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Original Review Article

Extraintestinal pathogenic *Escherichia coli* in Saudi Arabia: A review of antimicrobial resistance and molecular epidemiology

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Abstract

Extra-intestinal pathogenic Escherichia coli (ExPEC) is commonly associated with causing urinary tract and bloodstream infections. Over the past two decades, the antimicrobial resistance of ExPEC has increasingly been reported [1]. Given that Saudi Arabia annually hosts mass religious events, such as Hajj, this review investigated several aspects of antimicrobial resistance of ExPEC in this country including the current prevalence of resistance and molecular epidemiology of ExPEC isolates. Generally, the overall prevalence of antibiotic resistance of ExPEC in Saudi Arabia is on increase. The current emergence of colistin resistance in ExPEC represents a major challenge to public health. Local molecular epidemiological studies have shown the dominance of E. coli sequence type 131 (E. coli ST131) over other major ExPEC STs. This is an important observation given that this clone has been associated with high multidrug resistance and extended-spectrum β-lactamases carriage. To reduce the burden of this resistance in the future, it would be crucial to avoid uncontrolled use of antibiotics in either clinical settings or animal food industry.

Keywords: *Extra-intestinal pathogenic Escherichia coli, Antimicrobial resistance, ST131, Saudi Arabia, Colistin resistance, Extended-spectrum β-lactamases*

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INTRODUCTION

Extra-intestinal pathogenic *Escherichia coli* (ExPEC) is associated with causing urinary tract infections (UTIs), bloodstream infections (BSIs), neonatal meningitis and pneumonia [2].

In the recent years, the level of antibiotic resistance of *E. coli*, particularly ExPEC, to first-line agents such as ciprofloxacin and cephalosporins, has increased markedly [1]. Furthermore, this resistance has further increased globally to include many powerful antibiotic families such as polymyxins [3].

The Kingdom of Saudi Arabia is the annual host of mass religious events, known as Umrah and Hajj. These events are associated with high risk of infectious disease transmission [4] which makes the kingdom a potential center for the

spread of antimicrobial resistant bacterial strains around the world.

This review aimed to summarize the current knowledge of antimicrobial resistance of ExPEC in Saudi Arabia, focusing on the overall local prevalence of antimicrobial resistance and molecular epidemiology of ExPEC isolates. The PubMed database was used to search the literature from 1987 to 2018, with the following phrases: *Escherichia coli*, extra-intestinal pathogenic *E. coli*, ESBL-producing *E. coli*, molecular epidemiology of extra-intestinal pathogenic *E. coli*, Saudi Arabia, antibiotics and antimicrobial resistance. Reference lists of relevant research articles were searched for more information.

Current prevalence of antimicrobial resistance of ExPEC in Saudi Arabia

In this section, the current local prevalence of antimicrobial resistance of ExPEC isolates, to major antibiotic classes is demonstrated.

Resistance to β-lactams

Penicillins/penicillin-beta-lactamase inhibitor combinations

Early local reports showed that *E. coli* resistance to penicillins, such as amoxicillin and ampicillin, was reported in more than 50 % of isolates [5, 6]. Nonetheless, penicillin-beta-lactamase inhibitor combinations showed better activity against *E. coli* compared to penicillins [7] (Table 1). Recently, the spectrum of ExPEC resistance to penicillins has increased significantly. For instance, it has been demonstrated that all UPEC isolates were resistant to ampicillin [8], and that 85 and 100 % of UPEC isolates were resistant to piperacillin and amoxicillin, respectively [9]. Although ExPEC resistance to penicillin-beta-lactamase inhibitor combination agents, particularly piperacillin/tazobactam, has recently been found to be low [10, 11], Al-Agamy and colleagues have shown that resistance to amoxicillin/clavulanic acid and piperacillin/tazobactam was found in 96 and 50 % of the tested UPEC isolates, respectively [9].

The current high local resistance levels to penicillins and penicillin-beta-lactamase inhibitor combinations among ExPEC isolates have strongly been associated with ESBL carriage. It has been found that ESBL-producing ExPEC isolates were completely resistant to ampicillin, pipracillin and amoxicillin/clavulanic acid [9]. Resistance to piperacillin/tazobactam was also high among ESBL-producing ExPEC isolates, with 77.4 % of these isolates showing resistance to this agent [9] (Table 1).

Cephalosporins

Previous data demonstrated that about 70% of all *E. coli* isolates were susceptible to first-generation cephalosporins including cefazolin [6]. However, it was found that cefalotin was associated with low activity against *E. coli* [7, 12]. *E. coli* resistance to second-generation cephalosporins such as cefoxitin and cefuroxime, was found to be significantly variable between agents, with a relatively low resistance to cefoxitin (range: 5 - 7 %) [6] when compared to much higher resistance to cefuroxime (range: 13 - 56 %) [6,13]. Furthermore, the range of *E. coli* resistance to third-generation cephalosporins was between 6 and 49 % of all *E. coli* isolates [6,9,10,12,13], while it was between 2 and 54% of all *E. coli* isolates for fourth-generation cephalosporins [9,10,12].

Recently, the level of ExPEC resistance to cephalosporins has increased markedly. For example, Al-Mijalli has reported that about 99 % of the all tested *E. coli* isolates were resistant to cefalotin, ceftriaxone, cefuroxime and ceftazidime, while resistance to cefoxitin and cefepime was reported in 14 and 96.7 % of isolates, respectively [14]. Another report has demonstrated that ESBL-producing UPEC isolates were associated with complete resistance to cefotaxime, ceftazidime and cefepime, and it also showed that 70.3% of these isolates were cefoxitin-resistant [9] (Table 1).

Monobactams

Previous local reports showed that the range of *E. coli* resistance to monobactams such as aztreonam, was between 36 and 63% [6,10,13]. However, the level of ExPEC resistance to aztreonam has recently increased. For instance, it has been found that 74.4% of ESBL-producing UPEC isolates were aztreonam-resistant [14] (Table 1). Another study has demonstrated that all tested ESBL-producing UPEC isolates were aztreonam-resistant, while aztreonam resistance remained very low among non-ESBL-producing ExPEC isolates and it was only detected in 1.65% of the tested isolates [9].

Carbapenems

Over the past decade, *E. coli* resistance to carbapenems, such as imipenem and meropenem, has been uncommon, and the range of resistance was 0 - 8.5 % for imipenem and 0 – 1.1 % for meropenem [6,14,15].

Currently, although the majority of recently published reports have concluded that ExPEC isolates remained totally susceptible to imipenem and meropenem [9,16], AlYousef and others have demonstrated that 15 and 22.5 % of UPEC isolates were resistant to imipenem and ertapenem, respectively [8] (Table 1). This finding is important given that carbapenems are used for treating serious infections caused by multidrug resistant (MDR) ExPEC isolates, and such resistance makes the management of patients more complicated.

Resistance to aminoglycosides

Until early 2000s, the local prevalence of *E. coli* resistance to aminoglycosides was low; with less than 10% of *E. coli* isolates showing resistance to aminoglycosides [5,6,8,10,17]. However, a substantial increase in the level of resistance of ExPEC to some aminoglycosides agents, particularly amikacin and tobramycin, has been reported. For example, it has been found that 78% of ExPEC isolates were resistant to amikacin, 47.8% were non-susceptible to gentamicin while 56.5 % were resistant to tobramycin [18] (Table 1).

Resistance to fluoroquinolones

Early local studies reported high *E. coli* resistance to fluoroquinolones, such as ciprofloxacin, norfloxacin and levofloxacin. For example, resistance to ciprofloxacin ranged between 25.8 and 51 % [6,11], while resistance to norfloxacin was observed in 10 % of *E. coli* isolates [6]. More recent studies have shown higher levels of fluoroquinolone resistance in ExPEC isolates than was reported previously. For instance, Al Mously and others have detected ciprofloxacin resistance in about 70% of all tested ExPEC isolates [15], while Alyamani and co-authors have demonstrated that about 80% of ExPEC isolates were ciprofloxacin-resistant [19]. Norfloxacin resistance of ExPEC has also recently increased, and this resistance has been reported in as many as 44% of ExPEC isolates [10]. ExPEC resistance to levofloxacin has also been high, ranging between 28 and 63 % [8,11,14] (Table 1).

Resistance to colistin

Globally, *E. coli* resistance to colistin has recently been reported [3]. Until 2016, *E. coli* resistance to colistin was not reported locally. Although the majority of past local studies did not include colistin in the antibiotic panels used to determine the antibiotic susceptibility profiles of *E. coli*, a previous study showed that all tested ExPEC isolates were completely susceptible to colistin [9]. However, Sonnevend and others described the first case of colistin resistance among ExPEC isolates in 2016, and they found a colistin resistant ExPEC blood isolate harboring the gene conferring resistance to colistin, namely *mcr-1* [20]. This finding is of great importance given that colistin is currently used to treat many MDR ExPEC isolates that show resistance to powerful antibiotic families e.g. carbapenems, and such resistance might lead to the emergence and dissemination of pandrug resistant (PDR) ExPEC isolates in the future.

Resistance to other antibiotics

Many previous reports showed that *E. coli* resistance to nitrofurantoin has been very low, with more than 90% of isolates showing susceptibility to this agent [6,15]. More recently, the prevalence of nitrofurantoin resistance among UPEC isolates has increased, and this resistance was observed in as high as 15 % of UPEC isolates [14] (Table 1).

Before 2010, *E. coli* resistance to tetracycline ranged between 50 and 54.5 % of total *E. coli* isolates [6]. More recently, the spectrum of ExPEC resistance to tetracycline has increasingly been reported, and this resistance has been found in as high as 65.2 % of ExPEC isolates [18]. Tigecycline is highly active against *E. coli* and a previous report found a complete susceptibility of *E. coli* isolates to this agent [13]. However, higher tigecycline resistance has recently been detected locally, with 13% of isolates showing resistance to tigecycline [18] (Table 1).

According to many previous reports, the local prevalence of *E. coli* resistance to sulfamethoxazole-trimethoprim ranged between 40 and 66 % of *E. coli* isolates [13, 17] (Table 1). With regard to ExPEC resistance to fosfomycin, Al-Agamy and others have found full susceptibility to fosfomycin among a collection of UPEC isolates [9]. Interestingly, by contrast, AlYousef and colleagues have recently demonstrated that 37.5% of ExPEC isolates were resistant to fosfomycin [8] (Table 1).

The role of extended-spectrum β-lactamases carriage in increasing local antimicrobial resistance of ExPEC

It has been shown that the current high rates of resistance to β-lactam antibiotics are attributed to the worldwide dissemination of extended-spectrum β-lactamases (ESBLs), particularly among ExPEC [16].

Table 1: Reported antimicrobial resistance patterns of ExPEC isolates from Saudi Arabia

Agent	Resistance	Number of studies reporting resistance rates within the range [Ref]						
	Range (%)	0%	≤10%	>10-25%	>25-50%	>50-75%	>75%	100%
Penicillins/combinations								
Amoxicillin	61-100						1 [19]	1 [9]
Ampicillin	60-100					2 [5, 6]	2 [10, 13]	1 [8]
Pipracillin	33-100					2 [5, 6]	1 [9]	1 [9]
Amoxicillin/ clavulanic acid	20-96			2 [7, 11]	1 [13]	2 [8, 10]	1 [9]	
Pipracillin/ tazobactam	0-50	1 [10]		1 [8]	1 [9]			
Cephalosporins								
Cefazolin	19-77.5			1 [6]	1 [10]		1 [8]	
Cefalotin	48-98.9				1 [12]	1 [7]	2 [10, 14]	
Cefoxitin	5-71.7		1 [6]	1 [14]	1 [8]	1 [9]		
Cefuroxime	13-98.9			1 [6]	1 [10]	1 [13]	1 [14]	
Ceftriaxone	6-98.9		2 [6, 12]		1 [13]		1 [14]	
Cefotaxime	6-100		1 [12]	1 [9]	1 [10]	1 [8]	1 [19]	1 [9]
Ceftazidime	6-100		1 [12]	1 [6]	2 [10, 13]		1 [14]	1 [9]
Cefepime	2-100		1 [12]	1 [9]	1 [10]	1 [13]	1 [14]	1 [9]
Monobactams								
Aztreonam	21.1-98.9			1 [9]	2 [10, 13]	1 [6]	1 [14]	
Aminoglycosides								
Gentamicin	1.6-48.4		2 [5, 6]	1 [11]	3 [8, 10, 13]			
Tobramycin	10-62.5		1 [17]	2 [6, 11]		1 [18]		
Amikacin	0-78.3	1 [17]	2 [10, 13]		1 [9]		1 [18]	
Sulphonamides								
Sulfamethoxazole-trimethoprim	40-66				1 [17]	1 [13]		
Carbapenems								
Imipenem	0-15	2 [9, 16]	3 [6,14,15]	1 [8]				
Meropenem	0-1.1	2 [9, 16]	2 [6, 14]					
Ertapenem	1.1-22.5		1 [14]	1 [8]				
Nitrofurans								
Nitrofurantoin	3-37.3		2 [6, 15]	1 [14]				
Fluoroquinolones								
Ciprofloxacin	25.8-79.7				2 [6, 11]	1 [15]	1 [19]	
Levofloxacin	28-63.2				2 [8, 11]	1 [14]		
Norfloxacin	10.5-44			1 [6]	1 [10]			
Tetracyclines								
Tetracycline	49-65.2				1 [6]	1 [18]		
Tigecycline	0-48	2 [9, 13]	1 [14]	1 [18]				
Fosfomycins								
Fosfomycin	0-37.5	1 [9]	1 [18]		1 [8]			
Polymyxins								
Colistin	0	2 [9, 13]						

With regard to the prevalence of ESBL-producing ExPEC in Saudi Arabia, a previous study showed that the prevalence of ESBL-production among ExPEC isolates was 6.5 % in 2002 [21]. Recently, this prevalence has increased markedly, ranging between 20.4 and 41.9 % of ExPEC isolates [8, 9, 15, 16] (Table 2).

Molecular characterization of ESBL genotypes among ExPEC isolates has shown that *bla*$_{CTX\text{-}M}$genes, encoding for CTX-M enzymes, were highly prevalent when compared to the traditional β-lactamases encoding genes such as *bla*$_{TEM}$, *bla*$_{SHV}$ and *bla*$_{OXA}$, and that *bla*$_{CTX\text{-}M\text{-}15}$ was the most common CTX-M variant [9,16] (Table 2). Interestingly, the spread of CTX-M-15 enzyme has been strongly associated with high levels of resistance to penicillins, cephalosporins, amino-glycosides, nitrofurans and fluoroquinolones among ExPEC isolates [9,16]. These findings highlight the major role of ESBL carriage in driving the high resistance levels among ExPEC isolates.

Molecular epidemiology of MDR ExPEC in Saudi Arabia

In Saudi Arabia, multilocus sequence typing (MLST)-based studies have generally shown considerable clonal diversity within ExPEC

populations [19, 22-24]. However, *E. coli* ST131 was the most common ST type among the tested ExPEC isolates [19, 22, 24]. This section focuses on the most common ExPEC STs circulating locally.

E. coli ST131 complex

Recent studies have demonstrated that *E. coli* ST131 was the predominant ST type among all ExPEC STs in Saudi Arabia (Table 3) [19,22,24,25]. The local prevalence of ST131 isolates ranged between 17.3 and 61.7% of all ExPEC isolates. Alqasim and co-authors have found that ST131 accounted for 61.7% of all tested isolates, that *H30* was the most frequent ST131 sub-clone, and that *H30* isolates were higher than other ST131 sub-clones in terms of ESBL carriage and fluoroquinolone resistance [25]. Alghoribi and others have shown that this clone was highly assoacited with ESBL production and antimicrobial resistance compared to other ExPEC clones [22]. Abd El Ghany *et al* have characterized 10 carbapenem resistant ExPEC isolates recovered from bacteremia, and identified the presence of one *E. coli* ST131 isolate harboring the New Delhi metallo-β-lactamase gene, bla_{NDM-1} [23].

E. coli ST73 complex

In Saudi Arabia, Alghoribi *et al* have demonstrated that *E. coli* ST73 was the second most dominant ExPEC ST, accounting for 11.4 % of the total isolates identified in the study [22] (Table 3). However, Alyamani *et al* have demonstrated that *E. coli* ST73 was less commonly identified among the tested urine isolates, with only 1 of 58 (1.7 %) isolates belonging to this clone [19].

E. coli ST69 complex

Locally, a previous study found that *E. coli* ST69 isolates accounted for 7.4% of the total STs identified in the study [22] (Table 3). However, another report did not identify *E. coli* ST69 in the UTI strain collection [19]. Abd El Ghany *et al* found one *E. coli* ST69 isolate of ten ExPEC bacteremia isolates harboring the carbapenem resistance determinant, bla_{NDM-1} [23].

E. coli ST95 complex

In Saudi Arabia, Alghoribi *et al* have found that *E. coli* ST95 accounted for 5.4 % of the total isolates identified in the study [22]. However, two recent studies did not identify this ST in their strain collections [19,23].

E. coli ST10 complex

Genotyping studies in Saudi Arabia have identified members of ST10 complex in their strain collections. For example, Alyamani *et al* have identified 7 of 58 (12 %) *E. coli* urine isolates belonging to *E. coli* ST10 complex [19]. Another study has found that ST10 isolates accounted for 6.4% of the total tested ExPEC isolates [22] (Table 3).

Other clonal ExPEC STs

Local studies have identified a number of other STs that are variable in terms of antimicrobial resistance levels and ESBL carriage. For instance, a study has shown that *E. coli* ST38 accounted for 7.4% of the total isolates, and this ST was highly associated MDR phenotype and high CTX-M carriage [22]. Alyamani *et al* have also found that 6.9 % of all tested *E. coli* urine isolates belonged to *E. coli* ST38 [19].

The MDR *E. coli* clone ST405 was identified among a collection of UPEC isolates, accounting for about 3 % of the total isolates [22]. Abd El Ghany *et al* has recently identified 8 out of 10 carbapenem resistant *E. coli* bacteremia isolates belonging to two ST complexes: ST448 complex and ST23 complex [23] (Table 3). ST448 isolates were associated with carrying the carbapenem resistance gene, $bla_{OXA-181}$, while the ST23 isolates harbored the carbapenem resistance determinant, bla_{NDM-5}.

Table 2: The prevalence of ESBL carriage and common ESBL genotypes among ExPEC isolates from Saudi Arabia

Year of sampling	Sample source	Number of ExPEC isolates	Number of ESBL-producing ExPEC isolates (%)	Common ESBL genotypes	Reference
2002-2003	Urine	1116	72 (6.5%)	NT[1]	[21]
2010-2011	Urine	152	31 (20.4%)	CTX-M-15, TEM-1 & CTX-M-27	[9]
2011-2012	Urine	3967	1086 (27.4%)	NT	[15]
2014-2015	Urine	520	218 (41.9%)	NT	[8]
2018	Urine	100	33 (33%)	CTX-M-15, OXA & TEM	[16]

Table 3: Summary of MLST analysis of ExPEC isolates obtained from population-based studies in Saudi Arabia

Year of sampling	Sample source	Number of ExPEC isolates	Number of unique STs	Predominant ST(s)	Other major STs	Reference
2011-2012	Urine	202	51	ST131	ST73, ST38, ST69, ST10, ST127 & ST95	[22]
2014-2015	Urine	58	10	ST131	ST10, ST38 & ST648	[19]
2014-2015	Urine, blood and wound swabs	80	32	ST131	ST38 & ST648	[24]
2014-2015	Urine	10	4	ST448 & ST23	ST131 & ST69	[23]

CONCLUDING REMARKS

This review has shown that the local prevalence of antimicrobial resistance of ExPEC to many front-line antibiotics has increased drastically in the recent years. More importantly, ExPEC isolates have currently developed resistance to the last-line antibiotics such as carbapenems and polymyxins.

The current high antimicrobial resistance of ExPEC can be attributed to many factors. Firstly, the dominance of MDR ExPEC clones, particularly ST131, has recently been identified locally. This is alarming given that this clone is highly associated with resistance to many first-line agents such as fluoroquinolones and third generation cephalosporins, making the treatment of patients more complicated. In the future, it would be important to launch rapid diagnostic tests to identify these clones in order to reduce the burden of resistance.

Unoptimized use of antibiotics has also resulted in high antimicrobial resistance locally Therefore, monitoring the use of antibiotics in clinical settings or animal food industry is essential to combat resistance issue.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

I declare that this work was done by the author named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the author.

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