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Review

# Colistin-resistant Gram-negative bacteria in Saudi Arabia: A literature review

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ABSTRACT

Gram-negative bacteria (GNB) represent a major source of morbidity worldwide. The antimicrobial resistance of GNB has recently increased worldwide, that led to using colistin to treat multidrug resistant (MDR) GNB infections. Annually, Saudi Arabia hosts mass religious occasions, where the risk of infectious disease transmission is very high. This review aimed to provide an update on the current prevalence and molecular epidemiology of colistin-resistant GNB locally. It also assessed the role of mass gatherings in triggering colistin resistance. Although colistin is still highly effective against GNB isolates locally, high colistin resistance has been identified among major GNB such as *Acinetobacter baumannii* and *Klebsiella pneumoniae*. Colistin resistance among certain MDR *Escherichia coli* clones, such as ST131, has recently emerged and this is alarming given the rapid global dissemination of this clone. Local data has shown the role of mass religious gatherings in triggering the acquisition of colistin resistance, which makes the screening of colistin resistance determinants very important to limit the spread of colistin resistant GNB between pilgrims.



**Contents**



## 1. Introduction

Gram-negative bacteria (GNB) cause a wide range of serious infections such as urinary tract and bloodstream infections (Hormozi et al., 2018). Over the past decades, the spectrum of resistance of GNB to many first-line agents, such as ciprofloxacin and cephalosporins, has increased substantially (Meier et al., 2011). More recently, GNB resistance to more powerful antibiotics, such as carbapenems, has also been increasingly reported (Hussein

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et al., 2013). This makes treatment options of infections due to GNB limited to last-line agents such as polymyxins (Alotaibi, 2019).

Colistin, a polymyxin E agent, was first introduced into clinical setting in 1959 and is considered a last line agent to treat multidrug resistant (MDR) infections caused by GNB. Although colistin has high nephrotoxicity and neurotoxicity that affected its use clinically, the use of this agent in the clinical practice has been resumed due to the increasingly reported resistance among GNB globally (Li et al., 2006). Over the past decade, however, the heavy use of colistin has driven the global emergence of colistin resistance among many bacterial species (Leangapichart et al., 2016).

Saudi Arabia is one of the largest countries in Asia that annually hosts millions of pilgrims during religious occasions such as Hajj (Memish et al., 2012). Given the proposed association between mass religious gatherings and the escalating risk of infectious disease transmission, and the increased levels of antibiotic resistance among major Gram-negative pathogens reported locally (Alqasim, 2020; Yezli et al., 2014) Saudi Arabia can be a center for the spread of drug resistance globally.

This review aimed to provide an update on the current local prevalence of colistin resistance of GNB in Saudi Arabia. It also determined the molecular epidemiology of colistin-resistant GNB circulating locally, and the role of mass religious gatherings in triggering this resistance. The PubMed was used to obtain research articles, published between 2003 and 2020, using these terms: colistin, antimicrobial resistance, Gram-negative bacteria, multidrug resistance, *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, molecular epidemiology of colistin resistant pathogens, Saudi Arabia.

## 2. Current prevalence of colistin resistance of major Gram-negative pathogens in Saudi Arabia

The local level of colistin resistance of major GNB, including *Escherichia coli*, *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, is demonstrated here.

### 2.1. Colistin resistance of Escherichia coli

*Escherichia coli* (*E. coli*) is the principal cause of urinary tract and bloodstream infections in humans (Russo and Johnson, 2003). Since 2000, the antimicrobial resistance of *E. coli*, particularly extraintestinal pathogenic *E. coli* (ExPEC), has increased markedly (Foxman, 2010). Additionally, the current global rise in antimicrobial resistance has been ascribed to the rapid dissemination of one ExPEC clone, known as *E. coli* sequence type 131 (*E. coli* ST131) (Alqasim, 2020). This clone is usually MDR and has high extended-spectrum β- lactamase (ESBL) carriage (Nicolas-Chanoine et al., 2014).

In Saudi Arabia, colistin resistance of *E. coli* was not reported until 2016, and many previous local studies showed entire colistin susceptibility among *E. coli* isolates (Al-Agamy et al., 2014; Ibrahim, 2018;Abdalhamid et al., 2014) (Table 1). Nonetheless, two recent reports have described the local emergence of colistin resistance among two ExPEC isolates (Sonnevend et al., 2016; Alghoribi et al., 2019).

### 2.2. Colistin resistance of Acinetobacter baumannii

*Acinetobacter baumannii* (*A. baumannii*) is a major etiological agent of many hospital-acquired infections such as nosocomial

**Table 1**
Colistin resistance rates among major GNB species in Saudi Arabia.

| Bacterial species | Year of sampling | Total no. of isolates | No. of colistin resistant isolates (%) | Reference |
|---|---|---|---|---|
| *A. baumannii* | 2006 | 506 | 0 (0%) | Al-Obeid et al., 2015 |
| | 2006–2008 | 253 | 8 (3%) | Aly et al., 2014 |
| | 2006–2014 | 503 | 8 (1.5%) | Aly et al., 2016 |
| | 2008–2012 | 83 | 0 (0%) | Al-Sultan et al., 2015 |
| | 2009 | 510 | 0 (0%) | Al-Obeid et al., 2015 |
| | 2010 | 27 | 8 (30%) | Al-Agamy et al 2017 |
| | 2010 | 84 | 0 (0%) | Somily et al., 2012 |
| | 2010–2012 | 141 | 0 (0%) | Abdalhamid et al., 2014 |
| | 2012 | 936 | 0 (0%) | Al-Obeid et al., 2015 |
| | 2012 | 64 | 2 (3.1%) | Alsultan et al, 2014 |
| | 2014 | 10 | 0 (0%) | El-Mahdy et al., 2017 |
| | 2014 | 47 | 0 (0%) | Aljindan et al., 2015 |
| | 2014–2015 | 105 | 0 (0%) | Al Bshabshe et al., 2016 |
| | 2016 | 9 | 1 (11%) | Badger-Emeka et al., 2018 |
| | 2016 | 6 | 2 (33%) | Azim et al., 2019 |
| | 2016–2018 | 75 | 3 (4%) | Ibrahim, 2018 |
| | 2017 | 50 | 0 (0%) | Ramadan et al., 2018 |
| *K. pneumoniae* | 2003–2012 | 9 | 5 (55.6%) | Garbati et al., 2013 |
| | 2009 | 95 | 3 (3%) | Saeed et al., 2010 |
| | 2011–2012 | 98 | 0 (0%) | Al-Al-Qahtani et al., 2014 |
| | 2015 | 5 | 0 (0%) | Abdalhamid et al., 2016 |
| | 2016–2018 | 14 | 0 (0%) | Ibrahim, 2018 |
| *P. aeruginosa* | 2009 | 123 | 10 (8%) | Saeed et al., 2010 |
| | 2010 | 33 | 2 (6%) | Somily et al., 2012 |
| | 2011 | 34 | 1 (2.9%) | Al-Agamy et al., 2017 |
| | 2014–2015 | 108 | 6 (5.5%) | Ahmed, 2016 |
| | 2014–2015 | 28 | 6 (21.6%) | Ahmed and Asghar, 2017 |
| | 2015 | 22 | 0 (0%) | Abdalhamid et al., 2016 |
| | 2016 | 25 | 0 (0%) | Azim et al., 2019 |
| | 2016–2018 | 10 | 3 (30%) | Ibrahim, 2018 |
| | 2017 | 43 | 0 (0%) | Ramadan et al., 2018 |
| | 2017–2018 | 174 | 29 (16.7%) | Fatima et al., 2019 |
| | 2019 | 17 | 3 (17.6%) | Bandy and Almaeen 2020 |
| *E. coli* | 2009 | 39 | 0 (0%) | Saeed et al., 2010 |
| | 2010–2011 | 152 | 0 (0%) | Al-Agamy et al., 2014 |
| | 2015 | 3 | 0 (0%) | Abdalhamid et al., 2016 |
| | 2016–2018 | 4 | 0 (0%) | Ibrahim, 2018 |
| | 2019 | 4 | 0 (0%) | Bandy and Almaeen 2020 |

pneumonia, and is associated with a remarkable capability of acquiring resistance to nearly all available antibiotic families (Dijkshoorn et al., 2007). Colistin resistance of *A. baumannii* was first reported in 1999 (Hejnar et al., 1999), and since then the prevalence of this resistance of this pathogen has increased globally. For example, resistance to colistin was identified in 40.7% of *A. baumannii* isolates in Spain (Cai et al., 2012).

Locally, several previous studies, from different geographical regions, have concluded that *A. baumannii* isolates were entirely susceptible to colistin (Al-Obeid et al., 2015; Saeed et al., 2010) (Table 1). Others, however, have demonstrated variable resistance levels to colistin among *A. baumannii* isolates. For instance, Ibrahim et al have reported low colistin resistance rate, with 3 of 75 (4%) isolates showing insusceptibility to this agent (Ibrahim, 2018). Nonetheless, Al-Agamy and co-authors have found that colistin resistance was observed in 8 of 27 (30%) *A. baumannii* isolates (Al-Agamy et al., 2017) (Table 1).

### 2.3. Colistin resistance of Klebsiella pneumoniae

*Klebsiella pneumoniae* (*K. pneumoniae*) is associated with causing life-threatening infections such as pneumonia and bacteraemia (Paczosa and Mecsas, 2016). Recently, *K. pneumoniae* resistance to antibiotics has increased drastically, and the dissemination of carbapenem-resistant *K. pneumoniae* isolates has been reported globally (Pitout et al., 2015).

In Saudi Arabia, many reports have found full colistin susceptibility among *K. pneumoniae* isolates (Abdalhamid et al., 2016; Al-Qahtani et al., 2014). Others, however, have identified colistin resistance among *K. pneumoniae* isolates. For example, Saeed et al have concluded that 3 of 95 (3%) *K. pneumoniae* isolates were colistin-insusceptible (Saeed et al., 2010), while Gabarti and others have found that *K. pneumoniae* accounted for 5 of 9 (55.6%) colistin-resistant *Enterobacteriaceae* isolates (Garbati et al., 2013).

### 2.4. Colistin resistance of Pseudomonas aeruginosa

*Pseudomonas aeruginosa* (*P. aeruginosa*) causes a wide range of nosocomial illnesses such as urinary tract and bloodstream infections (Nathwani et al., 2014). *P. aeruginosa* is usually MDR, and carbapenem-resistant *P. aeruginosa* isolates have also been reported globally (Potron and Poirel, 2015). This highlights the threat posed by this pathogen to public health.

In Saudi Arabia, although full sensitivity to colistin among *P. aeruginosa* isolates has been reported (Azim et al., 2019; Ramadan et al., 2018), Saeed et al have demonstrated that 10 of 123 (8%) *P. aeruginosa* isolates were colistin-insusceptible (Saeed et al., 2010). Additionally, Ibrahim and others demonstrated colistin resistance in 3 of 10 (30%) *P. aeruginosa* isolates (Ibrahim, 2018).

## 3. Molecular epidemiology of colistin-resistant Gram-negative isolates

In Saudi Arabia, many studies have been conducted to uncover the mechanisms and molecular epidemiology of colistin resistance of major GNB.

For *E. coli*, Sonnevend and co-authors reported, for the first time, the emergence of colistin resistance among ExPEC isolates in 2016, and they identified a colistin-resistant ST68 blood isolate harbouring the plasmid mediated transferable colistin resistance gene, namely *mcr-1*, on IncHI2 plasmid (Sonnevend et al., 2016) (Table 2). Another multi-locus sequence typing (MLST)-based study has demonstrated a considerable clonal diversity among 10 *mcr-1*-producing colistin-resistant *E. coli* isolates that collected from rectal swabs of North African pilgrims during Hajj, and showed that colistin resistance was detected in *E. coli* isolates belonging to low antibiotic-resistant STs such as ST10, ST93 and ST155 (Leangapichart et al., 2016). More recently, a whole genome sequence (WGS)-based analysis has described one colistin-resistant *E. coli* ST131 isolate carrying the *mcr-1* gene on IncHI2 plasmid (Alghoribi et al., 2019). This finding is important given the aforementioned high worldwide spread of *E. coli* ST131 and the role it plays in triggering drug resistance globally.

For *K. pneumoniae*, Zaman and colleagues have characterized the mechanisms and molecular epidemiology of 23 colistin-resistant *K. pneumoniae* isolates using MLST, and demonstrated the presence of mutations in *mgrB* and *phoP* genes that mediate colistin resistance in these isolates. They also found great clonal diversity within this colistin-resistant *K. pneumoniae* population, with *K. pneumoniae* ST14 being the predominant ST type and it accounted for 26% of total colistin-resistant isolates (Zaman et al., 2018). Another study has identified one *mcr-1*-producing *K. pneumoniae* isolate belonging to ST788 (Leangapichart et al., 2016) (Table 2). Taken together, studying the factors the drive the success of locally circulated colistin resistant *E. coli* and *K. pneumoniae* STs is crucial to combat this issue.

With regard to *A. baumannii*, Alsultan and colleagues have explored the clonal diversity of 64 carbapenem-resistant *A. baumannii* (CRAB) isolates, obtained from 16 different regions in Saudi Arabian intensive care patients, using pulsed field gel electrophoresis (PFGE) (Alsultan et al., 2014). They found that 20 of 64 (31.3%) isolates belonging to clone H, and that the 2 colistin-resistant *A. baumannii* isolates were also members of this clone.

## 4. The role of mass religious gatherings in the acquisition of colistin resistance

As mentioned earlier, Saudi Arabia hosts mass religious gatherings, such as Hajj, and these overcrowded occasions represent a major risk for propagation of antibiotic resistant bacteria between pilgrims. With respect to the association between mass religious gatherings and the acquisition of colistin resistant GNB, Lean-

**Table 2**
Summery of molecular epidemiological findings obtained from studies on colistin resistant GNB in Saudi Arabia.

| Bacterial species | Year of sampling | Colistin resistance mechanism(s) | ST(s)/PFGE clone | Reference |
|---|---|---|---|---|
| *E. coli* | 2009–2013 | *mcr-1*, on IncHI2 plasmid | ST68 | Sonnevend et al., 2016 |
| *K. pneumoniae* | 2011–2015 | Mutation in *PhoP* gene | ST974, ST37, ST709, ST348 | Zaman et al., 2018 |
| | | Mutation in *mgrB* gene | ST14, ST15, ST16, ST22, ST48, ST101, ST152 & ST307 | |
| | | Mutations in *PhoP* & *mgrB* genes | ST15 | |
| *A. baumannii* | 2012 | NA | PFGE clone H | Alsultan et al., 2014 |
| *E. coli* | 2013 | *mcr-1*, on IncHI2 plasmid | ST131 | Alghoribi et al., 2019 |
| *K. pneumoniae* | 2013–2014 | *mcr-1* | ST788 | Leangapichart et al., 2016 |
| *E. coli* | 2013–2014 | *mcr-1* | ST93, ST453, ST648, ST656, ST10, ST155, ST602 & ST1300 | Leangapichart et al., 2016 |

**Table 3**
Summery of colistin resistance patterns among GNB in Saudi Arabia.

| Surveillance period | Bacterial species | Total no. of isolates | Change in colistin resistance pattern | Comments | References |
|---|---|---|---|---|---|
| 2006–2010 | *A. baumannii* | 191 | No | All isolates were colistin-susceptible over the study period | Al-Mously and Hakawi, 2013 |
| 2006–2012 | *A. baumannii* | 1952 | No | All isolates were colistin-susceptible over the study period | Al-Obeid et al., 2015 |
| 2010–2011 | *A. baumannii* | 1307 | Yes | Resistance to colistin increased from 2.6% in 2010 to 4.7% in 2011 | Baadani et al., 2013 |
| 2010–2013 | *A. baumannii* | 1176 | No | All isolates were colistin-susceptible over the study period | Al Mobarak et al., 2014 |

gapichart and others have evaluated the level of colistin resistance among pilgrims, before and after their pilgrimage, by testing the presence of the *mcr-1* gene in 440 rectal swabs collected between 2013 and 2014 (Leangapichart et al., 2016). They found a significant high increase in the prevalence of *mcr*-1-producing isolates upon pilgrims return (i.e. in 2013, 1.55% before the pilgrimage compared to 8.53% after the pilgrimage; in 2014, 1.02% before the pilgrimage compared to 9.18% after the pilgrimage (Leangapichart et al., 2016). This highlights the high chance of acquiring colistin resistance determinants between millions of pilgrims during Hajj, and demonstrates that Saudi Arabia might be a center for the spread of antimicrobial resistance globally. Therefore, it is important to screen the *mcr-1* carriage to prevent the risk of possible spread of colistin resistant bacteria among pilgrims.

## 5. Local colistin resistance trends of GNB

Few studies have assessed colistin resistance trends among GNB isolates, particularly *A. baumannii*, over time in many Saudi Arabian healthcare centers. For instance, Al-Obeid and co-authors have determined the antimicrobial susceptibility profiles of 506, 510 and 936 duplicate *A. baumannii* isolates collected during 2006, 2009 and 2012, respectively (Al-Obeid et al., 2015). They found similar colistin sensitivity rates for all *A. baumannii* isolates over the study period, with all isolates showing full susceptibility to colistin (Table 3). Likewise, AlMobarak et al have also demonstrated no change in colistin resistance pattern among 1176 *A. baumannii* isolates collected between 2010 and 2013, and they showed that all isolates were colistin-susceptible (Al Mobarak et al., 2014). Furthermore, Al-Mously and Hakawi have examined colistin resistance pattern, between 2006 and 2010, of *A. baumannii* blood isolates, and found similar full sensitivity to this agent over the surveillance period (Al-Mously and Hakawi, 2013). However, Baadani and colleagues have documented an increased pattern of colistin resistance among *A. baumannii* isolates over a 2-year period (2010–2011), and they demonstrated that the level of *A. baumannii* resistance to colistin increased from 2.6% in 2010 to 4.7% in 2011 (Baadani et al., 2013) (Table 3).

## 6. Concluding remarks and future perspective

This review has provided an update on the current local prevalence of colistin resistance of GNB. Although some reports have shown full susceptibility to colistin among major Gram-negative species, others have alarmingly documented the escalating levels of colistin resistance among *A. baumannii*, *K. pneumoniae* and *P. aeruginosa* isolates. This suggests the need to review the current guidelines used to treat MDR infections caused by these pathogens. Additionally, molecular epidemiological studies have recently demonstrated the emergence of colistin resistance among certain *E. coli* clones such as ST131. Given the rapid global dissemination of this MDR clone, it is crucial to identify the factors that drive the success of these clones. Finally, this review has shown the association between mass religious gathering and the acquisition of colistin resistance determinants during Hajj, and this implies the need to screen the presence of these determinants to prevent the risk of possible spread of colistin resistant bacteria among pilgrims. In the future, it is suggested that a nationwide antimicrobial resistance surveillance is required to accurately assess the level of colistin resistance locally, and that performing molecular-based studies on the factors that enhance this resistance in GNB is also crucial to combat this issue.

## Declaration of Competing Interest

The author declares that there is no competing interests or personal relationships that could have appeared to influence the work reported in this paper.

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