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Original Article

Intensive care unit drug utilization in a teaching hospital in Nepal

Shankar PR[1], Partha P[2], Dubey AK[3], Mishra P[4], Deshpande VY[5]
[1,3,4] Asst. Professors, [2]Clinical Tutor, [5]Professor, Manipal College of Medical Sciences

Abstract
Objectives: The intensive care unit (ICU) is a setting where a large number of drugs are administered to patients and the costs of hospitalization and drug treatment are high. Information on drug utilization in intensive care units (ICUs) are lacking in western Nepal. The present study was carried out to obtain information on the basic demographic pattern of the respondents , drug utilization during the study period, the antibiotic sensitivity patterns of isolated microorganisms and measure drug consumption in defined daily dose (DDD)/ 100 bed-days. Methods: A retrospective analysis of patients admitted to the ICU of the Manipal Teaching hospital, Pokhara, Nepal during the time period from 01/02/2002 to 31/05/2002 was carried out. The ICU mortality rate, length of stay greater than 7 days and median length of stay were calculated. Results: A total of 259 individuals were admitted. The ICU mortality rate was 15.4%; median length of stay was 4 days. *E.coli, H.influenzae, K.pneumoniae, S.aureus and P.aeruginosa* were the common organisms isolated and were found to be resistant to some of the commonly used antibiotics. Mean ± SD number of drugs and cost of drugs were 5.1 ± 2.7 and 1958.5 ± 1267.8 Nepalese rupees (25.1 ± 16.2 US$). Total drug consumption was 356.4 DDD/100 bed-days. Consumption of intravenous fluids was 25.8 litres/100 bed-days. Conclusions: An antibiotic use policy should be framed. Formation of a multidisciplinary team to oversee drug use and periodically review microbial sensitivity patterns will be helpful. Longitudinal surveillance of ICU drug use should be carried out.
Key words: Antibiotic sensitivity patterns, Defined daily dose, Drug utilization, Intensive care unit

Drug utilization has been defined as the marketing, distribution, prescription and use of drugs in a society with special emphasis on the resulting medical and social consequences.[1] Developing countries have limited funds available for health care and drugs and it becomes very important to prescribe drugs rationally so that the available funds can be utilized optimally.

The intensive care unit (ICU) is a setting where a large number of drugs are administered to patients and the costs of hospitalization and drug treatment are high. In many countries, antibiotic resistance in the ICU setting has emerged as an important problem influencing patient outcomes. Widespread use of broad-spectrum antibiotics, crowding of patients into geographically confined areas, presence of invasive medical devices and greater number of critically ill patients may be factors favouring the emergence and spread of resistant organisms.[2] Patients with critical illnesses are at risk of acquiring serious nosocomial infections which may lead to escalation in medical expenses, morbidity and mortality.[3] Keeping in mind all these factors periodic evaluation of drug utilization in the ICU, longitudinal surveillance of drug use and obtaining information on the sensitivity patterns of microorganisms over a period of time are important.

In order to compare drug utilization among different countries and even among health institutions within a country, the utilization has to be expressed in internationally accepted units. The defined daily dose (DDD) concept was developed to overcome objections against traditional units of measurement of drug consumption.[4,5] DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults.[4,5] DDD provides a fixed unit of measurement independent of price and formulation. For hospital inpatients, DDD/100 bed-days provide a rough estimate of drug consumption.

The Manipal Teaching Hospital is a 750 bedded hospital attached to the Manipal College of Medical Sciences, Pokhara, Nepal. The hospital has a ten-bedded ICU where critically ill patients from different specialties are admitted. Neonatal cases are admitted in a separate neonatal ICU. The antimicrobial use pattern in the intensive treatment unit (ITU) over a one-year period from June 15, 2000 to June 15, 2001 was previously studied.[6]

Correspondence
Dr. P. Ravi Shankar,
Department of Pharmacology,
Manipal College of Medical Sciences
Email: ravi_p_shankar001@hotmail.com

During that time period the ITU was in the first year of operation and the Department of Clinical Microbiology had just started functioning in our hospital. The ITU was upgraded to an ICU and a consultant from the Department of Internal Medicine was made in charge of the ICU. To obtain information on the drug utilization in the ICU and the antimicrobial sensitivity patterns, the present study was carried out over a four-month period from 01.02.2002 to 31.05.2002.

The objectives of the present study were to:
1) Obtain basic demographic information on patients admitted to the ICU during the study period
2) Obtain information on the patient outcomes and duration of hospitalization
3) Enumerate the main illnesses necessitating admission to the ICU
4) Calculate mean ± SD number of drugs and measure the drug consumption in DDD/100 bed-days
5) Calculate the number of patients who were prescribed antibiotics, intravenous fluids, thrombolytics, inotropic agents and blood products respectively
6) Quantify the specimens sent for culture and sensitivity testing and obtain data on the antibiotic sensitivity patterns of the isolated microorganisms and
7) Classify the antimicrobial use according to use for bacteriologically proven infection (BPI), non-bacteriologically proven infection (non-BPI) and prophylaxis.

Methods

A retrospective analysis of the case records of all patients admitted to the ICU during the time period from 1st February 2002 to 31st May 2002 was carried out. The age and sex distribution of the patients were noted. The duration of hospitalization in the ICU and the residential address of the patients were recorded. For calculating the duration of hospitalization, the day of admission was included but the day of discharge was excluded. The diagnosis/diagnoses recorded in the discharge summary were noted.

The patient outcome following the period of hospitalization in the ICU was studied. Patients could have been transferred to the ward, could have been discharged, referred for further management or may have left against medical advice. Some patients may have been discharged at request or may have died during the period of hospitalization. The ICU mortality rate, ICU length of stay (LOS) greater than 7 days, average ICU LOS and average number of days on mechanical ventilation were previously identified as outcome measures to judge the quality of care in an ICU.[7]

The median duration of hospitalization was determined. The drugs prescribed during the period of hospitalization in the ICU were noted. Mean ± SD number of drugs was calculated. The number of patients who had received an antibiotic during the period of stay in the ICU was determined. Use of an antibiotic was classified as for: bacteriologically proven infection (BPI), non-bacteriologically proven infection (non-BPI) and prophylaxis. The specimens sent for culture and sensitivity testing was enumerated. The organisms isolated and their antibiotic sensitivity patterns were recorded.

Number of drugs prescribed by the parenteral route was calculated. Frequency of prescribing of drugs belonging to different groups was recorded. The drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system and drug utilization was measured in DDD/100 bed-days. In the ATC classification system, the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties.[5] The DDD/100 bed-days was calculated using the following formula

$$\text{DDD/100 bed-days} = \frac{\text{Drug consumption in the study period (mg)} \times 100}{\text{DDD (mg)} \times \text{period of study} \times \text{bed strength} \times \text{average occupancy}}$$

Our study was carried out for a time period of 120 days. There were 10 beds in the ICU and the average occupancy index was 0.8.

Percentage of patients who were prescribed an intravenous fluid, a neuromuscular blocker and inotropic agents respectively was calculated. Percentage of admitted patients who had undergone thrombolysis, nebulization and were given blood products was determined.

Results

A total of 259 individuals were admitted to the ICU during the study period. One hundred and sixty one were male; 177 were aged above 49 years. One hundred and forty three individuals were hospitalized for a time period less than 4 days, 89 for a time period between 4 to 7 days and 27 patients for a time period greater than 7 days.

Ninety-two individuals were from Pokhara city and 51 were from the district of Kaski in which the city is located. Thirty-one and 28 individuals were from the

neighbouring districts of Syangja and Tanahun respectively.

The patient's outcomes following the period of stay in the ICU are shown in Figure 1. Seventy-nine patients were shifted to the general wards while 6 were referred to higher centres. The most common illnesses, which warranted admission to the ICU, were chronic obstructive pulmonary disease (COPD), cerebrovascular accident, myocardial infarction, alcoholic liver disease, congestive cardiac failure, pneumonia and septicaemia. One hundred and forty eight patients admitted to the ICU were suffering from more than one illness. In our study, the ICU mortality rate was 15.4%, 10.4% of patients had a LOS greater than 7 days, median LOS was 4 days and average number of days on mechanical ventilation was 0.03.

A total of 134 specimens were sent for culture and sensitivity testing. The specimens were collected from 108 patients. Blood (42 specimens), sputum (38 specimens) and urine (28 specimens) were the most common specimens collected. *E.coli*, *H.influenzae*, *K. pneumoniae*, *S.aureus* and *P.aeruginosa* were the most common organisms isolated on culture and sensitivity testing. The commonest organisms isolated from blood, sputum and urine are shown in Table 1. The antimicrobial sensitivity patterns of the common microorganisms are shown in Table 2.

Table 1. Microorganisms isolated from blood, sputum and urine specimens in the ICU

Specimen	Organism	Frequency
Blood	No growth	32
	E.coli	3
	S.typhi	2
	S.paratyphi	1
	S.aureus	1
	Others	4
Urine	No growth	10
	E.coli	7
	S.aureus	2
	Enterococci	2
	Mixed growth	3
	Others	3
Sputum	Normal flora	17
	H.influenzae	8
	S.pneumoniae	3
	K.pneumoniae	2
	P.aeruginosa	2
	Candida	2
	Others	5

Table 2. Microbial sensitivity patterns of common microorganisms isolated from the ICU during the study period

Antibiotic	Organism isolated % sensitivity (No. of cultures sensitive/No. tested)				
	E.coli (n=11)	H.influenzae (n=8)	K. pneumoniae (n=6)	P.aeruginosa (n=4)	S.aureus (n=4)
Ampicillin	16.7 (1/6)	80 (4/5)	0 (0/2)	0 (0/1)	0 (0/3)
Amoxicllin	0 (0/5)	100 (6/6)	0 (0/3)	0 (0/1)	0 (0/2)
Amikacin	100 (3/3)	100 (1/1)	100 (1/1)	100 (2/2)	100 (3/3)
Ciprofloxacin	50 (4/8)	100 (7/7)	33.3 (1/3)	100 (1/1)	100 (3/3)
Norfloxacin	37.5 (3/8)	NA	0 (0/2)	100 (1/1)	100 (2/2)
Ceftriaxone	75 (3/4)	100 (3/3)	0 (0/3)	50 (1/2)	100 (2/2)
Cefotaxime	100 (5/5)	100 (6/6)	0 (0/2)	50 (1/2)	100 (2/2)
Coamoxiclav	16.7 (1/6)	100 (8/8)	0 (0/1)	NA	0 (0/1)
Cotrimoxazole	16.7 (1/6)	33.3 (1/3)	33.3 (1/3)	0 (0/1)	NA
Gentamicin	66.7 (6/9)	NA	100 (3/3)	66.7 (2/3)	NA
Piperacillin	100 (1/1)	NA	0 (0/1)	66.7 (2/3)	100 (2/2)

Table 3. DDD/100 bed-days of commonly used groups of drugs in the ICU during the study period

Drug class	DDD/100 bed-days
Antibiotics	118.2
Ampicillin	35.7
Metronidazole	22.8
Crystalline penicillin	12.8
Cloxacillin	12.8
Ceftriaxone	7.9
Others	26.2
Bronchodilators	54.7
Salbutamol*	22.5, 0.5, 0.5
Ipratropium¶	20.8, 0.5
Others	9.9
Antiulcer drugs	37.4
Ranitidine	28.8
Omeprazole	6.8
Others	1.8
Diuretics	24.5
Furosemide	21.8
Others	2.7
Low dose aspirin	22.8
Others	98.8
Total	356.4

* Salbutamol has three DDDs: one for inhalat ion aerosol, one for inhalation solution and one for systemic use
¶ Ipratropium has two DDDs: one for inhalation aerosol and the other for inhalation solution

A total of 1334 drugs were prescribed during the period of stay in the ICU. Mean ± SD number of drugs prescribed was 5.1 ± 2.7. Parenteral drugs accounted for 52.8% of the total drugs prescribed. Injections and nebulized preparations accounted for the majority of the parenteral drugs. Antibiotics were prescribed in 149 patients (57.5%). Antibiotics were used for BPI in 49 patients, non-BPI in 92 patients and for prophylaxis in 8 patients. Seventy-four patients were given an intravenous fluid during the period of ICU stay, 31 patients had underwent nebulization while 23 patients were prescribed dopamine/dobutamine. Blood products were used in 24 patients.

The total drug consumption in the ICU during the study period was 356.4 DDD/100 bed-days. The consumption of intravenous fluids was 25.8 litres/100

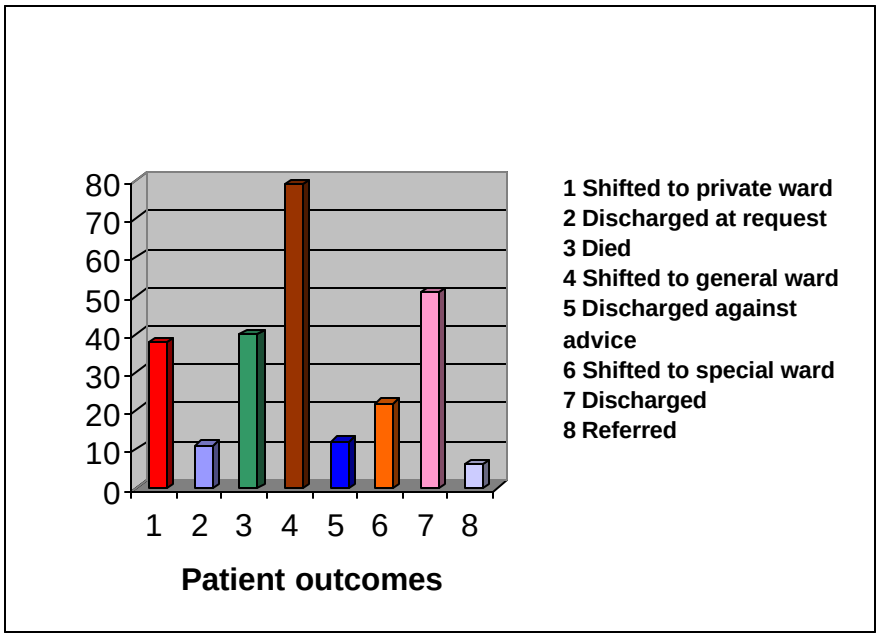
bed-days. The DDD/100 bed-days of the most commonly prescribed groups of drugs are shown in Table 3. Table 4 shows the ATC codes and DDD/100 bed-days of the ten most commonly used drugs in the ICU.

Table 4. ATC code and DDD/100 bed-days of the ten most commonly prescribed drugs in the ICU

Drug	ATC code	DDD/100 bed-days
Ampicillin	J01C A01	35.7
Ranitidine	A02B A02	28.8
Salbutamol*	R03C C02, R03A C02	22.5, 0.5, 0.5
Metronidazole	J01X D01	22.8
Low dose aspirin	B01A C06	22.8
Frusemide	C03C A01	21.8
Ipratropium	R03B B01	20.8, 0.5
Crystalline penicillin	J01C E01	12.8
Cloxacillin	J01C F02	12.8
Amlodipine	C08C A01	11.5

* Salbutamol has two ATC codes, one for inhalational use of the drug and the other for systemic use

Fig. 1 Patient outcomes following the period of hospitalization in the ICU



The mean ± SD cost of drugs was 1958.53 ± 1267.8 Nepalese rupees (25.1 ± 16.2 US$). The mean ± SD cost of hospitalization in the ICU was 4758.2 ± 1317.2 Nepalese rupees (64.3 ± 17.8 US$).

Discussion

The intensive care unit (ICU) is an identified, resource-intensive component of the health care services. Examining cost containment and clinical effectiveness in the ICU is highly appropriate.

A total of 259 individuals were admitted during the four-month study period. In a previous study, before the up gradation of the intensive treatment unit (ITU) to an ICU, a total of 297 patients were admitted during a one-year study period.[6] In the present study, 177 individuals were aged above 49 years. The age distribution is similar to that noted in the previous study.[6] One hundred and forty-three individuals were hospitalized for a time period less than 4 days and economic constraints were a major reason for seeking an early discharge from the ICU.

In a study from the United States, the mean LOS of the patients was 5.2 ± 9.8 days and the overall mortality rate was 33%.[8] In our study there was no significant decrease in the mean age of survivors compared to non survivors unlike in the American study.[8] Our mortality rate and mean LOS was less than that reported in the American study but since the illness pattern, treatment protocols and economic conditions may be different, comparison can be difficult.

Mean ± SD number of drugs prescribed in the ICU was 5.15 ± 2.67. In a study reported from a trauma ICU, mean ± SD number of drugs was 9.1 ± 6.5.[9] In another study [8] the number was 12.1 ± 7.6 while in a French medical ICU, mean ± SD number of drugs was 5 ± 4.[10] The average number of drugs in our study was less than or comparable to that reported in other studies. The average number of drugs should be kept as low as possible to minimize the risk of drug interactions, development of bacterial resistance and hospital costs.[11]

The utilization of antibiotics was 118.2 DDD/100 bed-days. The utilization of penicillins, fluoroquinolones, second-generation cephalosporins and third generation cephalosporins were 55.1, 5.34, 0.82 and 13.74 DDD/100 bed-days respectively. In a study reported from 35 German ICUs, the total antibiotic usage was 133.7 DDD/100 bed-days; the most commonly used antibiotic was penicillin with a beta-lactamase inhibitor followed by quinolones and second generation cephalosporins.[12] We have measured drug utilization only over a four-month period and seasonal variations in the morbidity profile and drug utilization were not taken into account. Antibiotic utilization varies between ICUs and with time in a given ICU. In a study of 38 Swedish ICUs there were up to fourfold differences between the ICUs in antibiotic consumption.[13] Antibiotics were used for BPI in 32.2% of individuals and for non-BPI in 60.5% of individuals who were prescribed antibiotics. In a previous study on antimicrobial use patterns, antibiotics were used for BPI and non-BPI in 18.1% and 51% of the patients.[6] Antibiotics were used for prophylaxis in 7.3% of patients prescribed antibiotics in the present study. The use for prophylaxis was less than the 13% and 10.3% reported in previous studies.[14,15]

Blood and sputum were the most common specimens sent for culture and sensitivity testing. Testing was done in 39.4% of patients compared to 24.8% reported in a previous study.[6] The organisms isolated were sensitive to the commonly used antibiotics but *E.coli*, *K.pneumoniae* and *P.aeruginosa* were found to be resistant to some of the common antibiotics. Resistance was also observed to the third generation cephalosporins. Methicillin resistant S.aureus (MRSA) was not isolated from the ICU during the study period. The small number of specimens analyzed makes it difficult to compare our findings with that reported in the literature.

Bacterial resistance to antibiotics has emerged as an important factor influencing patient mortality and morbidity. ICUs are frequently associated with the emergence and spread of bacterial resistance resulting from multiple factors, including severity of illness, need for prolonged hospitalization, frequent use of broad-spectrum antibiotics and lack of rigorous adherence to infection control practices.[16] External control over the use of antibiotics in the ICU and antibiotic cycling (scheduled rotation of workhorse antibiotics) have been suggested as strategies to reduce antibiotic resistance.[17] Management teams consisting of infectious disease specialists, intensive care specialists, pharmacologists/pharmacists and microbiologists may be helpful. Knowledge of antibiotics previously received by the patient and of local trends in antibiotic resistance will be useful. The prevention of bacterial resistance in the ICU setting should be discussed as part of the patient's daily management. Drug costs constituted 39% of the total costs incurred in the ICU. The results are comparable to an American study, where ICU drug costs accounted for 38.4% of the total costs.[18]

Our study had many limitations. We looked at drug use patterns over a four-month period only. The study was retrospective and data on the scales used to grade the severity of illness of admitted patients like APACHE where not available in the case record. So we were unable to correlate the drug prescribing patterns with the severity of patient illness.

The authors of a previous study in the ITU of our hospital had recommended that a senior consultant be appointed as in charge of the unit and an antibiotic use policy be framed for the ITU.[6] The ITU was upgraded to an ICU and a senior consultant from the Department of Internal Medicine has been appointed in charge of the ICU. The framing of an antibiotic use policy and guidelines for the use of different drugs is still at a preliminary stage. Formation of a team to oversee management of patients consisting of an intensive care specialist, an infectious disease specialist, a clinical pharmacologist/pharmacist and a microbiologist should be taken up as a matter of priority. Longitudinal surveillance of ICU drug use should be taken up to create a drug utilization database and to analyze and compare future trends in drug utilization.

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