

Original Research Article

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A retrospective chart review study on the prevalence of extended spectrum β -lactamases producing bacteria among ICU patients in a tertiary care hospital in Saudi Arabia

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ABSTRACT

Background: Antimicrobial resistance is a big concern that face the world. Every class of antibiotics agent has a unique resistant mechanism. The dominant mechanism for resistance to the β -lactam antibiotics in gram-negative bacteria is the production of β -lactamase. Extended-spectrum β -lactamases (ESBLs) production is an important mechanism which is responsible for the resistance to the third generation cephalosporins.

Methods: This is a retrospective study which was carried out in the intensive care unit department of King Fahad Specialist Hospital (KFSH), Buraydah, Kingdom of Saudi Arabia (KSA) to estimate the prevalence and associated risk factors of Extended-spectrum β -lactamase producing bacteria (ESBL) among Intensive care unit (ICU) patients.

Results: Our study showed that *K. pneumoniae* (50%) and *E. coli* (24.7%) were the most commonly isolated organisms as well as some high resistance rate to Meropenem and colistin. This rapid increase of resistance and decrease in sensitivity puts health care works at a serious problem and they must take urgent actions to face it.

Conclusions: Focusing more on the right use and good practice of antibiotics, such as prescribing and dispensing antibiotics only when they are needed according to the most recent guidelines, is also need of hour.

Keywords: ESBL, Antibiotic resistance, Antibiotic sensitivity, KFSH, Beta lactams

INTRODUCTION

Antimicrobial resistance is a big concern that face the world. Every class of antibiotics agent has a unique resistant mechanism. The dominant mechanism for resistance to the β -lactam antibiotics in gram-negative bacteria is the production of β -lactamase. Extended-spectrum β -lactamases (ESBLs) production is an important mechanism which is responsible for the resistance to the third generation cephalosporins. During the last 2 decades, ESBL producing gram-negative bacilli have emerged as a major challenge in many settings.¹ The ESBLs mediate

resistance to broad-spectrum cephalosporins e.g., ceftazidime, ceftriaxone and cefotaxime and aztreonam. The problems which are associated with ESBLs include multidrug resistance, difficulty in detection and treatment, and increased mortality. New study demonstrates that (Prior colonization was the main risk factor for subsequent infection, so proper use of antimicrobial agents and improved infection control methods must become health care priorities.² The objective of the present study was to estimate the frequency and sensitivity pattern of ESBL include *Acinetobacter baumannii* (*A. baumannii*), *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K.*

pneumoniae), *Proteus mirabilis* (*P. mirabilis*), *Pseudomonas aeruginosa* (*P. aeruginosa*) among Intensive care unit (ICU) patients in King Fahad Specialist Hospital (KFSH), Buraydah, Kingdom of Saudi Arabia. Recent study was conducted in KSA show that the infection with *E. coli* (62.7%) was the most common, followed by *K. pneumoniae* (23.6%), *P. mirabilis* (10.8%) and others with lower rates (2.8%).³ In other hand *A. baumannii* susceptibility to carbapenems showed a drastic reduction 2006, 2009 and 2012, the susceptibilities to meropenem and imipenem were 64-81.2%, 34.5-45.3%, and 8.3-11%, respectively.⁴

METHODS

Study design and population

A retrospective chart review study was performed at the intensive care unit of the King Fahd specialist hospital,

which is a tertiary hospital with 500 patient beds in Buraydah, Saudi Arabia. We screened all ICU admitted patients from January 2020 to June 2021. The data were retrieved from patients' medical records and Health information system (CareWare): age, gender, comorbidities, antibiotic use during the past 3 months, initial antibiotic therapy and length of ICU stay. Data from patients with the following characteristics were included in the analysis: (a) a positive culture for *Acinetobacter baumannii*, *E. coli*, *K. pneumoniae*, *proteus mirabilis* and *P. aeruginosa*; (b) clinical manifestations of infection; and (c) hospitalization and a complete clinical data set.

The infectious diseases include skin and soft tissue infection, pneumonia, bacteremia, and urinary tract infection which were defined. Oncology patients and those without complete medical records were excluded. If patient developed infections with two different micro-organisms we considered it as two samples (Figure 1).

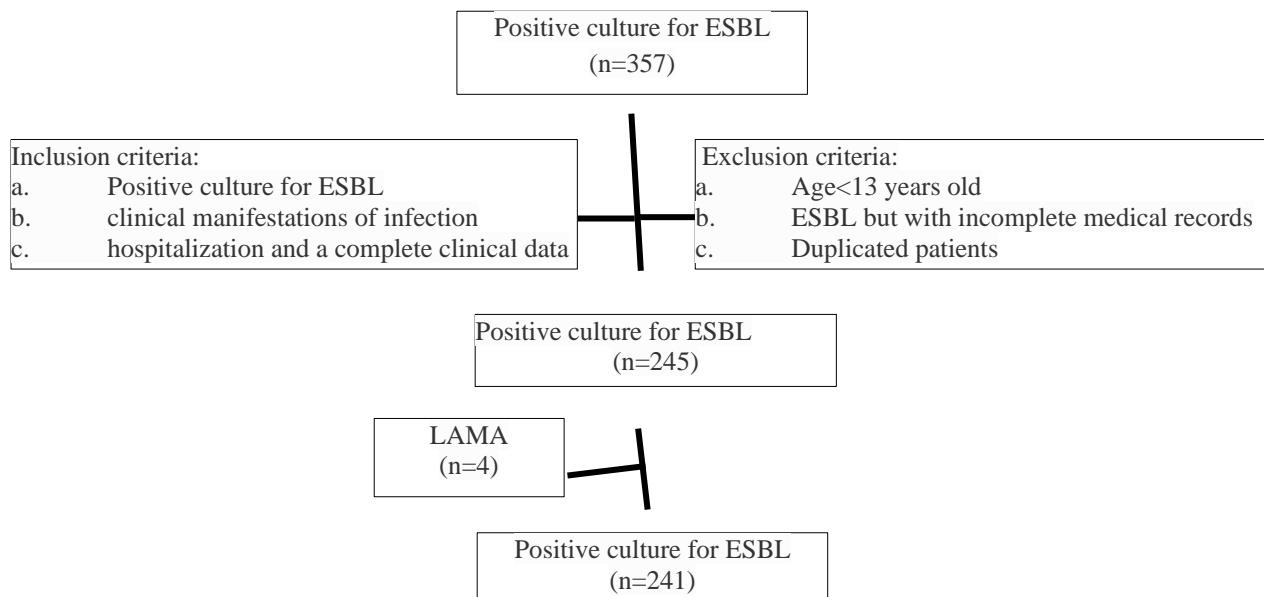


Figure 1: Flowchart of the case selection process.

Note: ESBL- Extended-spectrum beta-lactamase; and LAMA- Leave against medical advice.

Microbiological tests

Inoculum

0.5 McFarland at isolation (1-2 ml normal saline+colonies) was incubated using Mueller Hinton agar at 37°C for 16-20 hrs. ESBL production was determined using by disk diffusion method with ceftazidime and ceftazidime-clavulanic. Inclusion criteria isolates must be resistance to all cephalosporin and aztreonam.

The data were entered into Microsoft Excel, which cleaned it all up for analysis. Variables were then imported into SPSS (Statistical Package for Social Sciences, version 26) for statistical analysis. A total of 186 culture data were

included in the final analysis. Qualitative variables were expressed as frequencies and percentages.

Descriptive statistics were used to present demographics, infection rate, and isolation pattern of various organisms, sensitivity, and resistance pattern of antimicrobials.

Infection rates of various organisms were expressed in absolute numbers of the organisms with percentages. Sensitivity and resistance pattern tables and graphs were presented using percentages.

Fisher exact test was used to find the association between patient clinical outcomes and antimicrobial or combinations of antimicrobials used for different disease conditions. A column proportionality test was used to

determine the significant proportion of antimicrobials that resulted in a better clinical outcome.

A p value <0.005 was considered statistically significant.

RESULTS

A total of 186 cultures from 136 patients were included in the study (72 male and 64 female patients). Of these total patients, 34.9% of patients were older than 65 years of age, followed by 24.7% of patients in the 41-65 age group.

Table 1 shows the pattern of organism separation. *K. pneumoniae* (50%) and *E. coli* (24.7%) were the most commonly isolated organisms, while *Proteus mirabilis* (17.7%), *P. aeruginosa* (4.83%) and *Acinetobacter pneumoniae* (2.7%) were the least isolated organisms.

Table 2 shows the pattern of infection caused by different isolates. The most common infections were lower respiratory tract infections, or LRTIs, (29.03%) and wound/tissue infections (15.05%), followed by sepsis (12.90%), renal and CVD (8.06%). The organisms that caused LRTI the most were *K. pneumoniae* and *Proteus mirabilis*. In our study, *K. pneumoniae* causes 17.2% of lower respiratory tract infections and 4.84% of wound or tissue infections, followed by 6.9% of sepsis, 3.2% of renal complications, 5.9% of cardiovascular problems, 2.1% of gastrointestinal problems, 1.08% of urinary tract infections, thrombosis or embolisms, and haematological problems, respectively.

E. coli was the cause of 4.3% of wound/tissue infections and 4.3% of sepsis. And also, it leads to 3.76% lower respiratory problems and 3.2% renal problems. *Proteus mirabilis* was the third prevalent isolate present in the study patients, which caused 5.91% of LTRI's and 3.7% of wound/tissue infections.

Antibiotic sensitivity pattern of isolates

Klebsiella pneumoniae was most sensitive to tigecycline (75.3%), followed by colistine (71%), meropenem, imipenem and cilastatin (64.5% each), amikacin (41.9%), and ceftazidime avibactum (4.3%).

E. coli was most sensitive to meropenem (95.7%), followed by imipenem (87%), amikacin (76.1%), tigecycline (73.9%), and 63% colistine. Similarly, as demonstrated by the sensitivity pattern in Table 2, *proteus mirabilis* was more sensitive to meropenem (93.9%) followed by amikacin (81.8%).

Pseudomonas aeruginosa showed the highest sensitivity to amikacin (77.8%), followed by colistine (66.7%). *Acinetobacter pneumonia* showed 80% resistance to colistine and 60% to tigecycline.

Table 4 shows the rate of emergence of antibiotic resistant organisms to our basic antibiotics. *K. pneumoniae* showed resistance to colistin (7.5%), followed by meropenem

(21.5%), imipenem and cilastatin (5.4%), tigecycline (4.3%), and amikacine (1.1%).

E. coli (8.7%) and *Pseudomonas aeruginosa* (22.2%) showed resistance only to colistine. *Proteus mirabilis* showed resistance to meropenem (6.1%) only. *Acinetobacter pneumonia* showed resistance to colistine, meropenem, and tigecycline (20% each).

Meropenem reduced illness in 35.19 percent of patients with lower respiratory infections. Patients who used amikacin, ceftazidime-avibactam, colistin, and imipenem also showed improvement from respiratory illnesses.

In addition to that combination of colistin with meropenem (5.56%) and colistin (0.02%), among these, meropenem showed a significant reduction in their lower respiratory infections.

For the treatment of wound or tissue infection, meropenem (53.57%) was the most effective antimicrobial among the other users. When treating sepsis, meropenem (33.33%) was found to be the most effective antibiotic. Of the total sepsis cases, 12.50% of patients' conditions were improved by using imipenem, followed by the combination of meropenem and colistin, and tigecycline and imipenem and cilastatin (8.33% each).

Meropenem was found to be an effective antimicrobial for lower respiratory infections, wound/tissue infections, sepsis, renal complications, and cardiovascular disease. Both imipenem and meropenem reduced gastrointestinal problems (50%) each in patients. Meropenem was found to be the most effective in UTI (42.86 percent) and haematological (44.14 percent) patients (Table 5).

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Table 1: Frequency of microorganisms isolated.

Micro-organisms isolated	Frequency (%)
<i>Klebsiella pneumoniae</i>	93 (50%)
<i>Escherichia coli</i>	46 (24.7%)
<i>Proteus mirabilis</i>	33 (17.7%)
<i>Pseudomonas aeruginosa</i>	9 (4.83%)
<i>Acinetobacter pneumonia</i>	5 (2.7%)
Total	186

Table 2: Infection rate of various organisms (data are expressed in absolute numbers of the organisms with percentage values in parenthesis).

Organisms	LT- RI N (%)	Wou- nd/ti- ssue infe- ction N (%)	Sep-sis N (%)	Oth- ers N (%)	Re- nal N (%)	CVD N (%)	Haem- ato- log- ical N (%)	UTI N (%)	Thr- omb- osis and emb- oli- sms N (%)	GI N (%)	Carc- ino- ma N (%)	Me-n- ingit- is N (%)
<i>K. pneumonia</i>	32 (17.20)	9 (4.84)	13 (6.99)	11 (59.14)	6 (3.23)	11 (5.91)	2 (1.08)	2 (1.08)	2 (1.08)	4 (2.15)	0	1 (0.54)
<i>E. coli</i>	7 (3.76)	8 (4.30)	8 (4.30)	5 (2.69)	6 (3.23)	1 (0.54)	5 (2.69)	3 (1.61)	1 (0.54)	0	2 (1.08)	0
<i>Proteus mirabilis</i>	11 (5.91)	7 (3.76)	2 (1.08)	1 (0.54)	2 (1.08)	1 (0.54)	1 (0.54)	2 (1.08)	4 (2.15)	2 (1.08)	0	0
<i>Pseudomonas aeruginosa</i>	3 (1.61)	2 (1.08)	1 (0.54)	1 (0.54)	1 (0.54)	0	1 (0.54)	0	0	0	0	0
<i>Acinetobacter pneumonia</i>	1 (0.54)	2 (1.08)	0	0	0	2 (1.08)	0	0	0	0	0	0
Total	54 (29.03)	28 (15.05)	24 (12.90)	18 (9.68)	15 (8.06)	15 (8.06)	9 (4.84)	7 (3.76)	7 (3.76)	6 (3.23)	2 (1.08)	1 (0.54)

Note: LTRI: Lower respiratory tract infection; CVD: Cardio vascular disease; GI: Gastro intestinal; UTI: Urinary tract infection.

Table 3: Sensitivity pattern of isolates

Isolates	<i>K. pneumonia</i>	<i>E. coli</i>	<i>Proteus mirabilis</i>	<i>Pseudomonas aeruginosa</i>	<i>Acinetobacter pneumonia</i>
Meropenem	64.5% (60/93)	95.7% (44/46)	93.9% (31/33)	66.7% (6/9)	20% (1/5)
Colistin	71% (66/93)	63% (29/46)	6.1% (2/33)	66.7% (6/9)	80% (4/5)
Imipenem and cilastatin	64.5% (60/93)	87% (40/46)	48.5% (16/33)	55.6% (5/9)	20% (1/5)
Tigecycline	75.3% (70/93)	73.9% (34/46)	12.1% (4/33)	33.3% (3/9)	60% (3/5)
Amikacin	41.9% (39/93)	76.1% (35/46)	81.8% (27/33)	77.8% (7/9)	0% (0/5)
ceftazidime avibactam	4.3% (4/93)	2.2% (1/46%)	3% (1/33)	0% (0/9)	0% (0/5)

Table 4: Antibiotic resistance pattern of isolates.

Isolates	<i>K. pneumonia</i>	<i>E. coli</i>	<i>Proteus mirabilis</i>	<i>Pseudomonas aeruginosa</i>	<i>Acinetobacter pneumonia</i>
Meropenem	21.5% (20/93)	-	6.1% (2/33)	-	20% (1/5)
Colistin	7.5% (7/93)	8.7% (4/46)	-	22.2% (2/9)	20% (1/5)
Imipenem and cilastatin	5.4% (5/93)	-	-	-	-
Tigecycline	4.3% (4/93)	-	-	-	20% (1/5)
Amikacin	1.1% (1/93)	-	-	-	-
Ceftazidime avibactam	-	-	-	-	-

Table 5: Association between health condition and antimicrobials prescribed.

Health conditions	Antimicrobials	Health condition improved N (%)	Health condition not improved (Another antibiotic/combination)	P value
LTRI	Meropenem	19 (35.19)*	24 (44.44%)	<0.001
	Amikacin	1 (0.02)		
	Ceftazidime avibactam	1 (0.02)		
	Colistin	1 (0.02)		
	Imipenem and cilastatin	1 (0.02)		
	Meropenem+colistin	3 (5.56)		
	Tigecycline+meropenem	2 (3.07)		
	Tigecycline+colistin	1 (0.02)		
Wound/tissue infection	Meropenem	15 (53.57)*	3 (10.71%)	0.006
	Imipenem and cilastatin	4 (14.29)		
	Amikacin	1 (3.57)		
	Ceftazidime avibactam	1 (3.57)		
	Colistin	1 (3.57)		
	Imipenem and cilastatin +colistin	1 (3.57)		
	Tigecycline	1 (3.57)		
	Tigecycline+colistin	1 (3.57)		
Sepsis	Meropenem	8 (33.33)*	7(29.17%)	<0.001
	Imipenem and cilastatin	3 (12.50)		
	Meropenem+colistin	2 (8.33)		
	Tigecycline+imipenem and cilastatin	2 (8.33)		
	Tigecycline+meropenem	2 (8.33)		
CVD	Meropenem	6 (40)*	5 (33.33%)	<0.001
	Colistin	1 (6.67)		
	Imipenem and cilastatin	1 (6.67)		
	Imipenem and cilastatin+colistin	1 (6.67)		
	Tigecycline	1 (6.67)		
	Meropenem	4 (26.67)*		
Haemato-logical	Imipenem and cilastatin	2 (13.33)	8 (53.33%)	<0.001
	Meropenem+colistin	1 (6.67)		
	Meropenem	4 (44.14)		
UTI	Colistin	3 (33.33)	1 (11.11%)	0.222
	Tigecycline+meropenem	1 (11.11)		
Thrombosis and embolisms	Meropenem	3 (42.86)	3 (42.86%)	0.057
	Meropenem+amikacin	1 (14.29)		

Continued.

Health conditions	Antimicrobials	Health condition improved N (%)	Health condition not improved (Another antibiotic/combination)	P value
GI	Meropenem	3 (50)		
Carcinoma	Meropenem	1 (50)	1 (50%)	1
Meningitis	Other		1	

Note: *Column proportionality test significance; p values in the bold letter indicates statistical significance.

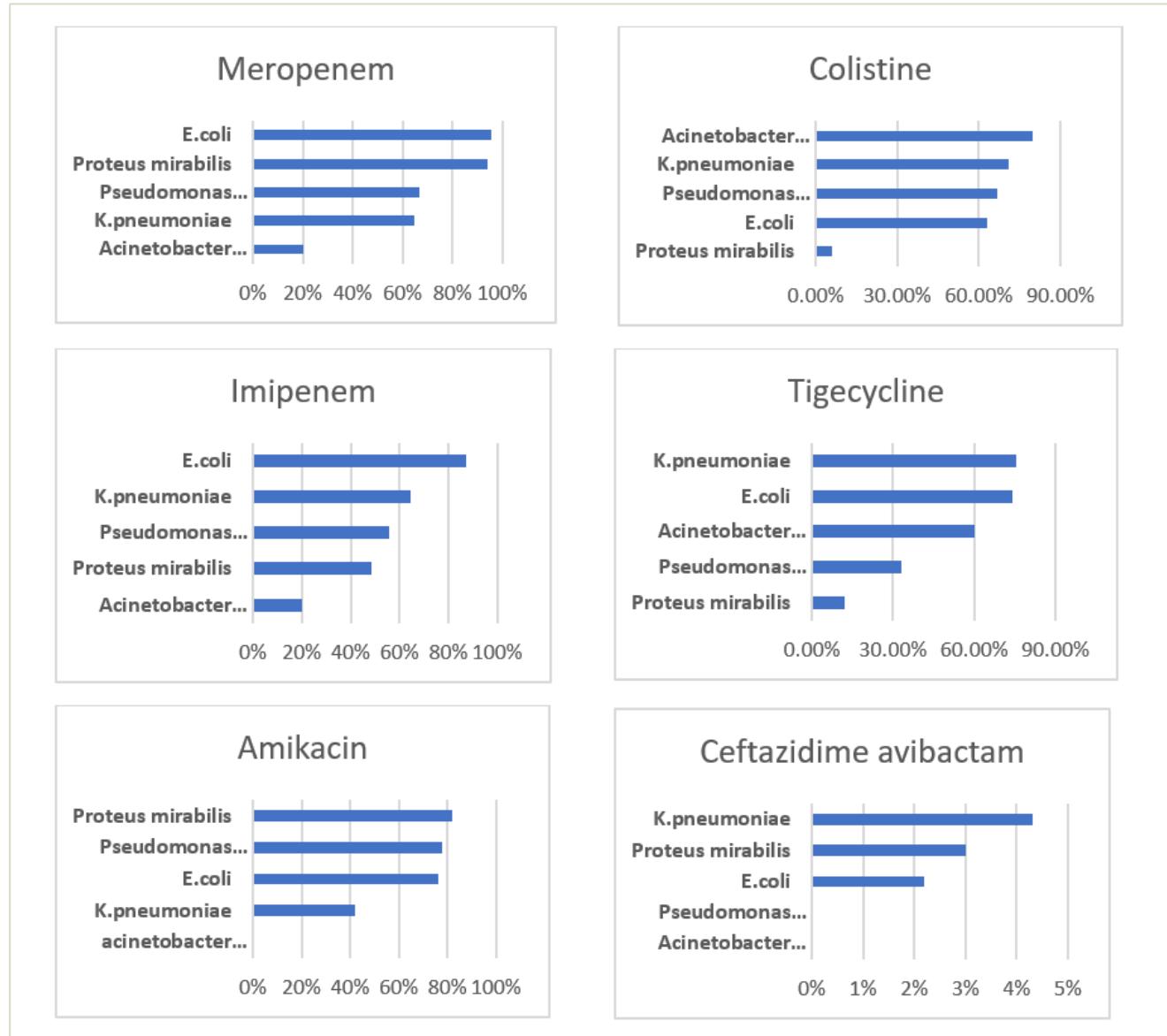


Figure 1: Sensitivity pattern of different antimicrobial agents.

DISCUSSION

The rapid spread of ESBL-producing bacteria is becoming a serious concern that has been described a pandemic. Antibiotic therapy, age 65 or older, recent hospitalization, prolonged hospital stay, recent surgery, recurrent UTIs, travel to other countries, severe illness, immobility, and

nursing home residency are all reported risk factors for carriage and infection.⁵

The results of our study depict that elderly individuals (those over 65 years old) are more susceptible to infection by bacteria that produce extended spectrum beta-lactamases (ESBLs) than younger patients. It also revealed that among other infection categories, lower respiratory

tract infections (29.03%) and tissue infections (15.05%) have the highest rates.

The two most common bacteria recovered from the patients in our investigation were *K. pneumoniae* (50%) and *E. coli* (24.7%).

A study carried out in a tertiary care hospital in Riyadh et al found that *Klebsiella pneumoniae* was found in 48.4 percent of the isolates, followed by *E. coli* and *Enterobacter cloacae* in 15.8 percent of the isolates which is similar to our findings.⁶

However, a study conducted by Shakya et al revealed 451 samples were found to have substantial bacteriuria, with 365 (80.9%) *E. coli*, 17 (3.8%) *Klebsiella pneumoniae*, and 3 (0.7%) *Klebsiella oxytoca*.⁷ MDR strains were detected in 236 (52.3%) of the 451 isolates. By using a combined disk test, 33 (91.7%) *E. coli* and 3 (8.3%) *Klebsiella spp.* were identified as ESBL producers.

Ceftazidime (100%), cefotaxime (89%), and cefuroxime (84%) were the most resistant antibiotics in the ESBL-producing *Klebsiella*, while, nitrofurantoin, and piperacillin/tazobactam (8 percent), imipenem (4%) exhibited the least resistance.⁸ However, in our study due to the delay in receiving the disk for Ceftazidime avibactam (March 2021), the results of Ceftazidime avibactam are inconclusive.

In our findings *Klebsiella pneumoniae* has a high level of resistance to meropenem and colistin. Similar results were revealed in a study conducted by Halaby et al in 2013 on enterobacteriaceae resistance to colistin in the ICU, which showed the emergence of colistin resistance in ESBL-producing *K. pneumoniae* strains subjected to extended colistin treatment.⁹

The rise of multidrug-resistant strains has made treating *K. pneumoniae* infections more difficult according to Aminul et al. Using traditional microbiological approaches, 150 *Klebsiella pneumoniae* were detected from several clinical samples.¹⁰ The majority of *Klebsiella pneumoniae* strains were resistant to multiple antibiotics (82 percent). Most-lactam antibiotics, aminoglycosides, ciprofloxacin, cotrimoxazole, carbapenem, piperacillin, and tazobactam were found to be resistant to the bacteria. A study by Ghasemi et al reveal that ICU patients have a high prevalence (60%) of ESBL-producing *K. pneumoniae*.¹¹ The most resistant and susceptible drugs identified in this investigation were ampicillin and imipenem, respectively, according to the major susceptibility tests of *K. pneumoniae*.

Meropenem was found to be the most effective antibiotic for lower respiratory tract infections, wound and tissue infections, renal, cardiovascular, septic, hematologic, and urinary tract infections in our investigation. In wound and tissue infections, sepsis, and cardiovascular infections, imipenem and cilastatin came in second to meropenem.

Later, meropenem and colistin in combination were found to be more effective than imipenem and cilastatin in treating lower respiratory tract infections, but less effective in treating sepsis and cardiovascular infections. This finding is consistent with Tamama et al who examined the mortality rates of 103 patients receiving piperacillin-tazobactam with 110 patients getting carbapenem, both with ESBL-producing bacterial infections.¹² When compared to empiric carbapenem therapy, individuals receiving empiric piperacillin-tazobactam had a 1.92 times higher risk of death. This means that patients with ESBLs who are given carbapenem have a better probability of surviving than those who are given other antibiotics.

Antibiotic resistance is a major concern in the treatment of infections in hospitals, particularly in ICUs. Cephalosporins, one of the most widely used and efficient antibiotics, are susceptible to resistance due to the formation of ESBLs. The incidence of ESBL-producing *E. coli* has risen over the world, and it is now a leading cause of treatment failure in ICUs. ESBL testing should be done on a regular basis to combat antibiotic resistance and successfully implement infection control strategies.¹³

Our study had few limitations. First, the data did not assess the provisional diagnosis or any other comorbidities. Other variables including immunocompromised patients and drug interactions. In addition, there were no follow up for renal or cardiac function to assess the outcome of the patients.

CONCLUSION

As ESBL-producing bacteria are growing increasingly resistant to antibiotics, infections are becoming more difficult to cure. As a result, health care providers must understand the clinical importance of these enzymes and implement appropriate infection-control strategies. Focusing more on the right use and good practice of antibiotics, such as prescribing and dispensing antibiotics only when they are needed according to the most recent guidelines, is also need of hour.

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Ethical approval: The study was approved by the General Directorate of Health Affairs, Ministry of Health of Al-Qaseem region

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