ORIGINAL ARTICLE

Antibiotics in ICU : The Challenges of Use, Cost and Response in a Tertiary Care Hospital

Rawshan Ara Perveen[1], Morshed Nasir[2], Nadia Farha[3], Mohammad Ashraful Islam[4]

Abstract:

Antibiotic resistance can lead to increased morbidity, mortality, length of hospital stay, and health care expenditures. The study is designed to observe the challenges of antibiotic consumption, related costs and their resistance pattern in critically ill patients. The study was conducted in ICU from July to December 2016, in Holy Family Red Crescent Medical College Hospital. The demographic data, antibiotic sensitivity report, the administration of different classes of antibiotics as well as individual drugs and their costs were recorded. In 216 patients, meropenem was the most commonly prescribed antibiotic followed by levofloxacin and ceftriaxone. Meropenem with one or more class of antibiotics had the higher cost (1985/- and 2800/- BDT/ per day) per patient. Though the cephalosporins are the initial choice as the safest, cheaper antibiotics in developed countries, but high rate of resistance was observed in this ICU. The overall sterilization and strict control of nosocomial infections may play vital role in overcoming the challenges. Use of local antibiogram, narrow spectrum antibiotics, infectious disease specialist consultation, and restricted authorization to prescribe antibiotics can effectively shift the antibiotic sensitivity and minimize the cost in ICU stay.

Introduction:

Patients with severe and life-threatening illnesses and injuries admitted in Intensive care unit, which require constant, close monitoring and support from specialized equipment and medications. ICUs are also different from normal hospital wards by a higher staff-to-patient ratio that specialized in critical care medicine and access to advanced medical resources and equipment that is not routinely available elsewhere. Patients may be transferred directly to an intensive care unit from an emergency department if necessary or from a general ward if they rapidly deteriorate, or immediately after invasive surgery and the patient is at high risk of complications. Intensive care service is 2.5 times more costly than other hospital stays[1].

ICU patients are more prone to develop infection, because some of them are admitted due to infection and some of them are immunosuppressed because of critical illness and the large number of invasive devices used in them. Antibiotics are the most frequently prescribed drugs among hospitalized patients especially in intensive care and surgical

1. Assistant Professor, Department of Pharmacology, Holy Family Red Crescent Medical College, Dhaka.
2 Professor and Head, Department of Pharmacology, Holy Family Red Crescent Medical College Dhaka.
3 Assistant Professor, Department of Pharmacology, Holy Family Red Crescent Medical College, Dhaka.
4. Assistant Professor, Department of Otolaryngology, International Medical College, Dhaka.

criteria to be included in the study. Of the total, 115 were males and 101 were females. Patients were in ICU for days ranging from 2 to 15 days with an average of 5 days. Among this period sixty two patients died in ICU which was 30% of total admission (Table- I). Total and average number of antibiotics prescribed was shown in Table- II

Table-I : Demographic characteristics of patients

	All (n= 216)
Male/ Female	105/ 101
Length of stay (LOS) in ICU; Mean (Range)	5.3 (2- 15)
Medical specialty	
Medicine	89
Neuro-medicine	44
Surgery	12
Neurosurgery	15
Orthopedics	05
Gynae	18
Cardiology	12
Nephrology	18
ENT	02
Urology	01
Mortality in ICU %	62 (30%)

Table-II: number of antibiotics prescribed per patients

No. of antibiotic prescribed	Total no. of patients (n=216)	Percentage (%)
1	54	25%
2	115	53.24%
3	33	15.27%
4	10	4.62%
5	02	0.92%
6	01	0.46%
7	01	0.46%

In Table- III, 75% of patients who received two or more combination of antibiotics reflect that meropenem, levofloxacin & ceftriaxone play the lead role. While combination with meropenem, had the highest rate 1985/- BDT per day in two drug combination, 2800/- BDT per day in three or more antibiotic combinations.

Among 216 admitted patients in ICU, all were advised for antibiotic sensitivity test. But reports were found in eighty three cases. Micro-organisms were absent in sixty two cases. Six different types of organism were found in twenty one cases.

Antibiotic resistance pattern shows in next table. Majority of isolates were resistant to cephalosporin, penicillin, floroquinolones, streptomicine and tetracycline. Organisms were showing sensitivity towards imipenem & meropenem. (Table- IV)

Table- III: Antibiotic sensitivity as per reports

Antibiotics	Resistant	Sensitive
Cefuroxime	16	05
Ceftriaxone	13	04
Ceftazidime	13	03
Cephalexin	11	05
Amoxiclav	11	02
Cloxacillin	11	-
Ciprofloxacin	11	07
Gentamicin	11	08
Azithromycin	10	03
Tetracycline	10	08
Cotrimoxazole	10	08
Amikacin	09	09
Meropenem	06	11
Imipenem	05	11
Piper-tazobac	04	06
Nitrofurantoin	03	04
Cefipime	01	01
Aztreonam	01	-
Macillinum	-	02
Vancomycine	-	01
Linezolid	-	02
Tegacycline	-	02

Table- IV: Combination of antibiotics with their cost per day

Combinations of antibiotics	No. of pt	Cost per day	Combinations of antibiotics	No. of pt	Cost per day
Meropenem + Moxifloxacin	19	1280/-	Meropenem + Levofloxacin+ Ceftriaxone	04	1940/-
Ceftriaxone + Metronidazole	13	760/-	Levofloxacine +Piper-Tazobac+ Azithromycine	03	1303/-
Meropenem + Levofloxacin	12	1340/-	Ceftriaxone+ Flucloxacilin+ Co-amoxiclav	02	1425/-
Levofloxacin + Ceftriaxone	11	700/-	Meropenam+ levofloxacine +Ceftazidime	02	2085/-
Levofloxacin+ Piper- tazobac	09	1103/-	Ceftriaxone + Gentamicin + Metronidazole	01	790/-
Levofloxacin +Ceftazidime	06	845/-	Levofloxacin +Ceftriaxone + Clarithromycin	01	780/-
Ceftazidime + Moxifloxacin	05	785/-	Levofloxacin +Ceftriaxone + Vancomycin	01	1250/-
Levofloxacin +Cefipime +	03	1204/-	Levofloxacin +Ceftriaxone + Azithromycin	01	900/-
Meropenem + Metronidazole	03	1400/-	Meropenem +Ceftriaxone + Moxifloxacin	01	1880/-
Meropenem + Clarithromycin	03	1280/-	Ceftriaxone+ Flucloxacilin+ Piper- tazobac	01	1828/-
Piper- tazobac + Moxifloxacin	02	1043/-	Meropenem + Levofloxacin+ Metronidazole	01	1510/-
Piper- tazobac + Lanezolid	02	1463/-	Meropenem + Cefipime+ Metronidazole	01	2504/-
Piper- tazobac + Azithromycin	02	1203/-	Meropenem + Moxifloxacin+ Lanezolid	01	1740/-
Ceftazidime + Metronidazol	02	915/-	Meropenem + Levofloxacin+ Clarithromycin	01	1380/-
Meropenam +Ceftriaxone	02	1840/-	Meropenem+ Flucloxacillin + Metronidazole	01	1625/-
Ceftriaxone+ Flucloxacilline	02	825/-	Meropenem + Moxifloxacin+ Clindamycin	01	1440/-
Co-amoxiclav + Clarithromycin	02	680/-	Ciprofloxacin+ Co-amoxiclav + Metronidazole + Amikacin	01	316/-
Co-amoxiclav + Moxifloxacin	02	640/-	Tegacycline+ Clindamycine	01	1810/-
Piper- tazobac + Ciprofloxacin	01	1353/-	Meropenem + Moxifloxacin+ Metronidazole+ Piper- Tazobac	01	2740/-
Imipenam + Amikacin	01	1396/-	Meropenem + Levofloxacin+ Clindaycine+ Piper- Tazobac	01	2800/-
Piper- tazobac + Clindamycin	01	1163/-	Levofloxacine +Ceftazidime+ Ciprofloxacine+Azithromycin+ Piper-tazobac+	01	2695/-
Ciprofloxacine+ Metronidazole	01	510/-	Meropenem + Levofloxacin+ Clarithromycin+ Piper- Tazobac+ Amikacin	01	2776/-
Meropenam + linezolid	01	1700/-			
Cefipime + Azithromycine	01	1304/-			
Meropenem + Vancomycin	01	1790/-			
Ceftazidime + Vancomycin	01	1295/-			
Ceftazidime + Amikacin	01	841/-			
Meropenam +Ceftazidime	01	1985/-			
Ceftriaxone + Moxifloxacin	01	640/-			
Ceftriaxone+ Piper-tazobac	01	1603/-			

Discussion:

Antibiotics are the most frequently prescribed drugs among hospitalized patients especially in intensive care and surgical department. Appropriate and less number of antibiotic prescriptions in intensive care unit is an important element in quality of care, infection control and cost reduction as well as length of hospital stay[2]. Average Length of stay (LOS) in ICU was found to be 5.2 days in our study. In other studies done in ICUs of North India, South India, Nepal, and USA, average LOS in ICU was 5.75, 6.22, 4.0, and 5.2 days, respectively[9,10,11] . The difference found in the mean LOS could be due to the difference in illness pattern among the population. The ICU mortality rate was found to be 30%, results are similar to several study done in India, reported ICU mortality rate as high as around 35%[9,10,12].

In this study, only 25% of patients treated with single antibiotic and remaining 75% patients received one or more antibiotics during their ICU admission period. Drug use pattern study from an ICU in Northern India and Bengaluru, 70% and 69% patients received more than one antibiotics[9,12] and 60% of the patients studied in a Caribbean ICU received two antimicrobials. Majority of the patients in a Danish university hospital ICU were on one antibiotic[13]. In another study, 36.7% of cases were treated with only one antibiotic agent, 14.1% were given a combination of 2, and 7.2% were given a combination of more than 3 antibiotic agents in a German surgical ICU[14]. Whereas it is recommended that for minimizing the risk of drug interactions, number of drugs per prescription should be kept low. It will also reduce hospital cost and development of bacterial resistance[15].

Three highly utilized antibiotics in this study were meropenem, levofloxacin and ceftriaxone, On reviewing similar studies from India, it was observed that five most utilized antibiotics are 3rd generation cephalosporins, meropenem, metronidazole, levofloxacin and ceftriaxone[12]. Cephalosporins, fluoroquinolones, combinations of penicillins including –β lactamase inhibitors and carbapenems were the most frequently prescribed antibiotics in another study[16].

Increasing cost of medicines is causing a huge economic burden on patients who bear the cost of treatment in Bangladesh. In view of this, the daily cost of antibiotics combination per patient used in our ICU setup was calculated. The most prescribed drug meropenem (1240/-BDT per day) with two or more combined drugs had the highest cost (1980/- & 2800/- BDT per day). A study from Turkey reported the similar result[17]. In 2007, Vandijck et al calculated that mean daily antimicrobial cost was 114.25€ equivalent to 11,618/- BDT. The daily antimicrobial costs per infected patient with multidrug-resistant strain (165.09€ equivalent to 16,788/- BDT) was 50% higher compared with those without (82.67€ equivalent to 8,406/- BDT; P<0.001)[18]. In another study held in Turkey, Buzkart et al calculated that the cost of total antibacterial consumption in ICU was 40.72€ equivalent to 4,140/- BDT per day in 2011 and 29.01€/ 2,950/- BDT per day in2012[12]. Compare with several study around the world, we observed that cost of antibiotic in Bangladesh was less from abroad. One of the cause is Bangladesh was categorized as Least-Developed country along with other 47 countries around the world will not be obliged, with respect to pharmaceutical products, to implement or apply the TRIPS (Trade-Related Aspects of Intellectual Property Rights) Agreement until 1 January 2016 but can manufacture drugs.

According to cultural sensitivity report, there were six type or organism were found. Most common organism isolated was *Staphylococcus Aureus*, *Acenetobactor* and *Pseudomonus.* Most senseitive drugs against micro-organism were Carbapenem and amikacin. From 2010 to 2014, several study around Dhaka city and worldwide reported that, carbapenem resistant rate started to increase[19,20,21]. Emergence of carbapenem resistance strains around the world is alarming and a threat for the treatment of the admitted patients in the ICUs. Most of the isolates were resistant against penicillin and cephalosporin group. Few study reported the similar findings[19,22,23] . This might be due to selective preference of extensive usage of these groups of drugs.

Several programs followed in ICU like infectious disease specialist intervention, establishment of local ambiogram, practice of descalation, switching to narrow spectrum antibiotic after day 3 whenever possible, restricted authorization to prescribe antibiotics could improve the quality of care, infection control and cost containment.

Conclusion:

Antibiotics are commonly prescribed in critically ill patients and form a significant proportion of the total drugs consumed in the ICU. Multi drug resistant organism did the situation more difficult both for patients and physicians. It may be concluded that the high utilization rates and costs of antibiotics prescribed in the ICU are a matter of concern and need to be improved by the use of local antibiogram guidelines, continuous surveillance and antibiotic restriction policies.

References:

1. Barrett ML, Smith MW, Elizhauser A, Honigman LS, Pines JM (December 2014). "Utilization of Intensive Care Services, 2011". HCUP Statistical Brief #185. Rockville, MD: Agency for Healthcare Research and Quality.
2. Krivoy N, El-Ahal WA, Bar-Lavie Y, Haddad S. Antibiotic prescription and cost patterns in a general intensive care unit. Pharm Pract (Granada) 2007; 5: 67– 73.
3. Røder BL, Nielsen SL, Magnussen P, Engquist A, Frimodt-Møller N. Antibiotic usage in an intensive care unit in a Danish University Hospital. J Antimicrob Chemother. 1993; 32: 633– 42.
4. Vincent JL., Basseti M., Francois B., Karam G., Chastre J., Torres A., Roberts JA., Taccone JA., Taccone FS., Rello J., Calandra T., Backer DD., Welte T and Antoneli M. (2016). Advances in antibiotic therapy in the critically ill. Crit Care 20, 133.
5. Akalin S, Caylak S, Ozen G, Turgut H. Antimicrobial consumption at a university hospital in Turkey. AJMR. 2012; 6(18): 4000-5.
6. Pınar N. Drug expenditures in our country. Journal of Inönü University Medical Faculty 2012; 19(1): 59- 65.
7. Peto Z, Benko R, Matuz M, Csullog E, Molnar A, Hajdu E. Results of a local antibiotic management program on antibiotic use in a tertiary intensive care unit in Hungary. Infection 2008; 36(6): 560-4.
8. Thursky KA, Buising KL, Bak N, Macgregor L, Street AC, Macintyre CR. Reduction of broad-spectrum antibiotic use with computerized decision support in an intensive care unit. Int J Qual Health Care 2006; 18: 224-31.
9. John LJ, Devi P, John J, Guido S. Drug utilization study of antimicrobial agents in medical intensive care unit of a tertuart care hospital. Asian J Pharm Clin Res. 2011; 4: 81–4.
10. Amit GS. Drug use evaluation study in a tertiary care corporate hospital with special reference to use of antibiotics in ICU department. Int J Adv Pharm Biol Chem. 2013; 2: 179–89.
11. Biswal S, Mishra P, Malhotra S, Puri GD, Pandhi P. Drug utilization pattern in the intensive care unit of a tertiary care hospital. J Clin Pharmacol. 2006; 46: 945–51.
12. Williams A, Mathai AS, Phillips AS. Antibiotic prescription patterns at admission into a tertiary level intensive care unit in Northern India. J Pharm Bioallied Sci. 2011; 3: 531–6.
13. Hartmann B, Junger A, Brammen D, Klasen J, Quinzio L. Review of antibiotic drug use in a surgical ICU: management with a patient data management system for additional outcome analysis in patients staying more than 24 hours. Clin Ther 2004; 26:915-24.
14. Meyer E, Jonas D, Schwab F, Rueden H, Gastmeier P, Daschner FD. Design of a surveillance system of antibiotic use and bacterial resistance in German intensive care units. Infection 2003; 31(4):2 08-15.

15. Stratton CW, 4th, Ratner H, Johnston PE, Schaffner W. Focused microbiologic surveillance by specific hospital unit: Practical application and clinical utility. Clin Ther. 1993; 15(Suppl A): 12–20.
16. Bozkurt F, Kaya S, Tekin R, Gulsun S, Deveci O, Dayan S, Hosoglu S Analysis of antimicrobial consumption and cost in a teaching hospital. JIPH. 2014; 7: 161—169.
17. Usluer G, Ozgunes I, Leblebicioglu H Turkish Antibiotic Utilization Study Group. A multicenter point-prevalence study: Antimicrobial prescription frequencies in hospitalized patients in Turkey. Ann Clin Microbiol Antimicrob. 2005; 4: 16.
18. Vandijck DM, Depaemelaere M, Labeau SO, Depuydt PO, Annemans L, Buyle FM, Oeyen S, Colpaert KE, Peleman RP, Blot SI, Decruyenaere JM. Daily cost of antimicrobial therapy in patients with Intensive Care Unit-acquired, laboratory-confirmed bloodstream infection. Int J Antimicrob Agents. 2008; 31(2): 161-5.
19. Akter T, Murshed M, Bugum T, Nahar K, Duza SS and Shahnaz S. Antibiotic resistance pattern of bacterial isolates from intensive care unit of a tertiary care hospital in Bangladesh. Bangladesh J Med Microbial 2014; 08 (01): 07- 11.
20. Barail L, Fatema K, Haq JA, Faruq MO, Ahsan ASMA, Morsehed MAHG et al. Bacterial profile and their antimicrobial resistance pattern in an intensive care unit of a tertiary care hospitalin Dhaka. Ibrahim Med Coll. J 2010; 4: 66- 69
21. Jain S, Khety Z. Changing antimicrobial resistance pattern of isolates from an ICU over a 2 year period. JAPI 2012; 60: 27-33.
22. Jamshidi M, Javadpour S, Eftekhari TE, Moradi N and Jomehpour F. Antimicrobial resistance pattern among intensive care unit patients. African J Micro Res. 2009; 3(10): 590- 94.
23. Gagneza D, Goel N, Aggarwal R and Chaudhary U. Changing trend of antimicrobial resistance among gram negative bacilli isolated from lower respiratory tract of ICU patients: a 5 year study. Indian J Crit Care Medicine 2011; 15 (3): 164- 67.

departments[2]. Total Antibiotic consumption in ICU is approximately ten times higher than the general hospital wards[3]. Rational use of antibiotic is important but actual situation is complicated because identification of microorganisms is delayed, critical illness itself give an impact, mechanism of antibiotics, and increase the number of antibiotic-resistant strains[3].

Indiscriminate and excessive use of antimicrobial agents promotes the emergence of antibiotic-resistant organisms. Antimicrobial resistance increases already risen health care costs and also increases patient morbidity and mortality[2]. Antibiotics are the drugs compared with the other drugs, have highest costs worldwide and account for20- 30% of total drug expenditures[5,6]. It causes a huge economic burden on patients who bear the cost of treatment in Bangladesh.
It is recommended that the number of drugs per prescription should be kept as low as possible to minimize the risk of drug interactions, development of bacterial resistance, and hospital costs[6].

The use of a computerized decision support tool and increased the number of switches to narrow spectrum antibiotics[7], implementation of local antibiogram, infectious disease specialist consultation, and restricted authorization to prescribe antibiotics have all been reported to result in marked reductions in antibiotic consumption[8]. Here in this study, antibiotic use and their cost pattern in a general ICU ward over a 6 month period were observed. Special emphasis was given to the number of antibiotic consumption per patients, related costs and the combinations of antibiotic use in teaching hospital.

Materials and method:

Holy Family Red Crescent Medical Hospital is a 400- bed hospital with 9 bed ICU facility. It serves as a referral hospital in the center of Dhaka city. Critically ill patients from multidiscipline and trauma patients requiring haemodylaisis monitoring and/or mechanical ventilation were admitted to ICU. The ICU was managed by a bunch of stuff from anesthesiology, internal medicine, surgery, neurology, neurosurgery department, with daily assistance from the departments of medical microbiology and radiology.

From May 2016 to December 2016 all adult patients (age above 14 years), with or without mechanical ventilator, who had been admitted in ICU received at least one antibiotic were studied prospectively. Patients admitted but not prescribed with any antibiotics were excluded from the study.

Data were collected from patient's records. The following parameters were recorded:

- Patient demographic profile
- Mean length of stay (LOS) in ICU
- Distribution of pattern of illness based on diagnosis
- Associated comorbidities (other illness)
- Prescription frequency of individual antibiotics:
- Number of beds in ICU = 09
- The cost of antibiotics utilized in ICU.
- Antibiotics sensitivity report

All collected data were analyzed by investigators.

Result:

A total of 216 patients were admitted in the ICU during the 6 month study period, who met the