



International Journal of Multidisciplinary Research and Growth Evaluation.

The Epidemiology and Antimicrobial Resistance Patterns of ESBL-producing- *Klebsiella pneumoniae*: A Narrative Review in Saudi Arabia

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Article Info

ISSN (online): 2582-7138

Volume: 05

Issue: 06

November-December 2024

Received: 09-09-2024

Accepted: 10-10-2024

Page No: 77-84

Abstract

Klebsiella pneumoniae is gram-negative nonmotile bacilli that inhabit the gastrointestinal, and respiratory tracts. They opportunistically cause infections once breaching these barriers into internal tissues or when immunity is compromised. Throughout the years, *K. pneumoniae* has become multidrug-resistant (MDR) by acquiring the genes for various antibiotic resistance mechanisms. One of which is the production of extended-spectrum- beta-lactamase (ESBL) enzymes, which confer resistance against beta-lactam antibiotics such as penicillins and cephalosporins. ESBL-producing *K. pneumoniae* (ESBL-KP) is a notorious MDR bacteria, causing increasingly severe infections and leaving few treatment options available, leading to high morbidity and mortality worldwide. Numerous reports on ESBL-KP in Saudi Arabia have come out in the past two decades, most of which came from the central region, whereas the least reports came from the southern region. These reports evidently demonstrate the exponential rise in ESBL-KP rates in Saudi Arabia, and the spread of antibiotic resistance genes among *K. pneumoniae* strains in healthcare facilities where occasional outbreaks of ESBL-KP occur, and in communities as well. In this review, we will examine these reports to determine the prevalence and dissemination of ESBL-KP in Saudi Arabia, as well as the associated antibiotic susceptibility patterns, resistance mechanisms, and molecular characterization of ESBL enzymes.

DOI: <https://doi.org/10.54660/IJMRGE.2024.5.6.77-84>

Keywords: *Klebsiella pneumoniae*, ESBLs, beta-lactamase, Saudi Arabia, multidrug resistance

Introduction

Klebsiella pneumoniae is a gram-negative, encapsulated, nonmotile bacilli belonging to the *Enterobacteriaceae* family ^[1]. It was first discovered in the 19th century by Carl Friedlander, who isolated the bacterium from the lungs of a deceased pneumonia patient, and it was dubbed then Friedlander's bacterium ^[2]. *K. pneumoniae* is ubiquitously found in soil and water, as well as innocuously colonizing mucosal surfaces of the gastrointestinal, and respiratory tracts of humans and animals. However, once they breach these barriers and make their way into other tissues, numerous infections occur ^[1, 3]. This leads to serious infections such as pneumonia, urinary tract infections, liver abscesses, and wound infections, as well as life-threatening cardiovascular and blood-stream infections, including endocarditis and septicemia ^[4]. Over the last few decades, *K. pneumoniae* has become notoriously multi-drug resistant (MDR) to almost every available antibiotic through several antimicrobial resistance mechanisms, and causes infections with much more severity ^[5]. *K. pneumoniae* has become one of the most prevalent hospital-associated pathogens, accounting for one-third of infections caused by *Enterobacteriaceae* ^[6]. This has made treatable infections more difficult to treat, and complicated infections have become more life-threatening with limited treatment options, leading to high morbidity and mortality rates worldwide ^[7]. The versatile pathogenicity of *K. pneumoniae* could be attributed to the ability to evade the immune system and evolve into hypervirulent strains by acquiring antimicrobial resistance genes. In fact, *K. pneumoniae* are considered reservoirs of antimicrobial resistance genes, which could be transmitted to other gram-negative

bacteria. Furthermore, many detected genes in MDR bacteria were identified first in *K. pneumoniae* [8, 9].

The opportunistic nature of *K. pneumoniae* is maintained by its resilient behavior, and diverse resistance mechanisms, including alterations in the plasma membrane permeability, variations in antibiotics binding sites, and the adaptability of its metabolic pathways to adverse surrounding conditions [6]. Nonetheless, the two main culprits contributing to multi-drug resistance are efflux pumps [10], and the ability to produce various degradative enzymes that target, and destroy antibiotics, mainly β -lactamase enzymes [11]. β -lactamases are the most well-studied group of bacterial enzymes that are capable of hydrolyzing β -lactam antibiotics [Hamilton-Miller & Smith 1979 cited in; [12]. It has been hypothesized that penicillin-susceptible enzymes involved in cell wall synthesis are the precursors from which beta-lactamases have evolved [12]. In 1980, the ambler classification was first devised as a molecular and structural classification of β -lactamases utilizing the difference in amino acid sequences to group the β -lactamases into four similar groups from A through D [12, 13]. In 1983, the first report of β -lactamases capable of hydrolyzing extended-spectrum cephalosporins in *K. pneumoniae* strains was documented in Germany [14]. These enzymes were denoted as extended-spectrum β -lactamases (ESBL). ESBLs are classified as a group of class A β -lactamases [12]. They are encoded by genes found on bacterial plasmids [15], and are isolated from a wide range of *Enterobacteriaceae* family and other gram-negative and some gram-positive bacteria. Nowadays, over 150 types of ESBLs have been described worldwide [16]. However, the most commonly identified ESBL types are derived from TEM-1, TEM-2, SHV-1 [17], and CTX-M type ESBLs [18]. ESBL-producing *K. pneumoniae* were found to be resistant to penicillins, first-, second-, and third-generation cephalosporins, the monobactam aztreonam, and can be inhibited by β -lactamase inhibitors such as clavulanic acid. [19]. Resistance has also been reported against other antibiotic classes, such as aminoglycosides, cotrimoxazole [20], fluoroquinolones [21], and sulfonamides [22]. This article aims to review regional reports and evaluate the prevalence of ESBL-KP in Saudi Arabia. We will also investigate the antimicrobial profile pattern, and examine the molecular characterization of ESBLs and other mechanisms of resistance expressed by ESBL-KP strains in Saudi Arabia.

Materials and Methods

Literature pertaining to the prevalence, current updates, and molecular characterization of extended spectrum-beta-lactamase-producing *Klebsiella pneumoniae* in Saudi Arabia was thoroughly searched, using various search engines, including Google Scholar, PubMed, and Web of Science. The search was filtered for research articles from 2009 to 2023 conducted in Saudi Arabia. Keywords were: 'Klebsiella pneumoniae,' 'Enterobacteriaceae,' 'Saudi Arabia,' and 'Extended-spectrum-beta-lactamase.' In addition, articles concerning *Klebsiella pneumoniae*, antimicrobial resistance, and international studies on ESBL-producing *K. pneumoniae* were reviewed, to gain a broader perspective on the subject and compare local findings with others from around the world.

Epidemiology

Prevalence of ESBL-KP in Saudi Arabia

The rapid spread of ESBL-producing *Enterobacteriaceae*,

particularly *K. pneumoniae*, in Saudi Arabia poses a significant public health threat. It is predicted that there is a yearly increase of 38% in ESBL cases, with most reports coming from the central region [23] and the lowest reported in the southern region. In addition, various studies were carried out in other regions to assess and predict antibiotic susceptibility patterns, risk factors, and resistance mechanisms. Table 1 summarizes the prevalence of ESBL-KP in Saudi Arabian regions. Several reports from the western region demonstrated the rising rates of ESBL-KP in healthcare facilities. A study by Al Zahrani *et al.* in the Taif region reported a 17.65% isolation rate of ESBL-KP [24]. However, a 2021 study found that the rates of ESBL-KP have risen to 33.33% [25]. In Makkah region, A study from 2012 concluded a 37.1% rate of ESBL-KP isolation [26]. However, these rates have increased exponentially in the last decade, as demonstrated by Kabrah, A., who in 2022 identified that 41.6% of *K. pneumoniae* isolates were ESBL-KP [27]. These findings are supported by research spanning over eleven years, which observed a significant increase in resistance against all classes of antibiotics [28]. Similarly, a more recent study in Jeddah found the prevalence of ESBL-KP was approximately 37% [39]. Meanwhile, Mogahid and others in Medina found in their study that the rate of ESBL-KP among other *K. pneumoniae* strains was 21.84% [29]. The high rates of ESBL-KP and the dissemination of antibiotic resistance in the western region could be linked to the mass religious gatherings in the Hajj and Umrah seasons, during which millions of people from around the world visit Makkah and Madina [30]. Few reports investigating ESBL-KP were reported in the southern region. For instance, a study looked into uropathogens isolated from adult females in Najran region found only one ESBL-KP isolate out of 123 isolated gram-negative bacteria [31]. However, the ESBL-KP rates increased to 19.4% in Al-Baha [31], and 54% in Khamis Mushait [32]. Furthermore, Almogbel and others from Hail region were the first to report an outbreak of ESBL-KP in a neonatal intensive care unit in the northern region, where 87.5% of *K. pneumoniae* isolates were ESBL-producing strains [33]. In a separate cross-sectional study from Al-Jouf region, an analysis of bloodstream infection revealed that *K. pneumoniae* was the most common causative pathogen (61%), with 19.05% found to be ESBL-KP [34]. Other studies in Hafer Albatan and Turaif regions reported ESBL-KP isolation rates of 22.8% and 27%, respectively [35, 36]. Whereas a high rate of 46.67% has been reported by Alqahtani and others in Tabuk [37]. In an earlier study from Al-Ahsa in the eastern region, it was found that 38.14% of 97 ESBL-producing isolates were ESBL-KP [38]. In contrast, 98% of *K. pneumoniae* isolates were producing ESBLs in a recent study from the Al-Hofuf region [39]. In Dammam, an earlier report indicated a lower ESBL-KP rate of 25.2% [40]. However, a study published a few years later reported an increase in ESBL-KP incidences in hospitals where the isolation rate reached 42.1% [41]. Varying data from the central region had been reported in the past. For instance, a 2009 study in Al-kharj region found that the rate of ESBL-KP was as low as 10.6% [42]. However, a study conducted in Riyadh the same year concluded a much higher rate of 55% [43]. The reports on ESBL-KP in Riyadh in the following years were consistent with previous findings; ranging between 35% [44, 45] and 90.1% [46]. Recently, the lowest rate of ESBL-KP in Saudi Arabia was reported from Al-Jouf region at 19.05%. Simultaneously, the highest rate of 98% was recorded in both

Riyadh and Al-Hofuf regions. The aforementioned data demonstrate the considerable variation in the dissemination of ESBL-KP between regions of Saudi Arabia. This could be due to the size of the samples investigated, and the increased consumption of different antibiotics at the time of sample collection at different healthcare facilities [40]. Nonetheless, these reports cemented the fact that ESBL-KP rates had

increased drastically compared to the past two decades. In comparison with international data, the rate of ESBLs in Saudi Arabia is considered in the middle of the spectrum. High rates were reported globally, as in Russia, at 60.8% [47]. While other countries reported comparatively low rates, such as 8.6% in the Netherlands [48].

Table 1: A summary of regions of Saudi Arabia and the rates of ESBL was reported.

Region of Research	Year of publishing	Total no. of <i>K. pneumoniae</i> isolates	No. of ESBL-KP isolates (rates).	Reference
Taif	2020	30	33.33%	[25]
	2016	16	18.75%	[24]
	2018	83	23.6%	[49]
Makkah	2012	191	22.5%	[26]
	2022	175	8.57%	[27]
	2023	9014	22%	[28]
Medina	2016	87	21.84%	[29]
Jeddah	2021	200	37.5%	[50]
Najran	2021	10	10%	[51]
Albaha	2020	67	19.40%	[31]
Khamis Mushayt	2015	43	53.49%	[32]
Ha'il	2021	48	87.5%	[33]
Aljouf	2020	63	19.05%	[34]
	2022	79	36.7%	[52]
Hafer Albatin	2014	412	22.8%	[35]
Turaif	2023	37	27%	[36]
Tabuk	2023	10	46.67%	[37]
Al-Ahsa	2009	35	17.14%	[53]
Al-Ahsa	2013	97	38.14%	[38]
Al-Hofuf	2021	78	98%	[39]
Dammam	2014	107	25.2%	[40]
	2019	352	42.1%	[41]
Al-kharj	2009	328	10.37%	[42]
Riyadh	2009	400	55%	[43]
	2014	98	37.75%	[44]
	2015	77	35%	[45]
	2017	21	90.5%	[46]
	2018	294	18.37%	[54]
	2020	50	98%	[55]

Antibiotic Susceptibility Patterns associated with ESBL-producing *K pneumoniae*

Several reports detailing antibiotic susceptibility profiles of ESBL-KP from different regions in Saudi Arabia were collected and analyzed to demonstrate the pattern of increasingly rising antimicrobial resistance, which could be seen across all antibiotic classes. For decades, ESBL-KP has been increasingly developing resistance against commonly used beta-lactam antibiotics; more specifically, ampicillin and cephalosporins have shown low reactivity against ESBL-KP. For ampicillin, numerous studies have proven 100% resistance. [25, 26, 31, 32, 38, 49, 50, 54], while other strains showed resistance greater than 90% [24, 27-29, 51, 56]. Intermediate resistance of 20% to 42% was detected against amoxicillin/Clavulanate [27, 31, 49, 50]. However, other studies showed that this percentage has risen to 91% [39, 43, 57]. Similarly, high resistance was reported against piperacillin, with most tested strains being resistant. [38, 43, 54, 58], while others reported resistance of at least 80% of tested ESBL-KP [25, 56].

Cephalosporins efficacy has greatly decreased due to the rising resistance of ESBL-KP. With first-generation cephalosporins, 100% resistance in test strains was detected while testing Cephalothin [50] and Cefazolin [38, 49, 54], whereas other studies recorded resistance of at least 90% of

strains for both antibiotics [29, 34, 57]. Second-generation cephalosporins were similar; with cefuroxime, the resistance rate was at least 73% [34, 56-58], soaring to 100% in several other studies [38, 49, 54]. Likewise, the resistance to third-generation cephalosporins is very well-documented. Ceftazidime and cefotaxime have been used extensively as indicators for ESBL production, and several studies have detected a 100% rate of resistance for both antibiotics [24, 44, 49, 54]. While resistance rates ranging between 70% to 95% for ceftazidime [27, 28, 34, 37, 39, 43, 46, 57, 58], and between 70% to 97% for cefotaxime [27, 28, 31, 34, 37, 43, 50, 56] were reported. Moreover, high resistance to the fourth-generation cephalosporin cefepime has been documented, with many studies highlighting rates ranging from 68% to 93% [27, 28, 34, 43, 46, 52, 56-58]; others reported complete resistance [24, 49, 54]. The monobactam aztreonam has become increasingly less effective against ESBL-KP strains as higher resistance rates starting from 79% [29, 34, 39, 46, 57] and reaching 100% were detected [44, 49]. Fluoroquinolones are also facing the same challenge; several studies have shown high resistance to ciprofloxacin, which has reached 86% [40, 46, 50], while other studies have shown moderate resistance between 48% and 61% [27, 49, 56]. Additionally, a higher resistance of 98% against Chloramphenicol was reported [50]. Another combination antibiotic, trimethoprim-sulfamethoxazole, has recorded

decreased susceptibility to 33% [43] most studies had proven high resistance rates starting from 72% to 93% [27-29, 40, 50, 57]. Recent reports have shown that resistance against Nitrofurantoin was at 75% [58] and reached 100% in other studies [24]. Aminoglycosides have been used widely to tackle resistance to first-, second-, and third-generation cephalosporins and in cases with carbapenemase production. However, ESBL-KP strains have started developing resistance to various aminoglycosides. Low to moderate resistance rates between 11% and 57% for gentamicin have been routinely reported [27-29, 31, 41, 46, 49, 56-58]. In recent years, higher resistance between 76% [46] and 100% was observed [33, 44]. Unlike gentamicin, reports on Amikacin have shown consistently effective against ESBL-KP, with almost all ESBL-KP strains being susceptible to amikacin in several conducted studies [31-33, 40, 41, 54]. Nonetheless, low to moderate rates of resistance between 10% to 47% were documented as well [28, 29, 43, 44, 46, 49, 56, 57]. In addition to amikacin, imipenem, tigecyclines, and colistin were found to have the highest effectiveness against ESBL-KP [25, 28]. Despite reports indicating high susceptibility of ESBL-KP strains reaching a rate of 100% [33, 38, 44, 49], Resistance against imipenem investigated in more recent studies showed low to moderate resistance rates between 6.6% and 52% [25, 27, 46, 50, 57]. Other reports found that this percentage has risen over the past decade, reaching over 60% [28, 34, 52]. Meropenem was shown to be slightly more active against ESBL-KP than imipenem. Numerous reports indicated that almost all ESBL-KP test strains were susceptible to meropenem [32, 38, 49], with low resistance between 32% and 43% [46, 57]. However, A 2020 study examining outbreaks of ESBL-KP in intensive care units found that 61% of isolated strains were resistant to meropenem [58]. On the other hand, ertapenem had reports of varying resistance; low to moderate rates between 7% and 65% were reported by different clinical studies [46, 54, 57, 58]. A 2022 study reported that resistance to ertapenem has reached 86% [52]. The latest finding confirms that ertapenem resistance is becoming increasingly linked with ESBL production in *K. pneumoniae*. Tigecycline is a common antibiotic of choice against ESBL-KP and carbapenemase-producing *K. pneumoniae*, which retained its efficacy against these bacteria in the past decade with low rates of resistance reported between 8% to 30% [28, 49, 57] and proven efficiency reaching 100% against ESBL-KP [24, 31, 34, 38, 41, 44, 46]. Colistin have also maintained high effectiveness against ESBL-KP at 100% [31, 44], with low resistance detected from 5% to 25% [28, 46]. However, the isolation of colistin-resistant *K. pneumoniae* has increased in the past years, as a 2020 study found that the susceptibility of test isolates had decreased to 65% [58]. These findings, along with continuous hospital reports, warrant immediate action to prevent the rising resistance and dissemination of resistant strains and further escalation in the severity of infections.

Risk Factors contributing to the acquisition and spread of ESBL-KP reported in Saudi Arabia

In our research, we have observed several factors that were closely associated with or directly causing ESBL-KP infections. Several studies from Saudi Arabia found that higher incidences of ESBL-KP infection and antibiotic resistance were observed in male patients in comparison to female patients [25, 50]. Moreover, there was a distinction between the antibiotic resistance profiles between genders. Although these findings were found to be statistically

insignificant [25]. Similar observations were made by other studies where higher rates of ESBL-KP isolates were recovered from male patients more than female patients [27, 28, 35, 41, 54, 58-61]. In addition, there was an association between the infection site and the rate of ESBL-KP isolation. Lagha and others reported the highest ESBL-KP rate in sputum specimens, followed by urine, blood, and wound specimens, despite not finding any statistical significance [25]. Other studies supported the observation of sputum being the most common specimens from which ESBL-KP were isolated, followed by blood and urine specimens [27, 58]. By contrast, most studies found that the majority of ESBL-KP isolates were recovered from urine specimens [26, 29, 35-38, 45]. However, an 11-year study on ESBL-KP in Makkah found that the highest rates of ESBL-KP were isolated from blood specimens, followed by sputum specimens [28]. This suggests the high possibility of ESBL-KP being one of the leading causes of bloodstream and respiratory tract infections [34, 62]. These conflicting results could be due to variations in research settings; in some studies, samples were obtained from general hospitals, while other studies were carried out in community settings [36]. In addition, older patients were more predisposed to the detrimental infections of ESBL-KP [34, 35, 41], as one study found that the average age of most affected individuals was 59.3 ± 2.8 [28]. This could be due to their weakened immune system, which is incapable of suppressing such infections. Furthermore, prolonged hospitalization appears to be one of the important factors contributing to acquiring ESBL-KP infections, as found in many studies [28, 34-36, 58]. Also, the overconsumption of antibiotics coupled with the lack of stewardship over the use of broad-spectrum antibiotics, as well as previous history of using cephalosporins and quinolones, were all strongly linked to the spread and persistence of ESBL-KP [36, 44, 53, 63]. Another significantly important factor contributing to the spread of infections and antibiotic resistance genes is mass religious gatherings during Hajj and Umrah seasons, which has facilitated the spread of antibiotic-resistant pathogens, especially ESBL-KP [30]. Most frequently, these genes co-exist in strains more than being carried individually. The co-existence of SHV- and CTX-M type ESBLs confer higher resistance than either of these genes alone, and TEM-type ESBLs were the least selected genes [39].

Antibiotic Resistance mechanisms

The multi-antibiotic resistance exhibited by ESBL-KP is acquired through the transmission of plasmid-encoded genes for ESBLs. Since the early discovery of ESBLs, most detected enzymes were derived from mutations of class A TEM-1, TEM-2, and SHV-1 type β -lactamases, which are closely related according to amino acid sequence homology. However, several other types which were not TEM- or SHV-derived were discovered [17], notably class A CTX-M β -lactamases [18]. In the last few decades, there has been a shift in the ESBLs population as CTX-M-type β -lactamases are becoming the most predominant ESBLs in clinical isolates, followed by SHV- and TEM-type ESBLs. High rates of CTX-M ESBLs were also reported globally; 83% in Spain [64], 82.1 % in India [65], 100% in China [66], 30% in Iran [67], 51% in Canada [68], 49% in Brazil [69], 40.4% in Kenya [70], and 34.9% in Russia [47]. In Saudi Arabia, several reports were made pertaining to the molecular pattern and prevalence of ESBLs. For instance, one study concluded that 98% of isolates harbored CTX-M ESBL genes [55]. Other studies have

also demonstrated this high prevalence of CTX-M-type ESBLs in *K. pneumoniae* [29, 40, 50]. As well as the co-expressions of ESBLs and other β -lactamases that are classified as carbapenemases, such as OXA-48, NDM, VIM, IMP, and KPC-type β -lactamases [52, 55, 61]. And AmpC β -lactamases genes such as blaCYM-2 were also found in ESBL-KP. Furthermore, several other studies detected the co-expression of ESBLs and other antibiotic-resistance genes, such as the loss of one or more porin channels. These are non-specific porin channels responsible for transferring antibiotics into the bacterial cell, and their downregulation could lead to pan-drug resistance [52]. The absence of OmpK35 and/or OmpK36 porin channels was detected in ESBL-KP strains [43, 52]. The loss of porins could account for the acquired carbapenem resistance in ESBL-KP strains [71]. This further supports the hypothesis stating that porin loss is a significant contributor to antibiotic resistance, especially β -lactam antibiotics [72]. In addition, the multidrug efflux pump systems contributed greatly to antibiotic resistance. A study investigating MDR *K. pneumoniae* found that most isolates (93.33%) harbored the acrAB gene (multidrug efflux pump systems), while few isolates had the mdtK gene encoding for the multidrug efflux pump system. Moreover, The tolC gene coding for the transport channel was prevalent among *K. pneumoniae* at 83.33% [25]. There is also a significant correlation between the expression of acrAB gene, which codes for both a periplasmic protein (AcrA) and a transporter protein (AcrB) [73], and the tolC gene that results in TolC, which is the outer membrane channel. This channel and periplasmic and outer membrane proteins work cooperatively to expel metabolites and antibiotics, contributing to antibiotic resistance [74].

Molecular characterization of ESBLs reported in Saudi Arabia

Numerous studies were carried out in Saudi Arabia to investigate the molecular patterns behind antibiotic resistance mechanisms in ESBL-KP. Generally, CTX-M types ESBLs are becoming the most predominant ESBLs in clinical isolates, followed by SHV- and TEM-type ESBLs [16, 29, 46]. Molecular analysis revealed that 80.4% of ESBLs were CTX-M type ESBLs [26]. The first detection of blaCTX-M genes in Saudi Arabia was reported by Al-Agamy and others in Riyadh, where high rates of blaCTX-M-1 and blaCTX-M-9 genes were found in ESBL-KP isolates [43]. The same findings of blaCTX-M-1 prevalence were also reported in other regions [24, 40, 45, 46, 52]. Among CTX-M group 1 β -lactamases genes, blaCTX-M-15 has become the most commonly detected ESBL causing antibiotic resistance in Saudi Arabia and globally [23, 40, 44, 55, 75]. BlaCTX-M-15 genes were reported in the majority of ESBL-KP isolates for the first time in an outbreak in NICU in Hail region, As well as blaSHV-12 and blaTEM-1 genes were co-expressed at a higher rate, conferring resistance to oxyimino-cephalosporins, and faster dissemination of infections [33]. This could explain the reason behind the outbreak, as the rapid dissemination and prevalence of ESBL-KP has been globally associated with the spread of blaCTX-M-15 genes [76]. Moreover, it has been reported the presence of CTX-M group 1 β -lactamases which are variants of blaCTX-M-15, including blaCTX-M-3, blaCTX-M-57, and blaCTX-M-82 genes, as well as blaCTX-M-27 which is a variant of blaCTX-M-14 and belongs to CTX-M group 9 in ESBL-KP isolates for the first time in Saudi Arabia [44]. These ESBL variants were further

confirmed by Al-Agamy and others in later years [46]. CTX-M-15 ESBLs were also the predominant ESBLs in Egypt, the United Arab Emirates, and Kuwait [43]. Furthermore, blaSHV-12, blaSHV-28, and blaSHV-5 were also among the most commonly detected SHV- type β -lactamases in Saudi Arabia, and blaTEM-25 and blaTEM-52 were found in fewer isolates [44, 52]. A study by Alqahtani and others was able to detect that blaSHV genes, including blaSHV-12, blaSHV-1, and blaSHV-5, were the most prevalent β -lactamases followed by blaCTX-M, with blaTEM-1 having the lowest rate. Other studies had found that blaSHV was more prevalent β -lactamases in ESBL-KP isolates [38, 40, 44, 45]; blaTEM was also detected, however, to a lesser degree [38, 44]. In several studies, the co-expression of CTX-M, SHV, and TEM was a common occurrence, with higher rates of the coexistence of CTX-M and SHV ESBLs [39, 40].

Conclusion

In the past two decades, ESBL-KP isolation has become a common occurrence in healthcare facilities around Saudi Arabia. In addition to the rising rates of ESBL-KP infections, reports have exhibited the dissemination of resistance genes, causing the bacteria to become resistant to a wider range of antibiotics to which they were previously susceptible. Various factors contribute to the widespread spread of ESBL-KP, including the lack of stewardship over antibiotics use, and the ease with which ESBL genes emerge and disseminate among *K. pneumoniae* strains. Numerous studies examining routine cases and in-hospital outbreaks of ESBL-KP found that CTX-M-15-type ESBLs were the most common ESBLs in Saudi Arabia, which is responsible for faster dissemination, and has a higher association with other resistance mechanisms, including the expression of several carbapenemase genes. Therefore, preventative measures, including strict infection control practices among healthcare providers, especially those working with hospitalized patients, are crucial, as well as early detection and treatment to contain the infection. Carbapenems and carbapenem-comprised treatment regimens, colistins and tigecycline, are the current treatment options for ESBL-KP. However, the rise of carbapenem and colistin resistance genes in ESBL-KP and other Enterobacteriaceae is a huge public health risk that necessitates finding new and efficient antimicrobial treatments.

References

1. Bagley ST. Habitat association of Klebsiella species. Infect Control. 1985;6(2):52-58.
2. Friedlaender C. Ueber die Schizomyceten bei der acuten fibrösen Pneumonie. Archiv für Pathologische Anatomie und Physiologie und für Klinische Medicin. 1882;87(2):319-324.
3. Dao TT, Liebenehm S, Hohmann T, *et al.* Klebsiella pneumoniae oropharyngeal carriage in rural and urban Vietnam and the effect of alcohol consumption. PLoS One. 2014;9(3).
4. Podschun R, Ullmann U. Klebsiella spp. as nosocomial pathogens: epidemiology, taxonomy, typing methods, and pathogenicity factors. Clin Microbiol Rev. 1998;11(4):589-603.
5. Vivas R, Barbosa A, Dolabella SS, *et al.* Multidrug-resistant bacteria and alternative methods to control them: an overview. Microb Drug Resist. 2019;25(6):890-908.

6. Tenover FC. Mechanisms of antimicrobial resistance in bacteria. *Am J Infect Control*. 2006;34(5 Suppl 1)–10; discussion S64-73.
7. Boucher HW, Talbot GH, Bradley JS, *et al*. Bad bugs, no drugs: no ESCAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(1):1-12.
8. Lam MMC, Wick RR, Wyres KL, *et al*. Genetic diversity, mobilisation and spread of the yersiniabactin-encoding mobile element ICEKp in *Klebsiella pneumoniae* populations. *Microb Genom*. 2018;4(9).
9. Holt KE, Wertheim H, Zadoks RN, *et al*. Genomic analysis of diversity, population structure, virulence, and antimicrobial resistance in *Klebsiella pneumoniae*, an urgent threat to public health. *Proc Natl Acad Sci U S A*. 2015;112(27)-81.
10. Zhong HQ, Hu WJ, Yan BL, *et al*. Influence of induced ciprofloxacin resistance on efflux pump activity of *Klebsiella pneumoniae*. *J Zhejiang Univ Sci B*. 2013;14(9):837–843.
11. Pages JM, Masi M, Barbe J. Efflux pump, the masked side of beta-lactam resistance in *Klebsiella pneumoniae* clinical isolates. *PLoS One*. 2009;4(3).
12. Ambler RP. The structure of beta-lactamases. *Philos Trans R Soc Lond B Biol Sci*. 1980;289(1036):321–331.
13. Hall BG, Barlow M. Revised Ambler classification of beta-lactamases. *J Antimicrob Chemother*. 2005;55(6):1050–1051.
14. Knothe H, Shah P, Krcmery V, *et al*. Transferable resistance to cefotaxime, ceftiofloxacin, cefamandole and cefuroxime in clinical isolates of *Klebsiella pneumoniae* and *Serratia marcescens*. *Infection*. 1983;11(6):315–317.
15. Petrocheilou V, Sykes RB, Richmond MH. Novel R-plasmid-mediated beta-lactamase from *Klebsiella aerogenes*. *Antimicrob Agents Chemother*. 1977;12(1):126–128.
16. Bradford PA. Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. *Clin Microbiol Rev*. 2001;14(4):933–951, table of contents.
17. Livermore DM. Beta-lactamases in laboratory and clinical resistance. *Clin Microbiol Rev*. 1995;8(4):557–584.
18. Bonnet R. Growing group of extended-spectrum beta-lactamases: the CTX-M enzymes. *Antimicrob Agents Chemother*. 2004;48(1):1–14.
19. Rupp ME, Fey PD. Extended spectrum β -lactamase (ESBL)-producing *Enterobacteriaceae*. *Drugs*. 2003;63(4):353-365.
20. Maragakis LL, Perencevich EN, Cosgrove SE. Clinical and economic burden of antimicrobial resistance. *Expert Rev Anti Infect Ther*. 2008;6(5):751-763.
21. Wiener ES, Berger K, Landrum L, *et al*. Are fluoroquinolones appropriate for the treatment of extended-spectrum β -lactamase-producing Gram-negative bacilli? *J Pharm Technol*. 2016;32(1):16–21.
22. Kashefieh M, Tajbakhsh E, Rahbar M, *et al*. The molecular epidemiology of resistance to antibiotics among *Klebsiella pneumoniae* isolates in Azerbaijan, Iran. *J Trop Med*. 2021;2021:9195184.
23. Alqasim A, Abu Jaffal A, Alyousef AA. Prevalence and molecular characteristics of sequence type 131 clone among clinical uropathogenic *Escherichia coli* isolates in Riyadh, Saudi Arabia. *Saudi J Biol Sci*. 2020;27(1):296-302.
24. Alzahrani AK, Mostafa FM, Said HA, *et al*. Antibiotic resistance profile and random amplification typing of β -lactamase-producing *Enterobacteriaceae* from the local area of Al-Taif and nearby cities in Saudi Arabia. *Asian Biomedicine*. 2016;10(3):219-228.
25. Lagha R, Albidewi IA, Karkar A, *et al*. Molecular characterization of multidrug resistant *Klebsiella pneumoniae* clinical isolates recovered from King Abdulaziz Specialist Hospital at Taif City, Saudi Arabia. *J Infect Public Health*. 2021;14(1):143-151.
26. Ashgar AH. Antimicrobial resistance of Gram-negative bacilli causing infections in intensive care units in Makkah hospitals- Saudi Arabia. *J Am Sci*. 2012;8(11).
27. Kabrah A. Extended-spectrum beta-lactamase and carbapenem-resistant Gram-negative pathogens in Makkah, Saudi Arabia. *Ethiop J Health Sci*. 2022;32(6):1221–30.
28. Jalal NA, Bahashwan SA, Albarqi HA, *et al*. Prevalence and antibiogram pattern of *Klebsiella pneumoniae* in a tertiary care hospital in Makkah, Saudi Arabia: an 11-year experience. *Antibiotics (Basel)*. 2023;12(1).
29. Elhassan MM, Ozbazk HA, Hemeg HA, Ahmed AA. Dissemination of CTX-M extended-spectrum β -lactamases (ESBLs) among *Escherichia coli* and *Klebsiella pneumoniae* in Al-Madenah Al-Monawwarah region, Saudi Arabia. *Int J Clin Exp Med*. 2016;9(6):11051–7.
30. Memish ZA, Stephens GM, Steffen R, Ahmed QA. Emergence of medicine for mass gatherings: lessons from the Hajj. *Lancet Infect Dis*. 2012;12(1):56–65.
31. Alzahrani MA, Ali MS, Anwar S. Bacteria causing urinary tract infections and its antibiotic susceptibility pattern at tertiary hospital in Al-Baha region, Saudi Arabia: a retrospective study. *J Pharm Bioallied Sci*. 2020;12(4):449–56.
32. El-Kersh TA, Abahussain SA, Alghamdi SA, *et al*. Prevalence and risk factors of community-acquired urinary tract infections due to ESBL producing Gram-negative bacteria in an Armed Forces Hospital in Southern Saudi Arabia. *Glob Adv Res J Med Med Sci*. 2015;4(7):321–30.
33. Almogbel M, Alyami M, Alfifi L, *et al*. CTX-M-15 positive *Escherichia coli* and *Klebsiella pneumoniae* outbreak in the neonatal intensive care unit of a maternity hospital in Ha'il, Saudi Arabia. *Infect Drug Resist*. 2021;14:2843–9.
34. Bandy A, Almaeen AH. Pathogenic spectrum of bloodstream infections and resistance pattern in Gram-negative bacteria from Aljouf region of Saudi Arabia. *PLoS One*. 2020;15(6).
35. Kandeel A. Prevalence and risk factors of extended-spectrum β -lactamase-producing *Enterobacteriaceae* in a general hospital in Saudi Arabia. *J Microbiol Infect Dis*. 2014;4(2):50–4.
36. El-Masry EA, Aljohani AM, Abdelsalam SF, *et al*. Prevalence of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* among clinical isolates in Turaif general hospital, northern borders- Saudi Arabia. *J Infect Dev Ctries*. 2023;17(4):477–84.
37. Alqahtani TMT, Alasmari FA, Albashri AS, *et al*. Study of plasmid-mediated extended-spectrum beta-lactamase-producing clinical strains of *Enterobacteriaceae* from Tabuk region. *Cureus*. 2023;15(6).

38. Alsultan AA, Aboulmagd E, Amin TT. ESBL-producing *E. coli* and *K. pneumoniae* in Al-Ahsa, Saudi Arabia: antibiotic susceptibility and prevalence of blaSHV and blaTEM. *J Infect Dev Ctries.* 2013;7(12):1016–9.
39. Badger-Emeka LI, Alokail M, Alsalamene E, *et al.* Genetic analysis, population structure, and characterisation of multidrug-resistant *Klebsiella pneumoniae* from the Al-Hofuf region of Saudi Arabia. *Pathogens.* 2021;10(9).
40. Hassan H, Abdalhamid B. Molecular characterization of extended-spectrum beta-lactamase producing Enterobacteriaceae in a Saudi Arabian tertiary hospital. *J Infect Dev Ctries.* 2014;8(3):282–8.
41. Aldrazi FA, Bageely H, Hakami R, *et al.* ESBL expression and antibiotic resistance patterns in a hospital in Saudi Arabia: Do healthcare staff have the whole picture? *J Infect Public Health.* 2020;13(5):759–66.
42. Ahmad S, Akhtar N, Tayyab M, *et al.* Prevalence, antibiotic susceptibility pattern and production of extended-spectrum beta-lactamases amongst clinical isolates of *Klebsiella pneumoniae* at Armed Forces Hospital in Saudi Arabia. *J Coll Physicians Surg Pak.* 2009;19(4):264–5.
43. Al-Agamy MH, Shibl AM, Tawfik AF. Prevalence and molecular characterization of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* in Riyadh, Saudi Arabia. *Ann Saudi Med.* 2009;29(4):253–7.
44. Al-Qahtani AA, Hassan MF, Alqahtani AS, *et al.* Characterization of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* from Riyadh, Saudi Arabia. *J Chemother.* 2014;26(3):139–45.
45. Somily AM, Absar MM, Aradati M, *et al.* Phenotypic and genotypic characterization of extended-spectrum β -lactamases producing *Escherichia coli* and *Klebsiella pneumoniae* in a tertiary care hospital in Riyadh, Saudi Arabia. *Ann Saudi Med.* 2015;35(6):435–9.
46. Al-Agamy MH, Jeannot K, Radwan HH, *et al.* Characterization of carbapenemases, ESBLs, and plasmid-mediated quinolone determinants in carbapenem-insensitive *Escherichia coli* and *Klebsiella pneumoniae* in Riyadh hospitals. *J Infect Public Health.* 2018;11(1):64–8.
47. Edelstein M, Pimkin M, Palagin I, *et al.* Prevalence and molecular epidemiology of CTX-M extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in Russian hospitals. *Antimicrob Agents Chemother.* 2003;47(12):3724–32.
48. Reuland EA, Al Naiemi N, Raadsen SA, *et al.* Prevalence and risk factors for carriage of ESBL-producing Enterobacteriaceae in Amsterdam. *J Antimicrob Chemother.* 2016;71(4):1076–82.
49. Al-Garni SM, Mahfouz AA, Shatoor AS, *et al.* Risk factors and molecular features of extended-spectrum beta-lactamase producing bacteria at southwest of Saudi Arabia. *Saudi Med J.* 2018;39(12):1186–94.
50. Alshehri, W.A. and Moussa, T.A.A. Extended-spectrum β -lactamase Enterobacteriaceae from patients in Jeddah, Saudi Arabia: Antibiotic susceptibility and molecular approaches. *Journal of Contemporary Medical Sciences,* 2021. 7(1): p. 28-33.
51. Alasmay, M.Y. Antimicrobial Resistance Patterns and ESBL of Uropathogens Isolated from Adult Females in Najran Region of Saudi Arabia. *Clin Pract,* 2021. 11(3): p. 650-658.
52. Ejaz, H. Analysis of diverse beta-lactamases presenting high-level resistance in association with OmpK35 and OmpK36 porins in ESBL-producing *Klebsiella pneumoniae*. *Saudi J Biol Sci,* 2022. 29(5): p. 3440-3447.
53. Memon, J.I., *et al.* Extended spectrum beta-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae* bacteremia. Risk factors and outcome in the eastern region of Saudi Arabia. *Saudi Med J,* 2009. 30(6): p. 803-8.
54. Balkhi, B., *et al.* Antimicrobial susceptibility of microorganisms causing Urinary Tract Infections in Saudi Arabia. *J Infect Dev Ctries,* 2018. 12(4): p. 220-227.
55. Khadry, H.N., *et al.* Investigation on the Genetic Signatures of Antibiotic Resistance in Multi-Drug-Resistant *Klebsiella pneumoniae* Isolates From National Guard Hospital, Riyadh. *Cureus,* 2020. 12(11): p. e11288.
56. Al-Zalabani, A., *et al.* Prevalence of *Klebsiella pneumoniae* Antibiotic Resistance in Medina, Saudi Arabia, 2014-2018. *Cureus,* 2020. 12(8): p. e9714.
57. Alsanie, W.F. Molecular diversity and profile analysis of virulence-associated genes in some *Klebsiella pneumoniae* isolates. *Pract Lab Med,* 2020. 19: p. e00152.
58. Al Bshabshe, A., *et al.* Rising *Klebsiella pneumoniae* Infections and Its Expanding Drug Resistance in the Intensive Care Unit of a Tertiary Healthcare Hospital, Saudi Arabia. *Cureus,* 2020. 12(8): p. e10060.
59. Ibrahim, M.E. High antimicrobial resistant rates among Gram-negative pathogens in intensive care units. A retrospective study at a tertiary care hospital in Southwest Saudi Arabia. *Saudi Med J,* 2018. 39(10): p. 1035-1043.
60. Nirwati, H., *et al.* Biofilm formation and antibiotic resistance of *Klebsiella pneumoniae* isolated from clinical samples in a tertiary care hospital, Klaten, Indonesia. *BMC Proc,* 2019. 13(Suppl 11): p. 20.
61. Alhazmi, W., Al-Jabri, A., and Al-Zahrani, I. The Molecular Characterization of Nosocomial Carbapenem-Resistant *Klebsiella pneumoniae* Co-Harboring blaNDM and blaOXA-48 in Jeddah. *Microbiology Research,* 2022. 13(4): p. 753-764.
62. Kern, W.V. and Rieg, S. Burden of bacterial bloodstream infection—a brief update on epidemiology and significance of multidrug-resistant pathogens. *Clin Microbiol Infect,* 2020. 26(2): p. 151-157.
63. Shibl, A.M., *et al.* High prevalence of acquired quinolone-resistance genes among Enterobacteriaceae from Saudi Arabia with CTX-M-15 beta-lactamase. *Diagn Microbiol Infect Dis,* 2012. 73(4): p. 350-3.
64. Colom, K., *et al.* Simple and reliable multiplex PCR assay for detection of blaTEM, bla(SHV), and blaOXA-1 genes in Enterobacteriaceae. *FEMS Microbiol Lett,* 2003. 223(2): p. 147-51.
65. Devi, L.S., *et al.* Increasing Prevalence of *Escherichia coli* and *Klebsiella pneumoniae* Producing CTX-M-Type Extended-Spectrum Beta-Lactamase, Carbapenemase, and NDM-1 in Patients from a Rural Community with Community Acquired Infections: A 3-Year Study. *Int J Appl Basic Med Res,* 2020. 10(3): p. 156-163.
66. Patil, S., Chen, X., and Wen, F. Exploring the phenotype

- and genotype of multi-drug resistant *Klebsiella pneumoniae* harbouring bla(CTX-M) group extended-spectrum beta-lactamases recovered from pediatric clinical cases in Shenzhen, China. *Ann Clin Microbiol Antimicrob*, 2019. 18(1): p. 32.
67. Yazdanesad, S., *et al.* Preliminary survey of extended-spectrum beta-lactamases (ESBLs) in nosocomial uropathogen *Klebsiella pneumoniae* in north-central Iran. *Heliyon*, 2019. 5(9): p. e02349.
 68. Denisuk, A.J., *et al.* Dramatic rise in the proportion of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* among clinical isolates identified in Canadian hospital laboratories from 2007 to 2016. *J Antimicrob Chemother*, 2019. 74(Suppl 4): p. iv64-iv71.
 69. Seki, L.M., *et al.* Molecular epidemiology of CTX-M producing Enterobacteriaceae isolated from bloodstream infections in Rio de Janeiro, Brazil: emergence of CTX-M-15. *Braz J Infect Dis*, 2013. 17(6): p. 640-6.
 70. Muraya, A., *et al.* Antimicrobial Resistance and Virulence Characteristics of *Klebsiella pneumoniae* Isolates in Kenya by Whole-Genome Sequencing. *Pathogens*, 2022. 11(5).
 71. Ferreira, R.L., *et al.* High Prevalence of Multidrug-Resistant *Klebsiella pneumoniae* Harboring Several Virulence and beta-Lactamase Encoding Genes in a Brazilian Intensive Care Unit. *Front Microbiol*, 2018. 9: p. 3198.
 72. Ho, P.L., *et al.* Characterization of carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* from a healthcare region in Hong Kong. *Eur J Clin Microbiol Infect Dis*, 2016. 35(3): p. 379-85.
 73. Ramos, P.I., *et al.* Comparative analysis of the complete genome of KPC-2-producing *Klebsiella pneumoniae* Kp13 reveals remarkable genome plasticity and a wide repertoire of virulence and resistance mechanisms. *BMC Genomics*, 2014. 15: p. 54.
 74. Rosner, J.L. and Martin, R.G. An excretory function for the *Escherichia coli* outer membrane pore TolC: upregulation of marA and soxS transcription and Rob activity due to metabolites accumulated in tolC mutants. *J Bacteriol*, 2009. 191(16): p. 5283-92.
 75. Algowaihi, R., *et al.* Draft Genome Sequence of a Multidrug-Resistant *Klebsiella pneumoniae* Strain Isolated from King Abdullah Medical City, Makkah, Saudi Arabia. *Genome Announc*, 2016. 4(3).
 76. Baek, E.-H., *et al.* Successful control of an extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* ST307 outbreak in a neonatal intensive care unit. *BMC Infectious Diseases*, 2020. 20(1).