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Original Article

Molecular epidemiology of antimicrobial-resistant *Klebsiella pneumoniae* in intensive care unit patients, southwestern Saudi Arabia

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Abstract

Antimicrobial resistance (AMR) in Gram-negative pathogens poses a critical threat in intensive care units (ICUs). This retrospective observational study aimed to determine the prevalence and phenotypic resistance profiles of extended-spectrum β-lactamase (ESBL)-producing and carbapenem-resistant Klebsiella pneumoniae among ICU patients at a tertiary hospital in southwestern Saudi Arabia (2020–2021). Clinical specimens (n=179) from patients with hospital-acquired infections were processed using standard culture, Vitek 2 identification, and phenotypic confirmatory tests (combination disc test for ESBLs and modified carbapenem inactivation method for carbapenemase). Of 543 total samples, 49 (9.0%) were identified as K. pneumoniae. ESBL production was detected in 15/49 (30.6%) and carbapenemase production in 6/49 (12.2%) of isolates. The highest resistance rates were observed against piperacillin-tazobactam (55.1%), cefotaxime (55.1%), imipenem (53.0%), and meropenem (53.0%), while tigecycline (100% susceptibility) and amikacin (93.9% susceptibility) remained the most effective agents. Notably, susceptibility to trimethoprim-sulfamethoxazole was 83.7% (corrected figure). Children under 10 years and adults aged 21–40 years showed the highest infection rates. The alarmingly high prevalence of ESBL and carbapenemase phenotypes, coupled with significant multidrug resistance, underscores the urgent need for routine molecular surveillance and targeted antibiotic stewardship in this region. Rapid phenotypic screening combined with genotypic confirmation is essential to guide empirical therapy and curb the spread of these high-risk clones in critically ill populations.

Keywords: Carbapenem-resistant *Klebsiella pneumoniae*; ESBLs producing *Klebsiella pneumoniae*; Healthcare workers; Multi-drug resistant; Saudi Arabia.

1. Introduction

Every organism living on the earth competes directly or indirectly for its survival. Humans are superior hierarchical creature that constantly evolves and are cautious in defending against numerous pathogens that are meant to be lethal [1]. In such cases, antibiotics are a class of chemotherapeutic agents that provide an effective cure against a wide spectrum of highly infectious bacteria. However, depending upon the mode of action and the specific target site, the antibiotics could be further categorized broadly into bactericidal and bacteriostatic [2]. It is well known that the doubling time of bacteria is ideally short. Bacteria possess plasmids, an extra-chromosomal DNA in their cytosol, which quickly gain resistance features to the antibiotics frequently used to treat bacterial infections. Therefore, it is mandated to constantly monitor the appearance or existence of resistance strains of bacterial species. As the bacteria gain resistance, the effective use of antibiotics as treatment becomes void [3]. In such a scenario, a routine surveillance study on microbial resistance is crucial for effective prophylaxis aimed at decreasing the bacterial load of the host.

The detection of emerging pathogens in national and international backgrounds and the in-depth analysis of the identification of infection incidence patterns of the particular pathogen, followed by its antibiotic resistance, is a crucial part of the routine surveillance studies [4]. A systematic investigation is vital for emerging and improving strategies for reducing antimicrobial resistance and assisting clinicians in deciding the best course of action [5]. Monitoring pathogen antimicrobial susceptibility has been the conventional strategy; many substantial studies have been conducted, and their trends have changed over time. Studies comparing the data across time could yield significant information, which makes it particularly helpful in longitudinal research [6]. Monitoring the regular use of antimicrobials is another mode of surveillance that can spot patterns in dosage and arrest the emergence of resistance. This strategy has been used in several investigations, and both sizable and small studies have attempted to match data on antibiotic use with data on antibiotic resistance. In general, care must be taken to coordinate programs for the best possible resource usage and to prevent effort duplication.

Previous reports from local, national, and international surveillance studies have shown that the prevalence

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of pathogens resistant to routine antibiotics is rising. For instance, the National Nosocomial Infections Surveillance (NNIS) System consortium reported the rising prevalence of *Pseudomonas aeruginosa* isolates from patients in US intensive care units (ICUs) who are reported to be resistant to third-generation cephalosporins, quinolones, and imipenem as per data gathered from 1997 to 2003 [7]. Public health is highly concerned about this rise in antibiotic resistance, which jeopardizes the use of previously efficient therapies for antimicrobial illnesses. According to a summary of the results of recent literature analysis, subjects with antimicrobial-resistant diseases inherently had a higher risk of death, morbidity, length of hospital stay, and medical expenses. This result was confirmed with infections brought on by third-generation cephalosporin-resistant *Enterobacter* species, *Enterococci* resistant to vancomycin, and methicillin-resistant *Staphylococcus aureus* (MRSA) [8]. The emergence of resistant *P. aeruginosa* was linked to a greater risk of death, extended hospital visits, and secondary bacteremia. In contrast, infection with ESBL-producing *Klebsiella pneumoniae* or *Escherichia coli* predicted higher mortality, extended hospital stays, and higher median hospital costs [9].

Peters et al, reported more detail about how infections with resistant pathogens can delay the start of appropriate antimicrobial therapy; these results are consistently correlated with the resistant infectious pathogens, which could be a frequent predictor of infection-associated mortality or a lengthened hospital stay, respectively [10]. International and national studies may provide information and instruction, limiting their prediction for anticipating specific patients. Contrarily, regular monitoring of antimicrobial usage identifies trends in dosing and enables comparisons of antimicrobial use data with antimicrobial resistance data, which can offer crucial insights into how specific use patterns affect resistance. The findings of antimicrobial usage surveillance are frequently transferable worldwide, in contrast to resistance-surveillance efforts, where local data have little international importance. The results of both types of surveillance may indicate the necessity of aspects of specifically prescribed procedures, which can subsequently be reviewed longitudinally using the same techniques.

Antimicrobial resistance and antimicrobial usage surveillance studies are unquestionably here to stay, given their importance in today's infection control environment. Future surveillance studies must maintain a diverse mix of the big and tiny, the global and the local, to provide the most critical and relevant information.

Given the escalating threat of antimicrobial resistance in hospital settings, particularly in intensive care units, and the scarcity of recent epidemiological data from southwestern Saudi Arabia, this study was designed to investigate the prevalence and resistance profiles of *Klebsiella pneumoniae* isolates at AL SHEFA HOSPITAL. Specifically, this study aimed to: (i) determine the frequency of extended-spectrum β-lactamase (ESBL)-producing and carbapenemase-positive *K. pneumoniae* strains among ICU patients, (ii) evaluate their antimicrobial susceptibility patterns against a panel of commonly used antibiotics, and (iii) analyze the demographic and clinical characteristics associated with these infections to guide empirical therapy and inform infection control strategies.

2. Materials and Methods

2.1. Study Setting

The current study was conducted as a retrospective observational study obtained from the information gathered from the data sheets of the patients in the intensive care unit at AL SHEFA HOSPITAL, a tertiary care facility in the southern part of Saudi Arabia, between 2020 and 2021. Patients who had been confined for more than 48 hours in the ICU and had a hospital-acquired infection made up the study group. Demographic, microbiological, antimicrobial treatment and patient outcomes data were gathered. In this investigation, 543 patients with bacteremia, pneumonia, and other infections were categorized as nosocomial infections (those developing within 48 hours of hospital admission) or illnesses acquired through healthcare.

2.2. Ethical Approval

The methods used in this study that involved sampling from and dealing with human subjects complied with ethical norms. The AL SHEFA HOSPITAL Ethics Internal Review Board Committee provided ethical approval (No: 20191203 Date: 10\12\2019). Before the study commenced, a letter of support was acquired from the study site. Additionally, written informed consent was obtained from all adult participants in the study, as well as from parents or guardians of the children and newborn infants who were involved in the study.

2.3. Sample and Demographic Data Collection

To gather demographic data, standardized questionnaires and patient record forms were used to collect information from each patient. In addition, during the febrile period, 5-10 mL or 1-3 mL of peripheral blood samples were collected from adult and pediatric patients, respectively.

2.4. Bacterial Isolates and Antimicrobial Susceptibility

Using traditional techniques, clinical samples from various illnesses in the ICU (n=80) were prepared for culture. Standard phenotypic assays were used for initial identification [11]. Following initial identification, the Vitek 2 identification system (BioMerieux, Marcy-l'Étoile, France) was used in the microbiology laboratory to confirm the isolates by manufacturer requirements. According to the manufacturer, antimicrobial susceptibility testing was also done with the Vitek 2 system. The in vitro susceptibility of the most common antibiotics (n=20) to the most prevalent ICU infections.

The blood sample was placed into BacT/ALERT® 3D (bioMeriéux-France) culture bottles and then incubated in an automated BacT/ALERT® 3D machine at 35°±2°C in 5% CO2. Bacterial identification was carried out by subculturing the sample on MacConkey agar (Mac, Oxoid UK), 5% sheep blood agar plate (BAP, Oxoid UK), and chocolate agar plate (CHA, Oxoid UK). To identify bacterial isolates, standard biochemical tests including indole, urea, triple sugar iron, citrate, lysine decarboxylase, motility, and Malonate were used.

In accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines, the Kirby-Bauer disc diffusion method was utilized to conduct antimicrobial susceptibility testing on Mueller-Hinton agar (Oxoid, UK). Antibiotics tested in this study included ampicillin (10 μg), levofloxacin (10 μg), amikacin (30 μg), cefotaxime (30 μg),

ceftriaxone (30 µg), ciprofloxacin (5 µg), sulphamethoxazol/trimethoprim (25 µg), piperacillin-tazobactam (20 µg), cefepime (30 µg), cefoxitin (30 µg), meropenem (10 µg), imipenem (10 µg), amoxicillin/clavulanic acid (20/10 µg), piperacillin-tazobactam (20/10 µg), tigecycline (20 µg) and Ceftazidime/Avibactam (30 µg), all supplied by BD USA.

To perform the Kirby-Bauer disc diffusion method, pure colonies of isolates with a turbidity equal to 0.5 McFarland standard were cultured on Mueller-Hinton agar (MHA) plates. Next, antimicrobial discs were placed on the MHA plates and incubated for 24 hours at 35°C. Following overnight incubation, the zone of inhibition was measured and interpreted according to the recommendations of CLSI [12].

2.5. Phenotypic Detection of ESBLs

To determine the presence of ESBL, Enterobacteriaceae isolates that were non-susceptible to at least one third-generation cephalosporin were screened using the combination disc-diffusion test (CDT) on Mueller-Hinton agar (MHA). Ceftazidime (CAZ) and cefotaxime (CTX) were used alone and in combination with clavulanic acid (CAZ/CLA and CTX/CLA) as recommended by CLSI 2018 [12]. An increase in zone size diameter by ≥5 mm for CTX/CLA and CAZ/CLA, compared to CTX and CAZ alone, confirmed the presence of ESBL.

2.6. Phenotypic Detection of Carbapenemase

To detect the presence of carbapenemase in isolates that showed resistance or intermediate susceptibility to meropenem or imipenem, the modified carbapenem inactivation method (CIM) was employed as per the guidelines provided by CLSI [12]. A colony of the test isolates taken from an overnight blood agar plate was mixed with 2 mL of nutrient broth (Oxoid UK), and a meropenem disk of 10 µg was added to the mixture. The tube was incubated without agitation at 37°C for 4 hours ± 15 minutes. After incubation, the meropenem disks were removed using a 10 µL inoculation loop and applied to Mueller-Hinton agar plates (Oxoid, UK) that were freshly inoculated with a 0.5 McFarland suspension of a carbapenem-susceptible strain (Escherichia coli ATCC® 25922). The plates were then incubated overnight, and the results were interpreted in accordance with CLSI guidelines [12].

2.7. Statistical Analysis

Descriptive analysis was performed on statistical variables, such as biodemographic information, clinical specimen source, and organism type. This analysis utilized methods including cross-tabulation, frequency, and proportion. The resulting data were then compared to determine trends in antimicrobial resistance rate, the prevalence of MDR A. baumannii, and resistance rates of this bacterium. Microsoft Excel 2019 was used for this analysis, and statistical significance was determined using SPSS version 26 software (SPSS Inc, Chicago, IL, USA). Any P values below 0.05 were considered statistically significant.

3. Results

The emergence of hospital-acquired pathogens that are resistant to antibiotics is a worldwide concern as they are hard to treat using standard preventative measures. It is crucial to monitor the emergence of new antibiotic-resistant strains due to their potential lethality. Although there are several pathogens that cause a significant impact in clinical settings, the recently identified resistant strains ESBLs and CRE *Klebsiella pneumoniae* have gained particular attention.

Out of 543 clinical isolates, 179 were collected from the ICU. Out of 543 isolates, 254 (46.7%) were Gram-positive and 289 (53.2%) were Gram-negative strains. The age group of the 543 patients involved in this study ranged from 0 to 90. Among the 179 ICU isolates, 67 (37.4%) were Gram-positive and 112 (62.5%) were Gram-negative microbes. Out of 179 ICU isolates, 49 (27.3%) strains were found to have the infection of *Klebsiella pneumoniae*. Among the *Klebsiella pneumoniae* isolates, 27 (55.1%) were male, and 22 (44.8%) were female, as shown in Table 1.

3.1. Distribution of *Klebsiella pneumoniae* Isolates.

Of the 179 ICU bacterial isolates that were found to be culture-positive, 49/179 (27.3%) were identified as *Klebsiella pneumoniae*. All of these isolates were obtained from inpatients in ICU wards. Of the total ICU isolates, isolated from the site of infections were: wound 6/179 (3.3%), respiratory tract 27/179 (15%), surgical area 11/179 (6.2%), urinary tract 64/179 (35.7%), vaginal swab 45/179 (25.1%), blood 14/179 (7.8%), and central venous catheter 12/179 (6.7%), and whereas *Klebsiella pneumoniae* were from wound 4/49 (8.1%), respiratory tract 7/49 (14.2%), surgical area 1/49 (2%), urinary tract 16/49 (32.6%), vaginal swab 8/49 (16.3%), blood 9/49 (18.3%), and central venous catheter 4/49 (8.1%). Of the total *Klebsiella pneumoniae* isolates, a higher proportion of the isolates (11/49, 22.4%) were obtained from patients with an underlying respiratory infection, 9/49 (12.7%) were from patients with diabetes mellitus and the least isolated from corticosteroid users, 2/49 (4%), as shown in Table 1.

3.2. Prevalence of ESBLs Producing *Klebsiella pneumoniae* Isolates

The prevalence of ESBL-producing *Klebsiella pneumoniae* obtained from inpatients in the ICU was investigated in one of the largest hospitals in Najran, using 49 non-duplicate isolates of *Klebsiella pneumoniae*. Of the total ICU isolates, isolates from the site of infection were: wound 3/15 (20%), respiratory tract 2/15 (13.3%), urinary tract 5/15 (33.3%), vaginal swab 1/15 (6.6%), and blood and central venous catheter were 2/15 (13.3%). Of the total ESBL-producing microbes, a higher proportion of the isolates (5/15, 33.3%) were obtained from patients with urinary tract infections, as shown in Table 2. Most of the ESBL-producing isolates were from patients with an underlying respiratory infection; diabetes mellitus and anemia medical conditions were similar (3/15, 20%), as shown in Table 2.

3.3. Prevalence of Carbapenemase-Producing *Klebsiella pneumoniae* (CPK) Isolates

Out of the 49 isolates of *Klebsiella pneumoniae* tested, 6/49 (12.2%) showed resistance to carbapenem and were subjected to the modified carbapenem inactivation method to test for carbapenemase production. Of the total ICU isolates, isolates from the site of infection were: wound 1/6 (16.6%), respiratory tract 1/6 (16.6%), surgical area 1/6 (16.6%), urinary tract 2/6 (33.3%), and central ve-

Table 1. Demographics and Clinical data of the total study group, ICU isolates and *Klebsiella pnemoniae* species isolated from ICU.

Variable	Total Group (n=543)	Total Group in ICU (n=179)	*Klebsiella pnemoniae* (n=49)
Total number of isolates microorganism	543 (100%)	179 (32.9%)	49 (9%)
Age (years)			
a. 0-10 years	138 (25.4%)	16 (8.9%)	5 (10.2%)
b. 10-20 years	38 (6.9%)	19 (10.6%)	3 (6.1%)
c. 20-30 years	26 (4.7%)	25 (13.9%)	9 (18.3%)
d. 21-40 years	276 (50.8%)	77 (43%)	22 (44.8%)
e. 60-90 years	65 (11.9%)	42 (23.4%)	10 (20.4%)
Sex			
a. Male	372 (68.8%)	108 (60.3%)	27 (55.1%)
b. Female	171 (31.1%)	71 (39.6%)	22 (44.8%)
Organism			
a. Gram Positive	254 (46.7%)	67 (37.4%)	0 (0%)
b. Gram Negative	289 (53.2%)	112 (62.5%)	49 (100%)
Site of the Infection			
a. Wound	62 (11.4%)	6 (3.3%)#*	4 (8.1%)
b. Respiratory tract	97 (17.8%)	27 (15%)#*	7 (14.2%)*
c. Surgical area	19 (3.4%)	11 (6.2%)*	1 (2%)*
d. Urinary tract	164 (30.2%)	64 (35.7%)#*	16 (32.6%)*
e. Vaginal swab	145 (14.9%)	45 (25.1%)#*	8 (16.3%)*
f. Blood	44 (26.7%)	14 (7.8%)#	9 (18.3%)
g. Central venous catheter	12 (2.2%)	12 (6.7%)	4 (8.1%)*
Diagnosis history			
a. No medical history	256 (47.1%)	54 (30.1%)#	8 (16.3%)*
b. Post Cardiac Arrest	36 (6.6%)	12 (6.7%)#	3 (6.1%)*
c. Respiratory	120 (22%)	34 (62.6%)#	11 (22.4%)*
d. Diabetes mellitus	72 (13.2%)	41 (7.5%)#	9 (18.3%)*
e. Bomb blast injury	6 (1.1%)	8 (4.4%)	5 (10.2%)
f. Infected Implant	4 (0.7%)	4 (2.2%)	0 (0%)
g. Corticosteroids user	6 (1.1%)	3 (1.6%)	2 (4%)
h. Severe anemia	28 (5.1%)	16 (8.8%)#	8 (16.3%)*
i. Chronic viral diseases	15 (2.7%)	7 (3.9%)#	3 (3.1%)

#* Represents the statistically significant. # Statistically significant comparison with total group to ICU clinical isolates. *Statistically significant comparison with ICU to *Klebsiella pneumonia* isolates. All comparisons were 2-tailed, and P values <0.05 were considered statistically significant.

nous catheter 1/6 (16.6%). Of the total CPKs produced microbes, a higher proportion of the isolates (2/6, 33.3%) were obtained from patients with respiratory tract infections, as shown in Table 2. See Table 4 for more details.

3.4. Antibiotic Resistance Pattern of *Klebsiella pneumoniae* Isolates

The resistance patterns of *Klebsiella pneumoniae* isolated from ICU were evaluated for 14 antibiotics in this study. We found that high rates of resistance were observed for piperacillin-tazobactam 27 (55.1%), ceftazidime/avibactam 26 (53%), cefotaxime 27 (55.1%), imipenem 26 (53%), meropenem 26 (53%), and colistin 21 (42.8%), among the tested antibiotics. *Klebsiella pneumoniae* isolates in this study had relatively lower resistance rates to cefazolin 17 (34.6%) and levofloxacin 19 (38.7%) (Figure 2). A few of them were resistant to amikacin 3 (6.1%), sulphamethoxazole/trimethoprim 8 (16.3%), and ciprofloxacin 5 (10.2%). However, to our knowledge, the isolated strains in our study revealed tigecycline (100%), vancomycin (100%) and sulphamethoxazole/trimethoprim (61.2%).

Figure 1 shows the overall susceptibility patterns of the isolates. The overall susceptibility pattern to antimicrobial agents is presented in Figure 1, tigecycline (100%), vancomycin (100%) and sulphamethoxazole/trimetho-

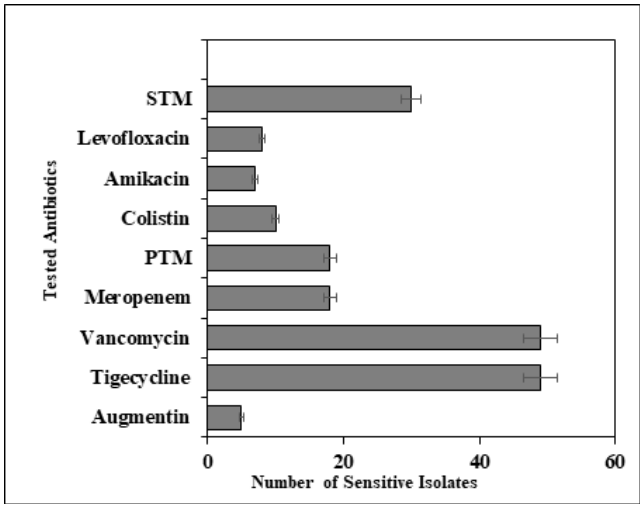


Fig. 1. Antibiotics susceptibility pattern *Klebsiella pneumoniae* isolates to tested antibiotics.

Table 2. Distribution of ESBLs, CRE Producing *Klebsiella pnemoniae* species isolated from ICU.

Variable	Extended-spectrum beta-lactamases (ESBLs) Positive (n=15)	Carbapenemase Positive (CRE) (n=6)	*Klebsiella pnemoniae* without ESBLs and CRE (n=28)
Total number of isolates microorganism	15 (30.6%)	6 (12.2%)	28 (57.1%)
Sex			
a. Male	9 (60%)	4 (66.6%)	17 (60.7%)
b. Female	6 (40%)	2 (33.3%)	11 (39.3%)
Type of cultures			
a. Wound	3 (20%)	1 (16.6%)	0 (0%)
b. Respiratory tract	2 (13.3%)	1 (16.6%)	4 (14.2%)
c. Surgical area	0 (0%)	1 (16.6%)	0 (0%)
d. Urinary tract	5 (33.3%)	2 (33.3%)	9 (32.1%)
e. Vaginal swab	1 (6.6%)	0 (0%)	7 (25%)
f. Blood	2 (13.3%)	0 (0%)	7 (25%)
g. Central venous catheter	2 (13.3%)	1 (16.6%)	1 (3.5%)
Diagnosis history			
a. No medical history	3 (20%)	1 (16.6%)	4 (14.2%)
b. Post Cardiac Arrest	1 (6.6%)	1 (16.6%)	1 (3.5%)
c. Respiratory	3 (20%)	2 (33.3%)	6 (21.4%)
d. Diabetes mellitus	3 (20%)	1 (16.6%)	5 (17.8%)
e. Bomb blast injury	0 (0%)	0 (0%)	5 (17.8%)
f. Corticosteroids user	0 (0%)	0 (0%)	2 (7.1%)
g. Severe anemia	3 (20%)	1 (16.6%)	4 (14.2%)
h. Chronic viral diseases	2 (13.3%)	0 (0%)	1 (3.5%)

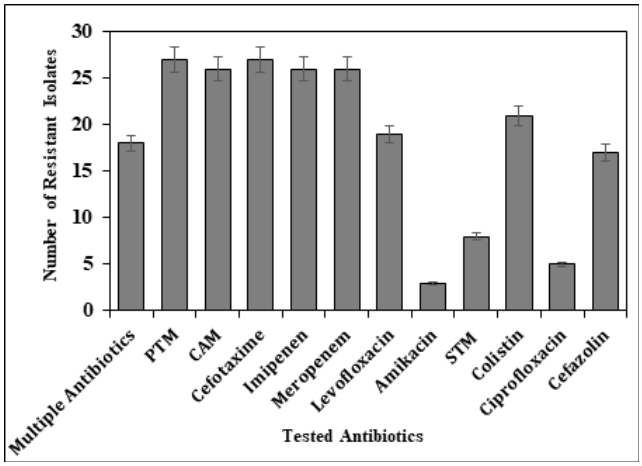


Fig. 2. Antibiotics Resistance Pattern of *Klebsiella pneumoniae* to common antimicrobial agents.

prim (61.2%) were the most active antimicrobial agents, whereas resistance against all other antibiotics was 50%. Out of the total patients studied, 18 (36.7%) belonged to the group with *Klebsiella pneumoniae* that was resistant to multiple antibiotics, while the remaining 31 patients (63.2%) were categorized as the group without multi-resistant *Klebsiella pneumoniae*.

4. Discussion

Globally, the incidence of multidrug-resistant organisms (MDR) in intensive care units (ICUs) is growing, with local, aetiological, and apparent hospital-specific disparities [13]. Gram-negative MDR bacteria and fungi presently impose serious health hazards, demanding stringent prophylactic actions and effective control, without which they even pose a threat to the patient's life. Classifications of compliance surveillance are required in order to compare outcomes across various alterations [14]. It is essential to follow certain standard protocols for empirically monitoring antibiotic resistance. Worldwide, Gram-positive, multidrug-resistant bacteria have been addressed in recent epidemiologic studies of ICU occurrence [15, 16]. Gram-negative organisms like *Acinetobacter baumannii* and *K. pneumoniae* are the foremost origins of illnesses acquired in healthcare settings, which are a severe global problem. Particularly, drug-resistant Enterobacteriaceae, in specific *Klebsiella* spp., have become a greater danger to world health. Therefore, keeping a close eye on the patient and finding the proper drug is indispensable for the successful management of the disease [17, 18]. MRSA, carbapenem-resistant *P. aeruginosa*, and extended-spectrum -lactamase (ESBL)-producing *K. pneumoniae* are significant health threats on a global scale.

The prevalence of ESBLs and Carbapenemase-producing *Klebsiella pneumoniae* (CPKs) has become a serious issue worldwide, as these multidrug-resistant organisms cause infections with high mortality rates and limited treatment options. In our study, ESBLs and CPKs were found in 30.6% and 12.2% of cases, respectively. Reports from different parts of the world have shown varying figures of ESBLs and carbapenemase-producing Enterobacteriaceae prevalence in patients. For example, lower reports of ESBL were observed in Brazil (21.3%) [19], Madagascar (26.3%) [20], Nigeria (41.7%) [21], and Egypt (48.93%) [22]. In contrast, higher figures of ESBL production were

reported in Ethiopia (78.57%) [23], Germany (83.6%) [24], and Cambodia (93.4%) [25].

The wide variation in the prevalence of ESBLs from different regions may be due to various risk factors such as excessive use of broad-spectrum antibiotics, a high rate of patient transfer from peripheral centers, prior multiple antimicrobial treatments, and a high rate of gastrointestinal colonization by ESBLs-producing microbes [26, 27]. These differences highlight the need to recognize and implement appropriate measures to contain the further spread of these resistant microorganisms globally.

In our study, the major ESBL-producing *Klebsiella pneumoniae* (30.6%) which is consistent with other reports from Saudi Arabia and India [28, 29]. *K. pneumoniae* showed significant ESBL production [30], possibly due to its ability to acquire antimicrobial resistance-determining genes via horizontal gene transfer mechanisms.

The occurrence of carbapenemase production in *Klebsiella pneumoniae* has risen globally, leading to bacteria that are resistant to multiple types of antibiotics and linked to high morbidity and mortality rates. In our research, the proportion of carbapenemase production was 6 out of 49, or 12.2%, which is higher than the rate in Kuwait (5.2%) [31] and earlier reports from Saudi Arabia (7.4%) [32]. However, the prevalence of carbapenemase-producing *Klebsiella pneumoniae* in our study was lower than previous reports from Saudi Arabia (14%) [33], and much lower than in France (36.2%) [34], Uganda (28.6%) [35], Germany (53.3%) [36], and a multicenter observational study from seven Latin American countries (20.8%) [37]. *K. pneumoniae's* ability to accumulate and spread resistance determinants results in the primary cause of hospital-acquired infections. Consequently, identifying carbapenemase-producing *K. pneumoniae* quickly in clinical laboratories is vital for timely diagnosis, controlling the spread, and setting up monitoring systems for these highly resistant organisms [38,39].

Our study used 14 antibiotics to treat the patients in prolonged ICU conditions; however, the isolated *Klebsiella pneumoniae* showed piperacillin-tazobactam 27 (55.1%), ceftazidime/avibactam 26 (53%), cefotaxime 27 (55.1%), imipenem 26 (53%), meropenem 26 (53%), and colistin 21 (42.8%), among the tested antibiotics. Therefore, treating such patients with the above-mentioned antibiotics will not be more effective and it may aggravate the disease conditions until and unless they are given a new generation of antibiotics (Figures 1 and 2). On a worldwide basis, immediate action is required to address the threat posed by carbapenem-resistant *Klebsiella pneumoniae*. Additionally, it causes several nosocomial illnesses, most notably respiratory tract infections; carbapenem-resistant *K. pneumoniae* is becoming a threat to public health. Exclusively, if carbapenem-resistant *K. pneumoniae* is the cause of those infections, hospitalized ICU patients are more likely to get *K. pneumoniae* infections [40]. Moreover, carbapenems activate through the inhibition of transpeptidases, which halts the creation of the structural component peptidoglycan; the β-lactam antibiotics, referred to as carbapenems, lyse cells. A study that looked at 49 studies found that the proportions of *K. pneumoniae* and *E. coli* resistant to carbapenem were 24.0% (95% confidence interval [CI] 18.0-31.0) and 5.0% (95% CI 2.0-8.0), respectively. *E. coli* and *K. pneumoniae* have evolved carbapenem resistance the most frequently due to the blaOXA-48 gene [41]. Notably, tigecycline remained highly effective against the resistant isolates, suggesting that this agent may offer a promising therapeutic alternative for emerging antibiotic-resistant Klebsiella pneumoniae.

5. Conclusion

The occurrence of ESBLs and carbapenemase production in *Klebsiella pneumoniae* in the intensive care unit is concerning, with isolates frequently carrying multiple antibiotic-resistant genes. ESBLs and carbapenemase-producing *Klebsiella pneumoniae* demonstrated a higher rate of multidrug resistance and co-resistance to other non-beta-lactam antibiotics. In our study, tigecycline and amikacin were the most effective agents against both ESBL- and CPK-producing isolates. Healthcare professionals face a challenging problem in handling patients with hospital-acquired bacterial infections since these patients primarily require empirical care and experience worse results in case of postponed effective initial antimicrobial therapy. Antibiotic resistance evaluation and proper microbiologic investigation are indispensable for thwarting nosocomial infections.

Abbreviation

ICU: Intensive Care Unit; **ESBLs**: Extended-Spectrum Beta-Lactamases; **CRE:** Carbapenem-Resistant Enterobacterales; **DNA:** Deoxyribonucleic Acid; **NNIS**: Nosocomial Infections Surveillance; **CLSI**: Clinical and Laboratory Standards Institute; **MHA:** Mueller-Hinton agar; **CDT**: Combination disc-diffusion test; **CAZ:** Ceftazidime; **CTX:** Cefotaxime; **CIM:** Carbapenem inactivation method; **CPK:** Carbapenemase-Producing *Klebsiella pneumoniae*; **MDR**: Multidrug-resistant organisms; **CI:** confidence interval.

Conflict of interests

The authors declared no conflict of interest.

Consent for publications

The author read & approved the final manuscript for publication.

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Ethical Approval

The study has been approved by the Research Ethical Committee at Najran University under the number No: 20191203, Date: 10\12\2019.

Author Contribution

Abdullah I. Aedh contributed to the conceptualization, methodology, investigation, data analysis, and manuscript preparation.

Generative AI Statement

The author used generative AI tools, including Grammarly and QuillBot, to improve the language and clarity of this work and takes full responsibility for its accuracy and integrity.

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