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Prevalence of Multidrug-Resistant Gram-Negative Bacteria in Saudi Arabia: Meta Review

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ABSTRACT

Antibiotic resistance bacteria developed abilities to resist antibiotics designed to kill them and mainly spread in hospitals compared to community. One of the biggest risks is getting an antibiotic-resistant infection from healthcare facility such as a hospital where patients are exposed to antibiotics. Moreover, resistant bacteria are more difficult to treat speciallyin immunocompromised patients Prevention of the spread of resistant bacteria can be done by recommended practices for identifying these bacteria, cleaning hands, wearing gowns and gloves, and cleaning medical equipment in addition to patient care areas. This article reviews the relevant knowledge of the epidemiology and molecular characteristics of resistant bacteria in Saudi Arabia. Multidrug-resistant Gram-negative (MDR-GN) bacteria are serious threats to public health especially extended-spectrum β-lactamase *Klebsiella pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa* which increased morbidity and mortality in hospitals. These pathogens raise serious concern in both hospitals and community settings and have become endemic in many tertiary hospitals and health care units worldwide. Moreover, the emergence and rapid spread of MDR-GN bacteria in hospitals have a significant impact on treatment outcomes and pose challenges to health care systems and medical care cost and effectiveness.

KEY WORDS: ANTIBIOTICS, RESISTANCE, K. PNEUMONIAE, A. BAUMANNII, P. AERUGINOSA.

INTRODUCTION

Multidrug-resistant Gram-negative bacteria (MDR-GN) are among the most serious threat to public health, due to their resistance to nearly all available antibiotics (Ventola, 2015; Exner et al., 2017; Alagna et al., 2020; Nijsingh et al., 2020). The Infectious Diseases Society of America (IDSA) has identified four Gram-negative pathogens of particular importance, extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae (E. coli)*, *Klebsiella pneumoniae, Acinetobacter baumannii*, and *Pseudomonas aeruginosa* (Bassetti et al., 2016; Fodor et al., 2020; Morris and Cerceo, 2020). Also, treatment options for these Gram-negative pathogens are rapidly declining, which leads to significant increases in morbidity and mortality (Karaiskos et al., 2019). These pathogens raise serious concern in both hospitals and community settings and have become endemic in many tertiary hospitals and health care units worldwide (Peleg and Hooper, 2010; Gray and Mahida, 2016). Moreover, the emergence and rapid spread of (MDR-GN) in hospitals pose challenges to health care systems, medical care cost and effectiveness (Santajit and Indrawattana, 2016; Serra-Burriel et al., 2020).

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Multidrug-resistant Gram-negative bacteria have been detected in Saudi Arabia since the 1990s. Many published studies from Saudi Arabia have focused on the molecular epidemiology of these pathogens (Zowawi et al., 2014; Zowawi, 2016). Several studies from different regions in Saudi Arabia have reported increasing carbapenem resistance among MDR-GN bacteria (Yezli et al., 2014, Faidah et al., 2017). Carbapenem-resistant *Acinetobacter baumannii* is the most common pathogens associated with nosocomial infection followed by *Pseudomonas aeruginosa*. Recently, the rate of carbapenem-resistant Enterobacteriaceae has been increasing (Alotaibi et al., 2017). The four Gram-negative pathogens identified by IDSA are the most frequent in KSA hospitals (Zowawi et al., 2014, Zowawi, 2016, Khan et al., 2018). This article reviews the relevant knowledge of the epidemiology and molecular characteristics of the four MDR-GN pathogens, extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae, Klebsiella pneumoniae, Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, in Saudi Arabia.

Multidrug-resistant gram-negative bacteria: A systematic search was conducted in specific online databases, including PubMed, Google Scholar, and Science Direct. The search strategy was focused on publications from the 2015 to 2020. Therefore, we used English key terms related to Multidrug-resistant gram-negative bacteria, molecular epidemiology, and antibiotic resistance. Different forms of the main terms were included in our search for example, MGN- extended Spectrum β Lactamase (ESBL), carbapenem resistant Enterobacteriaceae (CRE). The names of the four MDR-GN pathogens: *E. coli, K. pneumoniae, P. aeruginosa, A. baumannii* were also included. Since we are targeting studies about the Multidrug-resistant gram-negative bacteria in Saudi Arabia, the official name of Saudi Arabia, "Kingdom of Saudi Arabia" or "KSA", was included in the list of the key searching terms.

A total of 80 studies were selected for this review within the time window of the five-year. Most of these studies (23%) were published in 2019. The retrieved results for this review were classified based on the four MDR-GN pathogens. Each subsection starts with a brief background of MDR-GN pathogens under the study. The reported findings of the antimicrobial resistance rates and the resistant genes presented in each MDR-GN bacteria from all the studies collected in this review were summered. The retrieved results for this review were classified based on the four MDR-GN pathogens. Each subsection starts with a brief background of MDR-GN pathogens under the study. The reported findings of the antimicrobial resistance rates and the resistant genes presented in each MDR-GN bacteria from all the studies collected in this review were summered.

Multidrug-resistant Klebsiella pneumoniae: Over the years, *K. pneumoniae* has become an important opportunistic pathogen, that belong to the *Enterobacteriaceae* family, and a member of ESKAPE pathogens. Three to eight percent of hospital-acquired bacterial infections are related to *K. pneumonia* (Ashurst and Dawson, 2019). It is responsible for several diseases such as urinary tract infections, cystitis, pneumoniae, surgical wound infections and septicemia. *K. pneumoniae* demonstrated a significant resistance to antimicrobial groups such as β-lactam antibiotics, Cephalosporin's, aminoglycosides, fluoroquinolones, and Carbapenems (Dsouza et al., 2017). The emergence of *K. pneumoniae* strains resistant to broad-spectrum antimicrobial agents are a serious threats to the public health due to the limited treatment options (Navon-Venezia et al., 2017).

Numerous studies reported the prevalence of MDR-*K. pneumoniae* in Saudi hospital settings. In Riyadh Medical City, out of 227 of *Enterobacteriaceae* isolates 60% were MDR pathogens. *K. pneumoniae* accounted for 33% of infections. 51.4% of the total isolates were ESBL producers and10.1% were Carbapenemase-producing *Enterobacteriaceae* (Alkofide et al., 2020). At King Fahad Medical City at Riyadh, the most identified isolates were *K. pneumoniae* (47.4%) and E. coli (31.6%) (Alzomor et al., 2019). Another study by Bandy and Almaeen, (2020) was conducted in two specialist hospitals in Aljouf region, 222 non-duplicates Blood stream infections (BSI) samples from hospitalized patients, 62.2% were caused by gram-negative bacteria. *K. pneumoniae* was the most frequent (28.4%) pathogen. Moreover, 46% of *K. pneumoniae* isolates were carbapenemase producers and 52.2% of *E. coli* isolates were ESBL producers.

The prevalence of Carbapenem-resistant *K. pneumoniae* was 92.8%, followed by E. coli in 6.7%, and Enterobacter in 0.6%. In KAUH the percentage of CRE increased from 8% in 2017 to 13% in 2018. While in KAMC, the percentage was much higher throughout this study 43.2% in 2018 and 39% in 2019 (Taha et al.,2020). Another study performed by Ghanem et al.(2017) at King Fahd Hospital in Madinah, showed that *K. pneumoniae* species 100% resistance to Ampicillin. Among 15708 *K. pneumonia* isolates collected from 1149 patients at King Fahad Hospital in Medina, resistance rate was 38.4% for imipenem and 46.1% for meropenem, as well as high resistance rates for 40.7% and 53.3% for colistin and tigecycline, respectively (Al-Zalabani et al.,2020).

In Abha, a study conducted that *K. pneumoniae* isolates were highly resistant against ciprofloxacin, piperacillin-tazobactam, ceftazidime, cefepime, amikacin, and gentamicin (Al-Zahrani and Alasiri, 2018). At Aseer Central Hospital, *K. pneumoniae* had high rates of resistance to ampicillin, extended-spectrum β-lactamases-sulbactam (ESBL-SCM), piperacillin (100%), and to a lesser extent ceftazidime (92.5%), minocycline (80.2%), ceftriaxone (80.1%), and tetracycline (80%) (Al Bshabshe et al., 2020). *K. pneumoniae* ESBL-producing isolates (n-23) were collected from various body sites of patients at King Khalid University Hospital, Riyadh (Azim et al., 2019). Also, *K. pneumoniae* was one the most common UTI-causative and showed the highest resistance to ampicillin (97%) sulfamethoxazole/ trimethoprim (35%) and cefuroxime (30%) (Balkhi et al., 2018).

Several studies from Saudi Arabia have reported the prevalence of antimicrobial resistance genes and detected multiple resistance genes among *K. pneumoniae* isolates, such as CTX-M, TEM, BES and SHV genes that are associated with extended spectrum β-lactamases. NDM-1, OXA-48, SME, IMI, NMC, GES, and KPC are the predominant mechanisms of carbapenem resistance (Azim et al., 2019). Table 1 describes the molecular characteristics of MDR *K. pneumoniae* isolates, the regional distribution and number of cases from several studies from Saudi Arabia hospitals.

Table 1. Types of β-lactamase and carbapenems resistant genes carried by *K. pneumoniae* collected from various clinical specimens of patients at Saudi Arabia hospitals.

Region	City	Year of sampling	Setting	No. isolates	Types resistant genes	Refs.
Central	Riyadh	2016	KKUH	24	blaSHV blaCTX-M blaTEM blaKPC blaIMP	Azim et al., 2019
	Riyadh	2015	2 hospitals	4	OXA-1 TEM-1-BSBL AAC(6′)-Ib	Al-Agamy et al.,2019
	Riyadh	2011-2012	KAMC	54	NDM-1 OXA-48	Zaman et al., 2018
	Riyadh	2014	3 hospitals	21	blaOXA-48 blaNDM	Al-Agamyet al., 2018
	Riyadh	2011-2013	KKUH	5	blaNDM OXA-48	Alotaibi et al.,2017
Southern	Abha	2015	2 hospitals	49	VIM blaIMP blaOXA-48 blaVIM	Al-Zahrani and Alasiri, 2018
Western	Jeddah	2017-2019	KAUH KAMC	-	NDM OXA-48	Taha et al.,2020
	Jeddah	-	Private hospital	1	OXA-48-mediated CAZ-AVI	Al Dabbagh et al.,2019
	Jeddah	2018-2019	KAMC	1	blaKPC-2	Halaet al., 1019

KAMC: King Abdulaziz Medical City,KAU H: King Abdulaziz University Hospital, KKUH: King Khalid University Hospital, KFUH: King Fahad University Hospital, KFH: King Fahad Specialist Hospital

Multidrug-resistant Pseudomonas aeruginosa: *P. aeruginosa* is important opportunistic pathogen and a frequent cause of hospital-acquired infections mainly in patients with immunocompromised condition, which result in high mortality and morbidity rates in critically ill patients (Kaye and Pogue, 2015). *P. aeruginosa* is common agents of respiratory system infections, urinary tract infections, dermatitis, pneumonia, cystic fibrosis, bacteremia, surgical infections, soft tissue infections, and a variety of systemic infections (Rabani, and Mardaneh, 2015). The bacterium, *P. aeruginosa* is considered a multidrug-resistant if the isolate is resistant to three or more of the following antimicrobial agents: piperacillin, cephalosporins, fluoroquinolones, carbapenems, and aminoglycoside (Defez et al., 2004). These agents are representatives of the primary antibiotic classes used to treat *P. aeruginosa* infections.

In recent years, a considerable increase in the prevalence of MDR *P. aeruginosa* has been reported in Saudi Arabia. Furthermore, several studies have identified this prevalence of *P. aeruginosa* to be the most frequent pathogen in KSA hospitals (Khan et al., 2018). A study conducted at the ICU of King Khalid University Hospital in Riyadh reported a significant increase in resistance of *P. aeruginosa*. This resistance was reported as 84% to imipenem, 48%to meropenem, 40% to ceftazidime, and 32% to levofloxacin. Ciprofloxacin and piperacillin/tazobactam showed the same percentage of resistance (28%), followed by 4% to amikacin (Azim et al., 2019).

Cephalosporins proved to be ineffective with significant increase in resistance rate to cefuroxime and ceftazidime during the study period. Consistently, another study conducted at the Hammadi hospital and Habib hospital in Qassim, found that *P. aeruginosa* isolates were resistant

to multiple antimicrobial classes, including cefepime, ceftazidime, amikacin gentamycin, tobramycin, piperacillin/tazobactam, and carbapenem groups (Vijayakumar et al., 2016). Another study from Madinah, confirmed that *P. aeruginosa* tends to be resistant to several antibiotics (Saeed et al., 2018). Recent study performed over a 5-month period to determine quinolones susceptibility patterns. The *Pseudomonas* isolates were collected from different medical departments at a tertiary care hospital in Taif. The 42.4% (39/92) *P. aeruginosa* isolates were resistant to 1-7 of the tested quinolones. Gemifloxacin resistance rate was the lowest (28.3%) while the resistances to the other six quinolones were ≥ 35% (El-Badawy et al., 2019).

P. aeruginosa showed a gradual increase in carbapenems resistance due to its ability to develop resistance mechanisms to carbapenems and other antibiotics. Many studies informed the increasing rates of resistance to carbapenems among *P. aeruginosa* in KSA (Abdalhamid et al., 2016; Bosaeed et al., 2020). A study from Makah, 4803 Gram negative isolates collected from patients in Al-Noor Specialist Hospital. The rate of resistance to carbapenem was among *P. aeruginosa* (62.4%), K. pneumoniae (38%) and E. coli (5.59%) as reported by Faidah et al. (2017). Another study from the Western region was conducted by (Alkeshan et al., 2015). Clinical isolates of *P. aeruginosa* (n=121) were obtained from eight different hospitals in Makkah and Jeddah, *P. aeruginosa* isolates were highly resistant to meropenem (30.6%), ticarcillin (22.3%), imipenem (19%), piperacillin (17.3%), and (22.3%) to ticarcillin.

Another study carried out in tertiary care hospitals of Makkah and Jeddah over a 3-month period to determine the pattern of antimicrobial resistance of *P. aeruginosa* confirmed these findings(Khan and Faiz, 2016).The resistance rates in P aeruginosa isolates were 100% for carbapenem and most of them (89%) were non-susceptible to both ciprofloxacin and piperacillin-tazobactam (Bosaeed et al., 2020). During 2011, thirty-four isolates of *P. aeruginosa* collected from patients hospitalized in a tertiary hospital in Riyadh, were found to be highly resistant to carbapenems (Al-Agamy et al., 2016). Other study by Abdalhamid et al. (2016) evaluated the prevalence of carbapenem-resistant *P. aeruginosa* (CRPAE) colonization in the ICU patients at admission in two hospitals, found in Dammam and Khobar cities. hey reported the prevalence of CRPAE was 6.5% with resistance rate 45.1%.

Table 2. Types of resistant genes carried by *P. aeruginosa* collected from various clinical specimens of patients at Saudi Arabia hospitals.

Region	City	Year of sampling	Setting	No. isolates	Resistant genes	Refs.
Central	Qassim	2015	2 hospitals	11	cepA qacE	Vijayakumar et al.,2018
	Riyadh	2011	1 hospital	34	VEB-1a VEB-1b OXA-10 OXA-2 IMP	Al-Agamy et al.,2016
Western	Taif	2016-2017	1 hospital	92	qnrD qnrS, aac(6′)-Ib-cr	El-Badawy et al., 2019

KFUH: King Fahad University Hospital, KFH: King Fahad Specialist Hospital

Additionally, the major types of acquired b-lactamases that have been identified in *P. aeruginosa* strains including class A, B, and D β-lactamases, such as VEB-, PER-, GES-, TEM-, SHV- and OXA-types. Carbapenem resistance in P. aeruginosa was attributed to MBLs including IMP, VIM, SPM, GIM, AIM, and DIM enzymes and other enzymes, including KPC, GES, and OXA (Yezli et al., 2015; Sawa et al., 2020). Several studies from Saudi Arabia have been characterized by the molecular basis of β-lactamase and carbapenemase production in *P. aeruginosa*. Table 1 demonstrates the available data regarding the genetic determinants for ESBL and carbapenemase production by *P. aeruginosa*.

Multidrug-resistant Acinetobacter baumannii: *A. baumannii* is responsible for outbreaks and nosocomial infections such as ventilator-associated pneumonia, burn wound infections, bacteremia and urinary tract infections which occur in patients in intensive care units (Bassetti et al., 2016; Almasaudi, 2018; Ayoub Moubareck and Hammoudihalat, 2020). *A. baumannii* is one of the most troublesome bacteria due to its remarkable natural and acquired resistance to nearly all major antibiotics classes including broad-spectrum penicillins, cephalosporins, carbapenems, most aminoglycosides, fluoroquinolones, chloramphenicol, and tetracyclines, which compromises the ability to treat patients who are infected by this pathogen (Karaiskos et al., 2019).

Several reports on the epidemiological studies of nosocomial infections from different regions in Saudi Arabia have focused on the emergence of *A. baumannii* in healthcare settings and the ICU environment (Kharaba, 2017). At King Abdulaziz Medical City in Riyadh, the most prevalent Gram-negative bacteria in intensive care units was *A. baumannii* (17.97%). Ibrahim (2018) reported that the most secluded pathogens in ICU King Abdullah Hospital was *A. baumannii* (27.2%) followed by *P. aeruginosa* (23.8%) and *K. pneumoniae* (18.6%). In Ministry of National Guard Health Affairs (MNGHA) hospitals in Riyadh, Jeddah, Alhassa and Dammam, the highest MDR- Gram-negative isolates were *A. baumannii* (58.3%), *Klebsiella* spp. (20.4%) and *E. coli* (16.3%) (El-Saed et al., 2020).

Table 3. Types of β-lactamase and carbapenems resistant genes carried by *A. baumannii* collected from various clinical specimens of patients at Saudi Arabia hospitals

Region	City	Year of sampling	Setting	No. isolates	Resistant genes	Refs.
Central	Riyadh	2010	1 hospital	27	GES-11 GES-5 OXA-23	Al-Agamy et al., 2017
	Riyadh	2006-2014	1 hospital	503	bla -PER-1 bla -TEM	Aly et al., 2016
	Riyadh	2011	1 hospital	62	OXA-23 OXA-40	Alsultan, 2015
Southern	Abha	2013-2014	1 hospital	108	OXA-51 OXA-23 OXA-40 OXA-58	Elabd et al., 2015
Western	Jeddah	-	1 hospital	135	blaOXA-23 ISAba1 blaOXA-51	Shah et al.,2019
	Taif	2017	1 hospital	32	blaOXA-51	El-Badawy et al.,2019
Eastern	Dammam	-	1 hospital	103	OXA-51 OXA-23 NDM, VIM,	AlAmri et.al.,2020
	Al-Hassa	-	1 hospital	5	OXA-23	Alhaddad et al., 2018
	Eastern Region	2014	1 hospital	10	blaOXA-23 ISAba1 blaADC blaNDM-1	El-Mahdy et al., 2017

A. baumannii antimicrobial resistance rates in KSA have increased dramatically over the years to many antibiotics including carbapenems. The susceptibilities of *A. baumannii* to meropenem and imipenem in 2006 ranged between 64-81.2% while the susceptibility in 2012 ranged between 8.3-11% (Al-Obeid et al., 2015). Almaghrabi et al. (2018) recorded 94 clinical *A. baumannii* isolates collected from Aseer Central Hospital, 69% of these isolates were resistant to all antibiotics except colistin. A hospital-based, matched case–control study from Makkah, showed the highest resistance rate of *A. baumannii* was for imipenem (83.3%) followed by gentamicin (72.7%) (Al-Gethamy et al., 2017). *A. baumannii* isolates were highly resistant to carbapenem (99.13%), followed by P. aeruginosa (62.4%), K. pneumoniae (38%), and E. coli (5.59%) (Faidah et al., 2017).

Among 290 Gram-negative isolates collected from ICU at King Abdullah Hospital, Bisha, found that that *A. baumannii* was the most frequent pathogen with resistance rates from 93.4% to 97.5% for all tested antimicrobial agents except for colistin (Alsultan, 2015, Ibrahim, 2019). In the Aljouf region, all *A. baumannii* isolates revealed extended drug-resistance, with 70.6% resistance rate to trimethoprim/ sulfamethoxazole and showed resistance to gentamycin, and carbapenems (Bandy and Almaeen, 2020). A study conducted at a large tertiary care hospital in Taif, confirmed that *A. baumannii* tends to be resistant to different antibiotics (El-Mahdy et al., 2017, El-Badawy et al., 2019). Also, 66% of A. bumannii isolates were resistant to almost all tested antibiotics and no resistance to colistin was reported (Doi et al., 2015, Halwani et al., 2015).

Resistance to carbapenems is mainly due to carbapenemases and metallo-β- lactamases (MBLs) production (Leite et al., 2016; Vrancianu et al.,2020). In Saudi Arabia, many studies have shown prevalence of the different β-lactamases, with an emphasis on

carbapenemases among *A. baumannii* isolates and these studies reported that bla OXA-23 gene and a VIM-type metallo-β-lactamase are the most common genes responsible for resistance in *A. baumannii* (Shah et al.,2019; AlAmri et al., 2020). Table 2 summarized the distribution of β-lactamase and carbapenems resistant genes carried by *A. baumannii* collected from different regions across KSA.

CONCLUSION

The high prevalence of multidrug-resistant Gram-negative bacteria in hospitals and community settings has become a serious health concern and a growing threat in Saudi Arabia. The high morbidity and mortality associated with MDR-GN infections resulted in a significant impact on care cost and treatment effectiveness. Therefore, several measures need to be taken to control the spread of these pathogens, including improving infection control programs, early and accurate laboratory detection, judicious use of antimicrobial agents, and enhanced national disease surveillance. Finally, for better detection and control in Saudi Arabia, these procedures need to be combined with molecular typing methods of MDR-GN bacteria.

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