

Rational use of antibiotics in an intensive care unit: a retrospective study of the impact on clinical outcomes and mortality rate

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Background: Intensive care units (ICUs) are specialized units where patients with critical conditions are admitted for getting specialized and individualized medical treatment. High mortality rates have been observed in ICUs, but the exact reason and factors affecting the mortality rates have not yet been studied in the local population in Pakistan.

Aim: This study was aimed to determine rational use of antibiotic therapy in ICU patients and its impact on clinical outcomes and mortality rate.

Methods: This was a retrospective, longitudinal (cohort) study including 100 patients in the ICU of the largest tertiary care hospital of the capital city of Pakistan.

Results: It was observed that empiric antibiotic therapy was initiated in 68% of patients, while culture sensitivity test was conducted for only 19% of patients. Thirty-percent of patients developed nosocomial infections and empiric antibiotic therapy was not initiated for those patients ($P<0.05$). Irrational antibiotic prescribing was observed in 86% of patients, and among them, 96.5% mortality was observed ($P<0.05$). The overall mortality rate was 83%; even higher mortality rates were observed in patients on a ventilator, patients with serious drug–drug interactions, and patients prescribed with irrational antibiotics or nephrotoxic drugs. Adverse clinical outcomes leading to death were observed to be significantly associated ($P<0.05$) with irrational antibiotic prescribing, nonadjustment of doses of nephrotoxic drugs, use of steroids, and major drug–drug interactions.

Conclusion: It was concluded that empiric antibiotic therapy is beneficial in patients and leads to a reduction in the mortality rate. Factors including irrational antibiotic selection, prescribing contraindicated drug combinations, and use of nephrotoxic drugs were associated with high mortality rate and poor clinical outcomes.

Keywords: clinical outcomes, mortality rate, intensive care unit, rational use of antibiotics, nosocomial infections, medication review

Introduction

Intensive care units (ICUs), also known as intensive therapy units or critical care units, are special hospital wards that provide treatment and monitoring for critically ill patients. Since patients with critical infectious diseases are also managed in ICUs, they can become a major source of spreading infectious organisms which may lead to nosocomial infections. Such nosocomial infections are associated with increased morbidity, mortality, and health care costs.¹ Nosocomial infections are a serious patient safety concern in modern health care system, since it is the fifth leading cause of death among hospitalized patients. ICU patients are five to ten times more likely to acquire nosocomial infections than those in general ward.² Nosocomial infections occur worldwide and affect both developing and developed countries.³

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Empiric antibiotic administration is required in majority of ICU patients, but extensive use of both broad- and narrow-spectrum antibiotics may lead to development of resistant strains of bacteria and other pathogens.⁴ The extensive and irrational use of antibiotics has also been reported to increase the risk of toxicity and drug interactions.⁵

This study was aimed to determine the rational use of antibiotic therapy in ICU patients, its impact on clinical outcomes, and mortality rate. The study was also focused to identify factors affecting mortality rate in ICU patients undergoing antibiotic therapy.

Patients and methods

Ethical approval

Ethical approval was taken from the Ethics Review Board of Pakistan Institute of Medical Sciences, Hospital. Since this was a retrospective study in which all patients were either discharged after recovery or died during treatment, taking individual patient consent was not possible. Therefore, the Ethics Review Board waived the requirement of patient consent form. Patient data confidentiality and its compliance with the Declaration of Helsinki were ensured by the Ethics Review Board.

Study settings and design

This was a retrospective longitudinal (cohort) study including patients admitted in either medical or surgical ICU of the largest tertiary care hospital of the capital city of Pakistan.

Study sample

The study sample included all patients fulfilling the inclusion criteria and who were admitted and subsequently discharged/died between September 2016 and April 2017 in the ICU of the largest tertiary care hospital of capital of Pakistan. Patients aged 2–60 years with <30 days of ICU stay were included in the study, since the accurate renal function cannot be determined using Cockcroft–Gault (equation) method for patients <2 and >60 years of age.

Clinical evaluation

Daily clinical evaluation was performed for each patient using standard methods and approved guidelines. The difference in values of all studied variables was determined before and after the start of any therapy. The clinical outcomes were determined on the last day in terms of “discharge” or “death” after treatment. Renal function was determined using Cockcroft–Gault equation,⁶ and the need for dose adjustment and required dose after adjustment was determined using guidelines from

the Physician Desk Reference,⁷ British National Formulary,⁸ and Renal Pharmacotherapy.⁹ The adverse events for every administered drug were enlisted from clinical drug literatures approved by the US Food and Drug Administration, the Medicine and Healthcare Products Regulatory Agency, UK and the European Medicine Agency. Drug–drug interactions were determined by Stockley’s drug interaction.¹⁰ The control of infection was determined using reduction in white blood cell (WBC) count and fever, and the appropriateness of the antibiotic therapy was determined using the results of culture sensitivity test (CST) and the American Society of Infectious Diseases (IDSA) guidelines.

Study tool (evidence-based clinical checklist)

An evidence-based clinical checklist was adapted from an already developed clinical checklist.¹¹ The variables included in the checklist were also compared with previous reported studies and discussed among a focus group of clinical researchers and practitioners. The finally developed checklist was also subjected to content validity through a pilot study on 20 patients and to focus group discussion to identify any missed variable or clinical scenario. After validation, the final version of the checklist was used during the study.

Statistical analysis

All the data collected through clinical checklist were transcribed on a spreadsheet in SPSS after carefully defining all the variables under study. The analysis was performed in two steps including a descriptive analysis in which patient clinical situation and various variables were studied for their respective frequencies, percentages, and measure of central tendencies. Later, in the second step, inferential statistics was employed to determine the associations among patient- and therapy-related variables, clinical outcomes, and mortality rate using Pearson’s chi-squared test, and *P*-value <0.05 was considered statistically significant.

Results

This study involved 100 patients which fulfilled the inclusion criteria and were discharged from the ICU between September 2016 and April 2017, including both males (43%) and females (57%). Twenty patients were between 2 and 20 years age, while 44 patients were between 21 and 40 years old and 36 patients were in the age group of 41–60 years. The length of the ICU stay for all the patients under investigation was from 2 to 30 days.

In our study, 68% patients were being administered empiric therapy with broad-spectrum antibiotics; among them, samples for CST were drawn in only 7% of the patients ($P=0.001$). Antibiotic therapy was changed in 13% patients ($P=0.000$) after the CST reports were received. The concept of de-escalation therapy¹² was not followed in this hospital, and none of the initiated antibiotics were de-escalated or stopped; instead, new antibiotics were added after the CST results. The results are presented in Table 1 and Figure 1.

During our investigation period, 30% of the patients developed infections 3 days after their admission in hospital ICU, and therefore, it was declared that they had nosocomial infection.¹³ The pattern of nosocomial infection was statistically insignificant among the gender and age groups. It was observed that nosocomial infection developed in every

patient who was not administered empiric antibiotic therapy ($P=0.0002$), as shown in Table 2. In our study, 29 patients were on ventilator, and among them, 10 (34.5%) patients developed nosocomial infections with very high mortality rate (89.7%). Other than the common broad-spectrum antibiotics, some narrow-spectrum antibiotics were also prescribed (Table 3).

Since the study was carried out in ICU where patients are brought due to multiple reasons, one of the important factors while selecting a drug therapy to be prescribed is the route of metabolism and excretion of the drug and the renal/hepatic profile of the patients.¹⁴ Since a majority of the drugs are excreted through kidneys, assessing the kidney function is a key factor in ensuring administration of safe and effective therapy.¹⁵

In our study, it was determined that 41% of the patients were renally compromised, and they needed careful administration of renally excreted drugs.¹⁶ The use of nonsteroidal anti-inflammatory drugs was not seen in any of the patient, and instead, steroidal analgesics were used. Use of vancomycin, aminoglycoside, steroids, and proton pump inhibitors (PPIs) was observed, which need to be avoided or administered carefully among renally compromised patients.

Table 1 Frequency of various scenarios while prescribing empiric antibiotics

Clinical scenario	Frequency (n)
Empiric therapy initiated	68
CST performed	19
Therapy changed after CST	13

Abbreviation: CST, culture sensitivity test.

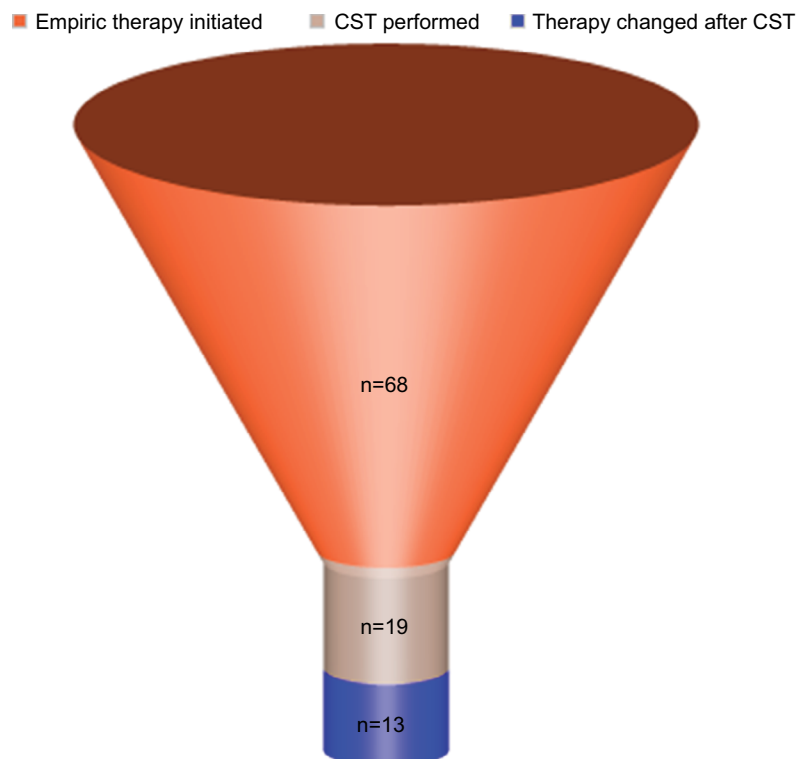


Figure 1 Funnel graph showing the frequency (n) of changes in antibiotic therapy after initiation of empiric therapy.

Abbreviation: CST, culture sensitivity test.

Table 2 Cross-tabulation of development of NIs against initiation of empiric antibiotic therapy

NIs	Empiric therapy		P-value (Pearson's chi-square)
	Yes, n (%)	No, n (%)	
Yes, n (%)	0 (0)	30 (100)	(0.0002)
No, n (%)	19 (27.1)	51 (72.9)	

Abbreviation: NI, nosocomial infection.

Table 3 Frequency of prescription of narrow-spectrum antibiotics

Drug	Frequency, n
Vancomycin	27
Colistin	1
Linezolid	10
Tigecycline	3

The use of PPI was high ($P=0.008$) in renally compromised patients as compared to those with normal renal function. The results of the frequency of nephrotoxic drugs prescribed are provided in Table 4.

Out of 41 renally compromised patients, 38 were being prescribed with nephrotoxic drugs for which dose adjustments were required. No renal dose adjustments were made in any of the patients and among the 41 renally compromised patients, 85.4% died at the end of the study.

In our study, only 14% patients were prescribed antibiotics as per the recommendations of IDSA and all these patients were discharged after recovery. Also, among the 86% patients in whom IDSA recommendations were not followed, statistically significant ($P=0.000$) mortality rate (96.5%) was observed. The results are presented in Table 5.

Among patients having recurrent infection even after antibiotic administration, 85% of them were initially prescribed with in appropriate antibiotics. Appropriate antibiotic therapy was not administered in majority (26 [89.7%]) of the ventilator patients. One hundred percent mortality rate was observed among all such patients on ventilator for whom appropriate antibiotic therapy had not been administered.

The signs of infection including raised WBC count and/or fever¹⁷ were observed in 60% of patients already on antibiotic therapy, with a mean WBC count of 41.6 in the infected patient group. The fever was well controlled in most of the patients, with only 15 patients having a temperature $>100^{\circ}\text{F}$ and only 2 patients having above 102°F , with a mean value of 98.54°F .

Table 4 Frequency of prescribing potentially nephrotoxic drugs among renally compromised patients

Drug	Renally compromised patients, n		P-value
	Yes	No	
Vancomycin	14	12	0.377
Penicillin	14	29	0.010
Fluoroquinolones	10	15	0.435
Cephalosporin	29	29	0.373
Aminoglycosides	16	18	0.944
Steroids	20	30	0.155
Antiepileptics	4	12	0.056
PPIs	38	33	0.008
Antivirals	0	2	0.192
Analgesics (steroidal)	22	17	0.099

Note: Bold P-values are statistically significant: $P<0.05$.

Abbreviation: PPI, proton pump inhibitor.

The associations of various factors affecting the end outcome in ICU patients were determined using chi-squared test. These associations are provided in Table 6.

It was found that patients treated with appropriate antibiotics were discharged from the hospital. CST was performed in 19 patients; but due to various other factors including renally compromised state of the patients, 17 (89.5%) died at the end of treatment. Renal dose adjustment is necessary in renally compromised patients, but it was not performed in 77 (89.5%) patients and all of them died at the end. Steroids should be used with caution in renally compromised patients,¹⁸ and in our study, 52 (91.2%) patients who were on steroid therapy died.

It was observed that major drug–drug interactions including fatal particulate precipitation occurred in the lungs due to co-administration of ceftriaxone along with calcium-containing intravenous solutions.¹⁹ Since drug therapy was not reviewed by any specialized clinical pharmacist, drug–drug interactions could not be reported, thus leading to high mortality rate.

An overall 83% mortality rate was observed in this study, while the mortality rate among various specified clinical conditions is provided in Table 7 and Figure 2.

It was observed that the mortality rate was affected by inappropriate use of antibiotics, failure to perform renal dose adjustments, presence of major drug–drug interactions, and use of nephrotoxic drugs without any control or dose adjustments.

Discussion

In the current study, empiric therapy with broad-spectrum antibiotics was administered in 68% of the patients. Since all

Table 5 Association of various clinical variables with appropriateness of antibiotic therapy

Variables studied	Appropriateness of antibiotic therapy		P-value
	Yes, n (%)	No, n (%)	
Infection even after antibiotic administration	9 (15)	51 (85)	0.031
Ventilator	3 (10.3)	26 (89.7)	0.501
Major drug–drug interaction	0 (0)	19 (100)	0.011
End outcome in which the patient died	0 (0)	83 (100)	0.000

Note: Bold P-values are statistically significant: $P < 0.05$.

Table 6 Clinical variables and their associations with end outcomes in ICU patients

Variables studied	End outcomes in ICU patients		P-value
	Discharge, n (%)	Death, n (%)	
Appropriate antibiotic therapy	14 (100)	0 (0)	0.000
CST performed	2 (10.5)	17 (89.5)	0.404
Renal dose adjustments required	9 (10.5)	77 (89.5)	0.000
Major drug–drug interactions	0 (0)	19 (100)	0.000
Use of steroids	5 (8.8)	52 (91.2)	0.012
Patients on ventilator	3 (10.3)	26 (89.7)	0.258
Infection even after use of antibiotic	10 (16.7)	50 (83.3)	0.084
Nosocomial infection	4 (13.3)	26 (86.7)	0.523
Renally compromised patient	6 (14.6)	35 (85.4)	0.973

Note: Bold P-values are statistically significant: $P < 0.05$.

Abbreviations: CST, culture sensitivity test; ICU, intensive care unit.

Table 7 Mortality rate in various clinical scenarios

Condition	Mortality rate (%)
Renally compromised patients	85.4
Nosocomial infection patients	86.7
Current infection (not well-controlled infection)	83.3
Patients on ventilator	89.7
Patients taking nephrotoxic drugs	89.5
Serious drug–drug interactions	100
Empiric therapy not initiated	81.5
No CST performed	81.5
Inappropriate antibiotic therapy	96.5

Abbreviation: CST, culture sensitivity test.

ICU patients are at high risk for developing infections due to intense pathological/surgical conditions, all measures are usually taken to prevent the spread of infection.²⁰ The hospital under study caters for the medical needs of ~6–7.5 million population,²¹ and due to high patient influx, the hygienic conditions were poor and proper sterilization and disinfection could not be attained at all levels.^{22,23} Certain previous studies have also reported the use of empiric antibiotic therapy in the ICU when the hygienic conditions are poor.^{24–26} Before initiation of empiric antibiotic therapy, samples for CST were drawn in very few, that is, only 7%, patients. CST

samples can give false results if empiric antibiotic therapy has been initiated. After the results of CST were obtained, antibiotic therapy was modified in only 13% of patients, that too, without following the principles of de-escalation, which are very important to consider while treating patients with acute infections.¹² The frequency of nosocomial infections in our study was found to be 30%, with the highest number of infections (ie, 34.5%) associated with ventilator since they are most difficult to manage.^{27,28} The frequency of ventilator-acquired nosocomial infection in our study was quite similar with previously reported data in Pakistan.²⁹ The practice of initiating empiric antimicrobial therapy among ICU patients was found to be associated with reduction in incidence of nosocomial infections, since none of the patients undergoing empiric therapy developed nosocomial infection. This practice was in accordance with previously reported benefits from initiation of empiric therapy in reducing nosocomial infection.²⁴ Since there was no antibiotic control or stewardship program in this hospital and none of the prescribed therapy was reviewed by infectious disease specialist or clinical pharmacist specialized in infectious diseases, appropriate therapy was prescribed in only 14% of patients, which is very low as compared to already reported data,³⁰ while the drug therapy in the remaining 86% of patients had errors such as

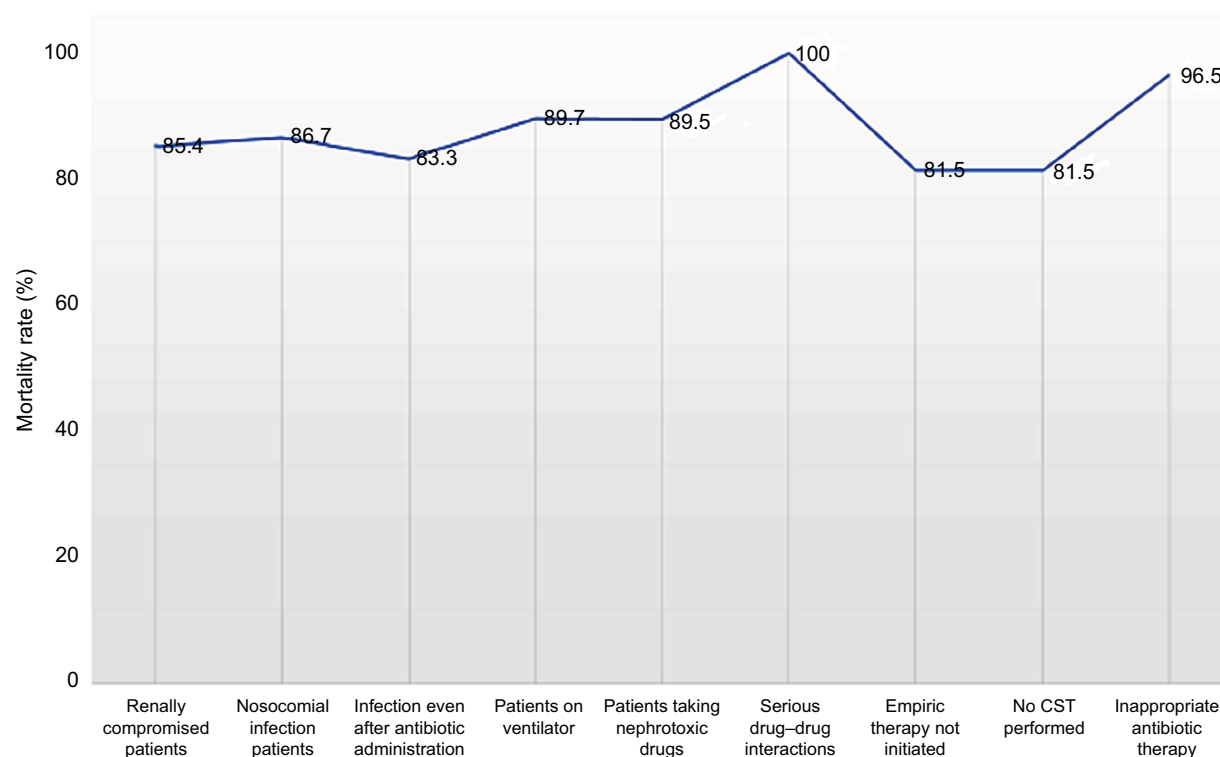


Figure 2 Mortality rate (%) in various clinical scenarios.

Abbreviation: CST, culture sensitivity test.

inappropriate drug or dose selection, serious interactions, and unwanted adverse reactions.

In this study, overall, 83% mortality rate was observed, which is very high as compared to previously reported literature.³¹ Mortality rate among patients with nosocomial infection was found to be 89.7%, which is quite high as compared to previous literature data.^{32,33} Very high mortality rate (85.4%) was observed in renally compromised patients prescribed with potentially nephrotoxic drugs as compared to previously reported studies.^{34,35} Among patients for whom appropriate antibiotics were not prescribed in adequate doses, a mortality rate of 96.5% was observed, which is very high as compared to previous study reports.³⁶ This high mortality rate, especially with inappropriate use of antibiotics, is a point of concern and should be addressed with appropriate measures by the concerned authorities.

High mortality rates, poor clinical outcomes, and poor hygienic conditions were observed among ICU patients of the largest tertiary care hospital of the capital city of Pakistan, which indicates lack of interest and commitment of higher officials and policymakers. Regardless of such high mortality rates, no measures for infection control have been taken and no protocols for antibiotic prescribing have been developed. The spread of infections and resistant strains is also putting health care providers at risk.

Conclusion

Empiric antibiotic therapy is beneficial in patients and leads to reduction in mortality rate. Irrational antibiotic prescribing along with co-administration of contraindicated drugs and use of nephrotoxic drugs without dose adjustments were found to be associated with high mortality rate and poor clinical outcomes. Medication review under the supervision of clinical pharmacist specialized in intensive care can help reduce various factors affecting mortality rate. Antibiotic control programs including stewardship and prescribing under the supervision of infectious disease specialist can further help to improve clinical outcomes and reduce mortality. It is time that health authorities of the capital of Pakistan take serious measures to control the mortality rate by implementing stewardship program, hiring competent infectious disease specialist and clinical pharmacists specialized in infectious disease, and training the medical staff regarding use and de-escalation of antibiotic therapy.

Disclosure

The authors report no conflicts of interest in this work.

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