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CLINICAL CHARACTERISTICS AND OUTCOMES OF ADULT PATIENTS WITH CARBAPENEM-RESISTANT ENTEROBACTERALES INFECTION IN A TERTIARY CARE HOSPITAL IN KARACHI

Original Research

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Acknowledgement: We sincerely thank the patients, healthcare staff, and all contributors for their support in this study.

Conflict of Interest: None
Grant Support & Financial Support: None

ABSTRACT

Background: The global rise of antimicrobial resistance (AMR) has become a critical healthcare challenge, threatening effective treatment of infections. Carbapenem-resistant *Enterobacterales* (CRE), which include pathogens such as *Escherichia coli* and *Klebsiella pneumoniae*, have emerged as significant contributors to morbidity and mortality, particularly in hospitalized patients. These bacteria are resistant to carbapenems, often the last-line antibiotics for multidrug-resistant Gram-negative infections. This study aimed to assess the clinical characteristics and outcomes of CRE infections in hospitalized patients at a tertiary care hospital in Karachi, Pakistan.

Objective: To identify the clinical characteristics of CRE infections and analyze their relationship with clinical outcomes among adult hospitalized patients.

Methods: This cross-sectional study was conducted at The Indus Hospital, Korangi Campus, Karachi, from September 2023 to May 2024. A total of 92 adult patients admitted with CRE infections were included using a non-probability consecutive sampling technique. CRE isolates were obtained from blood, urine, pus, deep tissue, and lung secretions. Species identification and susceptibility testing were performed using the Vitek-2 compact system. Demographics, comorbidities, and clinical parameters, including Sequential Organ Failure Assessment (SOFA) scores, were documented. Data were analyzed using SPSS version 26, with chi-square or Fisher's exact tests applied to assess significant associations ($p<0.05$).

Results: Of the 92 patients, 52.2% were male, with a median age of 44.5 years. The most common comorbidities were hypertension (28.3%) and diabetes mellitus (26.1%). The predominant CRE isolates were *Escherichia coli* (56.5%) and *Klebsiella pneumoniae* (40.2%). Median hospital stay was 10.5 days, with 88.0% of patients admitted through the emergency room. Mortality occurred in 30.4% of cases, with significant associations identified for chronic liver disease ($p=0.048$), mechanical ventilation ($p<0.001$), and high SOFA scores ($p<0.001$).

Conclusion: CRE infections caused by *Klebsiella pneumoniae* and *Escherichia coli* were associated with high mortality despite targeted antimicrobial therapy. Comprehensive AMR strategies, including stewardship and infection control, are essential to mitigate this growing healthcare crisis.

Keywords: Antimicrobial resistance, carbapenem-resistant Enterobacteriaceae, CRE, Escherichia coli, Klebsiella pneumoniae, mortality, SOFA score.

INTRODUCTION

Antimicrobial resistance (AMR) refers to the ability of microorganisms, including bacteria, viruses, fungi, and some parasites, to evade the effects of antimicrobial agents such as antibiotics, antivirals, antifungal agents, and antimalarials, rendering these treatments ineffective. The Centers for Disease Control and Prevention (CDC) has identified AMR as a critical global health threat and categorized resistant microbes into three levels based on their potential impact on human health: urgent, serious, and concerning. Among these, carbapenem-resistant Enterobacterales (CRE) is classified as an urgent threat due to its significant clinical and public health implications (1). CRE infections pose a formidable challenge for clinicians worldwide, as they are associated with high prevalence, rapid regional dissemination, limited therapeutic options, and prolonged hospital stays (2). These infections primarily cause severe conditions such as bloodstream infections, pneumonia, respiratory tract infections, complicated urinary tract infections (UTIs), and intra-abdominal infections. Carbapenems, which belong to the beta-lactam group of antibiotics, were historically considered the last resort for treating multidrug-resistant Gram-negative bacterial infections. However, since the emergence of CRE in the early 1990s, the incidence and resistance rates of these infections have risen alarmingly, particularly in South Asian countries like Pakistan, where rates have increased from 3.0% to 16.1% (3-7).

The spectrum of CRE infections often includes bacterial isolates such as Klebsiella pneumoniae, Escherichia coli, and Enterobacter cloacae complex, with Klebsiella pneumoniae being the most frequently identified pathogen (8, 9). Studies have reported a mortality rate exceeding 50% for bloodstream infections caused by CRE, and the attributable mortality for CRE-related infections globally is estimated to be more than 26% (10, 11). A meta-analysis encompassing 62 studies revealed a 54.3% mortality rate for bloodstream infections and a 13.5% mortality rate for urinary tract infections associated with carbapenem-resistant Klebsiella pneumoniae (CRKP) (12). These alarming statistics have prompted organizations such as the CDC and the World Health Organization (WHO) to underscore the urgent need for interventions to mitigate the burden of CRE infections (13, 14). In Pakistan, several factors contribute to the rise of AMR, including the irrational use of antibiotics, over-the-counter availability of medications without prescriptions, misleading advertisements, and the simultaneous use of multiple drugs to treat various conditions (5, 15, 16). The increasing prevalence of CRE infections and the complexity of their management underscore the necessity for timely identification and appropriate therapeutic interventions to reduce the associated morbidity and mortality.

This study was conducted to determine the clinical characteristics and outcomes of hospitalized patients with CRE infections in a tertiary care hospital in Karachi, Pakistan. Given the limited local data on this critical issue, the findings of this study are intended to assist physicians in anticipating and managing CRE infections more effectively, thereby improving patient outcomes and reducing the overall burden of disease. By addressing the gap in local literature, this study aims to contribute valuable insights for optimizing the clinical management of CRE infections in resource-limited settings.

METHODS

This cross-sectional study was conducted in the intensive care units, cardiac care units, and medical and surgical high-dependency units and wards at The Indus Hospital Karachi, a tertiary care teaching hospital, over nine months from October 2023 to June 2024. Approval for the study was obtained from the Institutional Review Board prior to its commencement, and the sample size was calculated as 92 using the WHO sample size calculator. The calculation was based on an anticipated frequency of *Klebsiella pneumoniae* of 13.51% (10), with a 7% margin of error and a 95% confidence level. A non-probability consecutive sampling technique was employed to recruit participants. Inclusion criteria encompassed patients of either gender, aged 15 years or older, with confirmed CRE isolates obtained from blood, pus, urine, deep tissue, or lung secretions. Patients with malignancies, immunocompromised conditions, pregnant or lactating women, and those unable to provide informed written consent were excluded from the study. Detailed clinical histories were obtained from patients or their attendants when patients were unable to provide the necessary information. Comprehensive clinical examinations were conducted, and samples from blood, urine, pus, deep tissue, or lung secretions were collected for CRE screening and bacterial isolate identification. CRE was defined as a member of the *Enterobacterales* order resistant to at least one carbapenem antibiotic (meropenem, imipenem, or ertapenem) or producing a carbapenemase enzyme. Antimicrobial susceptibility testing was initially

performed using the Kirby-Bauer disc diffusion method to assess resistance to a panel of antibiotics, including meropenem, imipenem/cilastatin, and ertapenem. The classification of isolates as susceptible, intermediate, or resistant adhered to Clinical and Laboratory Standards Institute (CLSI) guidelines. Species identification and further susceptibility testing were carried out in the clinical laboratory using the Vitek-2 compact system.

Demographic and clinical characteristics, including comorbidities and infection sites, were recorded. Other parameters such as the length of stay in the ward or ICU, requirement for mechanical ventilation, SOFA scores, and the specific CRE isolates were also documented. Patient outcomes were assessed in terms of in-hospital mortality. All patients with CRE infections were managed in accordance with established hospital protocols, and outcomes were monitored until discharge. The study's data collection was facilitated through a structured proforma designed specifically for the research. Data analysis was performed using IBM-SPSS Statistics, version 26. Quantitative variables, such as age and length of hospital stay, were summarized as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the normality of the data distribution. Categorical variables, including gender, residence, presenting complaints, mode of admission, place of admission, use of mechanical ventilation, bacterial isolates, sources of infection, and mortality, were reported as frequencies and percentages. The normality of quantitative data was assessed using the Shapiro-Wilk test. To control for potential effect modifiers such as age, gender, residence, place of admission, length of hospital stay, and mode of admission, stratification was performed. Post-stratification, statistical tests such as the chi-square test or Fisher's exact test were applied, with a p-value of <0.05 considered statistically significant.

RESULTS

In 92 patients, 48 (52.2%) were male. The median age was 44.5 (29.0 to 55.75), ranging between 15 and 65 years. The place of admission was the emergency room for 81 (88.0%) patients. Table 1 shows the distribution of baseline characteristics. The most frequent comorbid conditions were hypertension 26 (28.3%), diabetes mellitus 24 (26.1%), and chronic kidney disease 10 (10.9%) patients. (figure-1).

Table-1: Baseline characteristics of patients (n=92)

Characteristics		Frequency (%)
Gender	Male	48 (52.2%)
	Female	44 (47.8%)
Age	15-45	52 (56.5%)
	46-65	40 (43.5%)
Place of admission	Emergency room	81 (88.0%)
	Outpatient department	11 (12.0%)

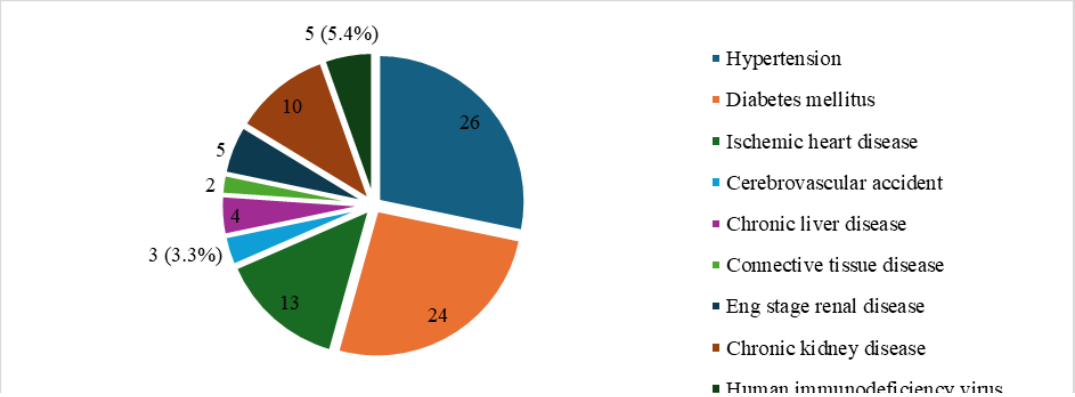

Figure 1 Frequency of most common comorbidities (n=92)

The most common CRE isolates were Escherichia coli and Klebsiella in 52 (56.5%) and 37 (40.2%) patients, respectively. Table-2 shows a comparison of gender (p=0.088), age (p=0.671), and specimen type (n=0.774) with respect to various carbapenem-resistant isolates, and no statistically significant associations were found.

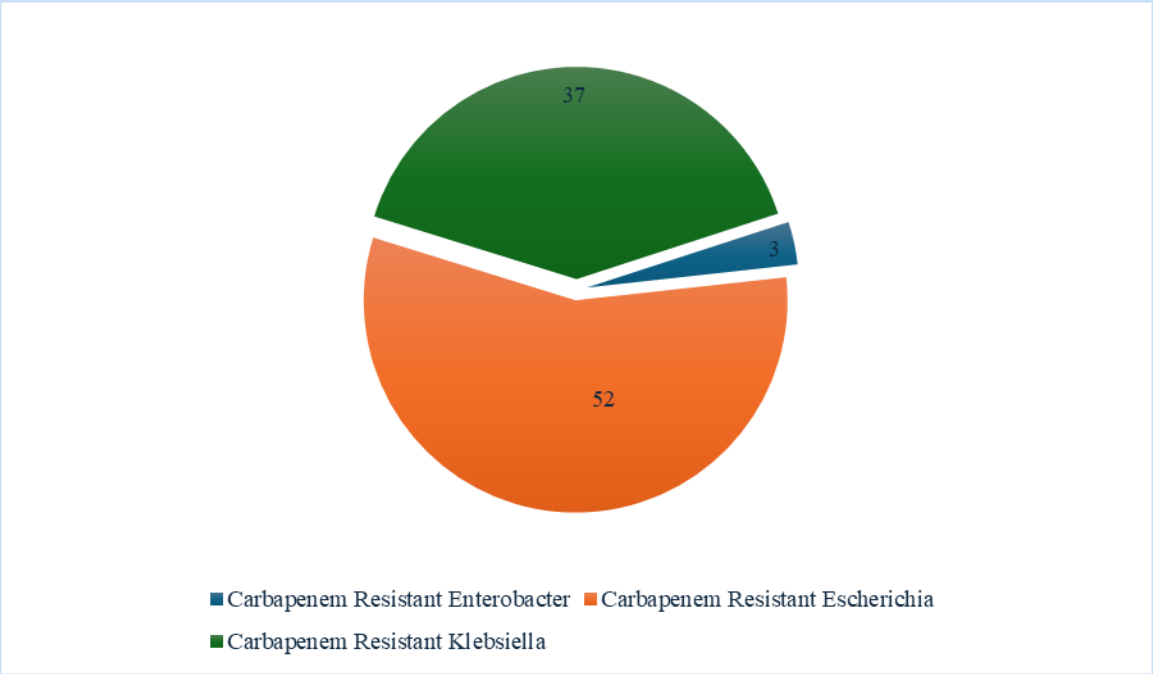

Figure 2 Frequency of carbapenem-resistant bacterial isolates (n=92)

Table 2 Comparison of gender, age, and specimen for various carbapenem-resistant isolates (n=92)

Variables		Carbapenem Resistant Enterobacter (n=3)	Carbapenem Resistant Escherichia Coli (n=52)	Carbapenem Resistant Klebsiella (n=37)	P-value
Gender	Male	3 (100%)	23 (44.2%)	22 (59.5%)	0.088
	Female	-	29 (55.8%)	15 (40.5%)	
Age	15-45	1 (33.3%)	29 (55.8%)	22 (59.5%)	0.671
	46-65	2 (66.7%)	23 (44.2%)	15 (40.5%)	
Specimen	Blood	1 (33.3%)	7 (13.5%)	7 (18.9%)	0.774
	Urine	-	20 (38.5%)	12 (32.4%)	
	Pus	1 (33.3%)	17 (32.7%)	10 (27.0%)	
	Tissue	1 (33.3%)	4 (7.7%)	5 (13.5%)	
	Sputum	-	4 (7.7%)	3 (8.1%)	

The median duration of hospitalization was 10.50 (7.00-15.00) days . Mortality was 28 out of 92 patients (30.4%). Assessment of study variables for mortality revealed that the co-existence of chronic liver disease ($p=0.048$), use of mechanical ventilation ($p<0.001$), and high SOFA score ($p<0.001$) were significantly associated with mortality. In contrast, all other study variables did not show any statistical significance ($p>0.05$), as shown in table-3.

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Table 3 Association of study variables with mortality (N=92)

Study variables		Mortality		P-value
		Yes (n=28)	No (n=64)	
Gender	Male	14 (50.0%)	34 (53.1%)	0.782
	Female	14 (50.0%)	30 (46.9%)	
Age (years)	15-45	15 (53.6%)	37 (57.8%)	0.706
	46-65	13 (46.4%)	27 (42.2%)	
Place of admission	Emergency room	27 (96.4%)	54 (84.4%)	0.101
	Outpatient department	1 (3.6%)	10 (15.6%)	
Frequency of comorbidities	Hypertension	6 (21.4%)	20 (31.3%)	0.336
	Diabetes mellitus	8 (28.6%)	16 (25.0%)	0.720
	Ischemic heart disease	4 (14.3%)	9 (14.1%)	0.977
	Cerebrovascular accident	2 (7.1%)	1 (1.6%)	0.166
	Chronic liver disease	3 (10.7%)	1 (1.6%)	0.048
	Connective tissue disease	-	2 (3.1%)	0.344
	Eng stage renal disease	1 (3.6%)	4 (6.3%)	0.602
	Chronic kidney disease	3 (10.7%)	7 (10.9%)	0.975
	Human immunodeficiency virus	1 (3.6%)	4 (6.3%)	0.602
Bacterial isolates	Carbapenem resistant Klebsiella	15 (53.6%)	22 (34.4%)	0.209
	Carbapenem Resistant Enterobacter	1 (3.6%)	2 (3.1%)	
	Carbapenem Resistant Escherichia coli	12 (42.9%)	40 (62.5%)	
Use of mechanical ventilation		23 (82.1%)	4 (6.3%)	<0.001
Length of ICU stay, Mean±SD		6.52±5.67	5.78±9.55	0.782
Duration of admission, Mean±SD		11.18±7.14	13.03±9.67	0.365

A comparison of final outcomes with respect to specimen types is shown in Figure 3, and no statistically significant differences were observed (p=0.090). Baseline high SOFA score was significantly associated with mortality (p<0.001), and the details are shown in Figure 4.

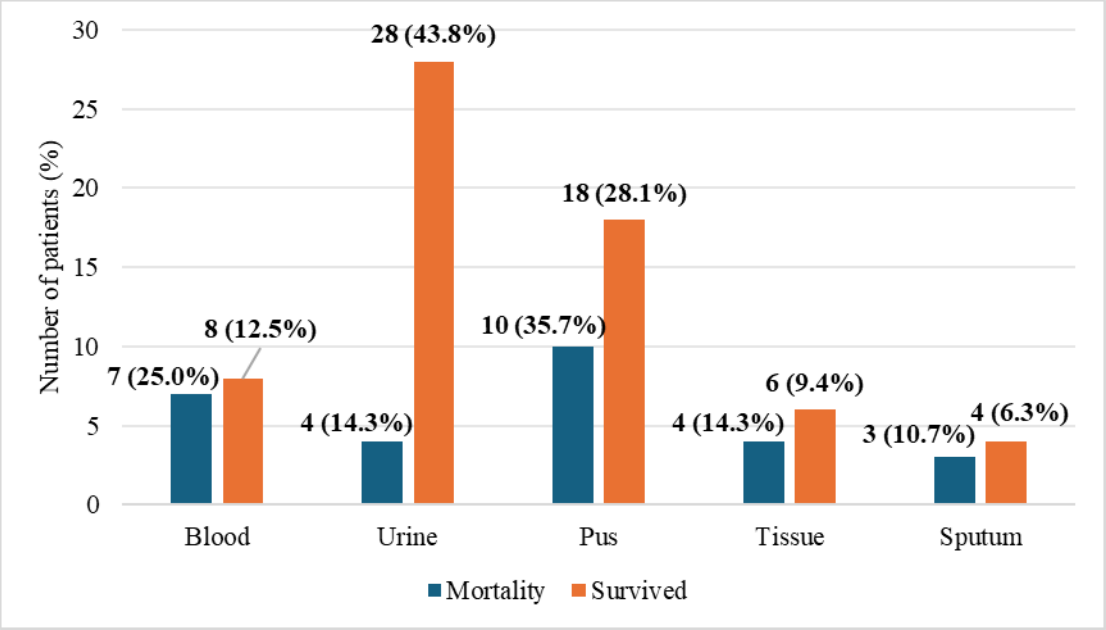

Figure 3 Comparison of outcome by specimen type

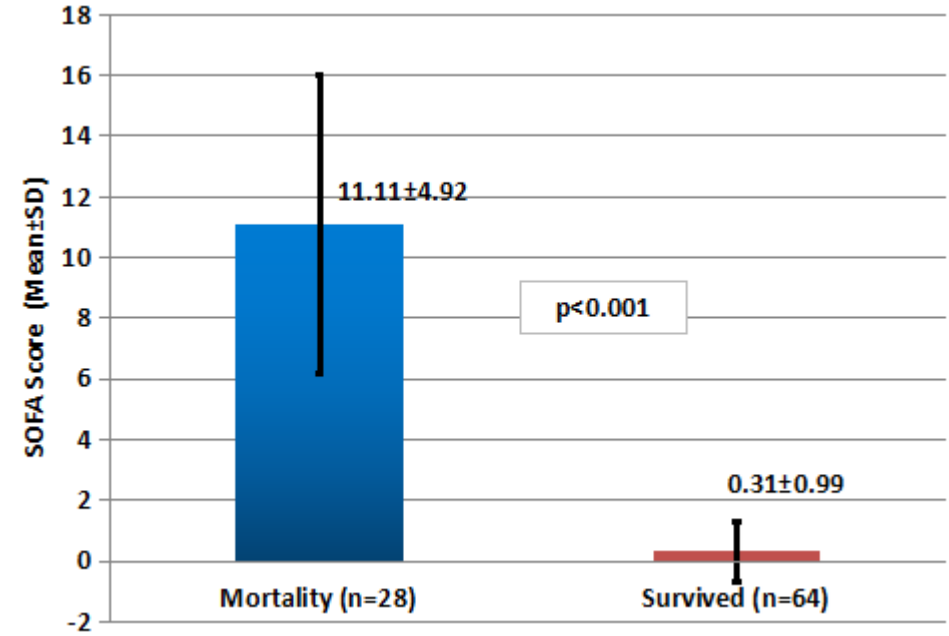

Figure 4 Comparison of final outcome with respect to baseline SOFA score.

DISCUSSION

In this study, the most common carbapenem-resistant *Enterobacterales* (CRE) isolates were *Escherichia coli* (56.5%) and *Klebsiella* species (40.2%). The findings align with prior regional and global studies that have highlighted the prevalence of *Klebsiella pneumoniae* and *Escherichia coli* as the predominant CRE pathogens (17, 18). Large-scale observational studies conducted in developed regions, such as data from 63 hospitals in the United Kingdom, reported *Klebsiella pneumoniae* as the most dominant CRE isolate (19, 20). Similarly, a study conducted in Lahore documented a significant burden of CRE infections, primarily involving *Klebsiella pneumoniae* (21). These findings reinforce the growing global challenge posed by CRE infections, particularly in regions with limited antimicrobial stewardship and infection control practices. The study highlights the alarming spread of CRE infections worldwide, driven by the inappropriate use and overuse of antimicrobials, which has fueled the rise in antimicrobial resistance (AMR). The rapid dissemination of carbapenemase-encoding genes through horizontal gene transfer enables CRE to colonize and infect even those who have not been exposed to carbapenem antibiotics. This

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mechanism contributes to the rapid proliferation of carbapenemase-producing bacteria in healthcare settings, often affecting individuals with prolonged hospital stays or those exposed to environments contaminated with CRE (22).

Mortality associated with CRE infections remains a critical concern, even with the use of combination antibiotic therapies. In this study, mortality was observed in 30.4% of patients, underscoring the severe clinical implications of CRE infections. Previous analyses of non-randomized studies revealed even higher mortality rates, with rates ranging from 50% to 80% depending on the treatment regimen, including monotherapies and combination therapies such as tigecycline, colistin, and carbapenems (23, 24). These findings highlight the limited efficacy of currently available treatment options and the need for novel therapeutic approaches. Furthermore, the global economic and health impact of drug-resistant infections is projected to be catastrophic, with an estimated 10 million deaths annually and a cumulative economic burden of 100 trillion USD by 2050, disproportionately affecting low- and middle-income countries, including Pakistan (25). Despite its contributions, this study has limitations that must be acknowledged. The relatively small sample size and single-center design reduce the generalizability of the findings. Larger, multicentric studies are essential to provide more comprehensive data on the burden, risk factors, and treatment outcomes of CRE infections. The lack of standardized treatment protocols in this study may also limit the ability to draw firm conclusions regarding optimal management strategies. Infectious disease consultants prescribed antibiotics based on individual drug sensitivities, resulting in heterogeneous treatment regimens that could introduce variability in outcomes. Additionally, while this study provides valuable insights into the prevalence and outcomes of CRE infections, it did not explore the impact of prior antibiotic use or other potential confounding factors, which are critical for understanding the dynamics of CRE emergence and resistance patterns.

One of the strengths of this study is its contribution to local data, addressing the scarcity of literature on CRE in Pakistan. The findings emphasize the urgent need for implementing AMR surveillance systems, improving infection control practices, and promoting antimicrobial stewardship programs to curb the spread of CRE and reduce associated morbidity and mortality (26-28). This study reinforces the necessity of global and regional collaboration to combat AMR and develop effective strategies to mitigate the impact of CRE infections in resource-limited settings. While the findings are significant, they should be interpreted in the context of the study's limitations, and further research is warranted to build upon these observations and guide clinical and public health interventions.

CONCLUSION

This study highlights the significant burden of carbapenem-resistant *Klebsiella pneumoniae* and *Escherichia coli* infections, emphasizing the critical need for effective strategies to combat antimicrobial resistance. Preventing such infections is as essential as treating them, necessitating the implementation of robust antimicrobial stewardship programs within healthcare settings. The rational use of antimicrobials must be strictly enforced, supported by educational initiatives such as seminars, scientific publications, and training programs for healthcare professionals at all levels. Regular dissemination of antibiograms by microbiology laboratories can guide evidence-based clinical practices, while stringent infection control measures are imperative to curb the transmission of resistant bacteria in hospitals. The urgency to address antibiotic misuse is paramount to safeguard patients from the growing threat of untreatable infections and to preserve the effectiveness of existing therapeutic options.

AUTHOR CONTRIBUTIONS

Author	Contribution
Muhammad Idrees*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Naseem Salahuddin	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published

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