxacin	8	8.9
7	Meropenem	5	5.6
8	Clindamycin	5	5.6
9	Cefotaxime	4	4.4
10	Metronidazole	3	3.3

Utilization pattern of AMA per prescription is given in Table 6. Eleven (17.7%) patients were prescribed one antibiotic and two antibiotics were prescribed in 29 (46.8%) patients. More than 3 antibiotics were prescribed in 11 (17.7%) patients. Ten (16.1%) patients were not prescribed any antibiotics.Total of 43 specimens for culture and antibiotic sensitivity test were received from 62 patients of which 8 were cerebrospinal fluid (CSF), 17 blood, 14 urine and 2 pus. All the CSF specimens were found to be sterile. Majority of the blood (94.11%), urine (57.14%) and pus (100%) specimens were found to be culture positive. The organisms isolated from the culture of blood, urine and pus are given in **Table 7**. A total of 44 organism were isolated from the cultures among which 28 (63.6%) were gram negative organisms. *Staphylococcus aureus* (31.8%) was the most commonly isolated organism followed by *Escherichia coli* (20.4%) and *Pseudomonas* (18.1%).

Table 6: Number of AMAs per prescription (n=62)

Number of antimicrobial agents per prescription	Frequency (%)
0	10 (16.1)
1	11 (17.7)
2	29 (46.8)
3	9 (14.5)
4	2 (3.2)

Overall sensitivity pattern of all isolated gram positive and negative organism is given in**Table 8** and **9**respectively. S. aureus was found to be most sensitive to Carbenicilin, Imipenem, Vancomycin and Amoxyclav and least sensitive toCefotaxime and Ceftriaxone. E. coli was found to be most sensitive toGentamicin, Imipenem and Chloramphenicol and least sensitive to most commonly used drugs like Ciprofloxacin, Cefotaxime and Amoxyclav. Pseudomonas was found to be most sensitive to Ceftazidime, Carbenicilin and Imipenem and least sensitive to Amoxyclav, Ceftriaxone, Vancomycin and Ciprofloxacin.

Table 7: Pattern of micro-organisms isolated from blood, urine and pus culture

Specimen	Micro-organisms		Frequency
	Gram positive	Gram negative	
Blood	S. aureus		12
	Enterococcus		1
		Acinetobacter	5
		Pseudomonas	4
		Klebsiella	4
		E. coli	3
		S. typhi	2
Urine		E. coli	6
		Pseudomonas	2
	Enterococcus		1
Pus	S. aureus		2
		Pseudomonas	2
Total	16	28	44

Table 8: Antimicrobial sensitivity pattern of isolated gram positive organisms

Antibiotics	Percent sensitivity (No. of cultures sensitive/No. tested)	
	S. aureus (n=14)	Enterococcus (n=2)
Amoxyclav	64.28 (9/14)	0 (0/2)
Cefotaxime	28.57 (4/14)	0 (0/2)
Ceftraixone	21.42 (3/14)	0 (0/2)
Vancomycin	92.85 (13/14)	100 (2/2)
Azithromycin	0 (0/14)	0 (0/2)
Ceftazidime	64.28 (9/14)	0 (0/2)
Ciprofloxacin	0 (0/14)	100 (2/2)
Carbenicillin	100 (14/14)	100 (2/2)
Imipenem	100 (14/14)	100 (2/2)
Chloramphenicol	0 (0/14)	100 (2/2)
Gentamicin	0 (0/14)	100 (2/2)

DISCUSSION

Infection is a major cause of morbidity and mortality in ICUs. Inadequate and ineffective antibiotic therapy may lead to spread of resistance to both Gram-negative and Gram-positive microorganisms. In the present study, utilization pattern of the AMAs and its culture sensitivity pattern in ICUs were evaluated retrospectively over a period of 3 months.

The study included analysis of case record sheet of 62 patients admitted in the ICUs during the study period. Majority of the patients were from local areas. Few patients were also from India. Most of the patients (56.5%) were over 50 years of age. This finding was not in consistent with that of Shankar et al.[7] Our study included patients from all ICUs and hence resulted in

Table 9: Antimicrobial sensitivity pattern of isolated gram negative organisms

Antibiotics	Percent sensitivity (%) (No. of cultures sensitive/No. tested)				
	Acinet-obacter (n=5)	Pseudo-monas (n=8)	S. typhi (n=2)	E. coli (n=9)	Klebsiella (n=4)
Amoxyclav	0 (0/5)	12.5 (1/8)	0 (0/2)	22.22 (2/9)	0 (0/4)
Cefotaxime	0 (0/5)	0 (0/8)	0 (0/2)	11.11 (1/9)	0 (0/4)
Ceftraixone	0 (0/5)	25 (2/8)	100 (2/2)	33.33 (3/9)	0 (0/4)
Vancomycin	NT	12.5 (1/8)	NT	NT	NT
Azithromycin	0 (0/5)	0 (0/8)	0 (0/2)	0 (0/9)	0 (0/4)
Ceftazidime	NT	75 (6/8)	0 (0/2)	NT	0 (0/4)
Ciprofloxacin	0 (0/5)	25 (2/8)	0 (0/2)	44.4 (4/9)	25 (1/4)
Carbenicillin	100 (5/5)	75 (6/8)	NT	NT	NT
Imipenem	100	100 (8/8)	NT	100 (9/9)	100 (4/4)
Chloramphenicol	0 (0/5)	37.5 (3/8)	100 (2/2)	55.55 (5/9)	50 (2/4)
Gentamicin	0 (0/5)	0 (0/8)	0 (0/2)	55.55 (5/9)	0 (0/4)

wide range of age distribution. Septicemia was the most common diagnosis at the time of admission in our study. Similar results were also reported by Shrestha R *et al* and Williams *et al*.[8,9] Our data revealed that most of the patients were initially treated empirically with broad spectrum antibiotics. Similar trend was also mentioned by Paolo Malacarneet al.[10]This may be due to severity of the disease at the time of admission and delay in the culture sensitivity test.

An important index of a prescription audit is the average number of drugs per prescription. The use of minimal number of drugs per prescription minimize the risk of drug interactions, development of bacterial resistance and hospital costs.[11] In our study, it was found that a mean of 3.2 drugs per patient were prescribed which was higher than the WHO guidelines. WHO recommended that average number of drug per prescription should be 2.0 or less.[12] However, it was lower than the others' data reported in the literature.[2,13] Hence our study revealed polypharmacy which could enhance drug interactions and drug related other problems. It is well known fact that multiple drugs are required to treat patients in the ICU with multiple co-morbidities, but at the same time, it is also essential to keep a balance between the number of drugs and effective pharmacotherapy. However, it is always preferable to keep the mean number of drugs per prescription as low as possible to minimize the adverse effects and drug interactions and to reduce the cost of the treatment.

Our study revealed that none of the drugs were prescribed by generic name and this might increase the cost of the treatment. In other study, 79.7% drugs were prescribed by generic name.[14] Prescribing by generic name helps the hospital pharmacy to have a better control of inventory, reduce the confusion among the pharmacists while dispensing, eliminates the chance of duplication of drug products and reduces the cost of the treatment. There is an urgent need of revision of current prescribing practice for promoting prescription of generic drugs in our hospital. The prescription by generics should be promoted more, for cost effective treatment. Fixed dose combination was 0.3 per patient which was very low.

In our study, AMAs were the most commonly prescribed drugs. It indicated a higher incidence of infection in the ICUs. Similar results were also reported in other studies. Capp et al. retrospectively reviewed the data on 1400 patients admitted to the ICU and concluded that antibiotics were prescribed in 82% of the patients.[15]Although majority of patients were prescribed some antibiotics, the number of antibiotics prescribed per patient (1.8 per prescription) was lower to that described in other studies.[2,16] In our study, majority of the patients (64.4%) were prescribed less than three antibiotics. Similar result was also reported byHariharan et al. in which 60% of the patients in ICU received two antibiotics.[17] A study in a Danish university hospital ICU reported that the majority of their patients were prescribed one antibiotic.[18] More than 3 antibiotics were prescribed to 17.7% of the patients in our study which was higher that the others' report. In a German surgical ICU, 36.7% of cases were treated with only one antibiotic agent, 14.1% were given a combination of two antibiotics, and 7.2% were given a combination of more than three antibiotics.[19] This could be due to prevalence of sepsis, multi organ dysfunction, acute respiratory distress, pneumonia and lower respiratory tract infections among the patients of the present study necessitating therapeutic as well as prophylactic utilization of antimicrobials. Antimicrobial protocol and guidelines can be used to improve rational usage of antimicrobials.

Our study revealed that the most commonly prescribed antibiotics in the ICUs were the Penicillins. Similar finding is also reported by Sharma PR et al and Shankar

et al which supports findings of our study.[2,20] However, in other studies done by SM Walther et al and Williams et al, Cephalosporins were the most frequently prescribed group of AMAs.[9,21] Among the Penicillins, Piperaciin/ Tazobactam was the most commonly prescribed antibiotic in our ICUs and similar result was also reported in an Indian study.[20] It may be due to their relatively lower toxicity and broader spectrum of activity. Cephalosporins are often used in combination with aminoglycosides due to synergistic activity and broader coverage of organisms for several serious gram negative infections. According to Biswal et al, the most frequently prescribed antibiotic in the ICU was Metronidazole followed by Cefotaxime, Amoxycillin/ clavulinic acid, Cefipime and Ciprofloxacin.[22] Antibiotic choices made during the first hour of treatment in severe sepsis have been recognized as an important predictor of clinical outcomes. In our study, utilization of newer AMAs such as Meropenem and Imipenem (carbapenems), Clarithromycin (macrolides), Clindamycin (lincosamides) and Vancomycin (glycopeptides) were observed.

Antimicrobial drug resistance is an increasing problem in ICUs. It is reported that the pattern of antibiotics use influences the development of resistant organisms.[23] Widespread and excessive use of broad-spectrum antibiotics, invasive medical devices, critically ill and immunosuppressed patients in ICU favor the spread of resistant organisms.[24]For culture and antibiotic sensitivity test, CSF, blood and urine were the most commonly used specimen. Culture positivity was highest (94.11%) with blood samples which was higher than that of the study done in other places.[25-27]It may be due to higher incidence of septicemia originated from pulmonary infection. The CSF culture yield was zero percent which may be due to early use of broad spectrum antibiotics. Gram negative bacteria were more common than Gram positive bacteria in our study and these results were in concordance with some of the other studies.[8,28-30]*Staphylococcus aureus* was the most common organism isolated followed by *E. coli* and *Pseudomonas* which reflects higher infection of urinary tract and blood. It also suggests that most of the patients were critically ill, and many were transferred from other hospitals with multiple devices and prior broad-spectrum antibiotic therapy.[20] The number of the specimens was small which makes it difficult to compare our findings with that reported in the literature.

According to antibiotic sensitivity test, most of the commonly used antibiotics were sensitive to the organism isolated. However, *S. aureus*, *E. coli* and *Pseudomonas aeruginosa*were found to be resistant to some of the commonly used antibiotics. Our study indicates that resistance to third generation cephalosporins and macrolides is increasing and these drugs cannot be used for empirical therapy in seriously infected patients in ICUs. Our study also indicates that Imipenem and Chloramphenicol can be used for treating *Enterococcus*, *S. typhi* and *Pseudomonas aeuriginosa*empirically. Similar finding is also reported by Khurram M et al.in other study, resistant bacteria were detected in up to 50% of microbiological samples from critically ill sepsis patients in ICUs of a low-middle-income country.[29,31] *P. aeruginosa* isamultiresistant organism making optimal therapy selection difficult; similar results are also mentioned by Jain S et al.[32]
Use of antibiotic rotation policies in the ICU, regular prescription audits, and feedback reviews are needed to check the use of irrational antibiotic therapy. Education of the prescriber is the cornerstone of any successful antibiotic stewardship program and teaching of guidelines and clinical pathways will aid in improving antimicrobial prescribing behavior to a large extent.[9] The strengths of our study is that it gives a general overview of utilization pattern of AMAs in the ICUs which may increase awareness among the prescribers by reflecting the their irrational prescription habits. It would further help to reduce inappropriate use of AMAs and bacterial resistance. However, this study was of short duration with small sample size and hence the results may not be generalized to other hospitals. Similar study of longer duration and with larger sample size would further validate our observations.Our study reveals that AMAs continue to be widely prescribed in critically ill patients and form a significant proportion of the total drugs consumed in the ICU. Resistant bacteria were detected in most of the microbiological samples in the patients in ICUs. Both gram positive and gram-negative organisms exhibited high resistance to most antimicrobial agents used for sensitivity test. Carbapenem resistance is still rare in our ICUs. Imipenem, Ceftriaxone and Piperacillin were found to be susceptible to most of the isolated organism and hence can be used as good empiric choices for treatment of most infection in the ICU. There isaconsiderable scope for improving the prescribing habits through rational prescription and providing feedback to the hospital authorities.

ACKNOWLEDGEMENT

The authors would like to acknowledge the assistance rendered for data collection by all nursing personnel, medical officers/ house officers of the ICUs.

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