Review

Molecular Epidemiology and Antimicrobial Resistance in Uropathogenic Escherichia coli in Saudi Arabia

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Molecular Epidemiology and Antimicrobial Resistance in Uropathogenic *Escherichia coli* in Saudi Arabia

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Abstract: Urinary tract infections (UTIs) caused by Uropathogenic Escherichia coli (UPEC) are a serious healthcare concern that must be treated with appropriate antibiotic therapy. However, antibiotic resistance among UPEC strains is increasing, particularly among individuals with recurrent illness. The proliferation of Extended-Spectrum Beta-Lactamase (ESBL) generating UPEC, as well as the increase of UPEC strains that display resistance to several antimicrobial drugs, adds to the difficulty of managing UTIs. UPEC strain genetic variants have a significant influence in their capacity to resist antimicrobial agents and adapt to changing environments. Understanding the genomic landscape of developing UPEC strains is critical for understanding the genetic basis of their resistance. Furthermore, tracking these genetic strains is critical for identifying patterns of resistance spread, directing infection control efforts, and educating.

Keywords: UTI; Urinary tract infection; *E. Coli*; UPEC

1. Introduction

Urinary tract infections (UTIs) are among most common and problematic infections and are a major burden for public health and particularly hospital settings, causing significant discomfort, morbidity, increased antimicrobial resistance risk, and economic costs (1,2). UTIs are categorized into two main groups: symptomatic and asymptomatic cases (3). Symptomatic UTI cases are mostly classified into three classes depending on the severity, pyelonephritis (referring to upper UTI, with kidney infection), cystitis (refering to lower UTI and bladder infection), and urosepsis (2,4). In The Kingdom of Saudi Arabia (KSA) UTI were reported to be responsible for 10 to 14% of all Emergency department visits (5,6). *Uropathogenic Escherichia coli* (*UPEC*) is one of the leading and most often the most common causative agent (2,7). The only treatment for UTI is antimicrobial therapy (2). However Multi drug Resistant Bacteria have become a major public health concern particularly among patients who are affected by recurrent infections (8). *UPEC*'s growing antimicrobial resistance poses an even greater threat and raises new challenges in the battel against the growing antimicrobial resistance rates among different pathogens (8).

UPECs are able to colonize the urinary tract in an ascending order from the urethra to the urinary bladder following to the ureter and ending up in the kidney and in severe cases enter the bloodstream (1,2). There are many virulence factors and specific genes present among *UPECs* that facilitate their breaching of host epithelium in the urinary tract and colonization (9). *UPEC* are a heterogeneous group of strains and are associated with particular O-serogroups and its virulence factors are mainly encoded on pathogenicity islands (10). Some strains of *E. coli* are responsible for most of UTI and also bloodstream infections particularly O25b:H4-ST131 *E. coli* (ST131) (11). An other threat of *E. coli* strains is the emerge of *Extended-Spectrum Beta-Lactamase (ESBL)-producing E. coli. ESBL-E. coli* prevalence among UTIs patients ranges from 23.1% to 33.49% and is some studies that reported from hospital settings the rate was reported as high as 51.4% (12–14). This suggests that a sizable proportion of illnesses are resistant to routinely used medicines like cephalosporins. Therapeutic of ESBL-E. coli infections is difficult due to a lack of treatment choices, which forces the use of powerful

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antibiotics. The use of powerful antibiotics has a number of disadvantages, including an increased risk of antibiotic resistance and adverse effects.

As there is minimal data on this issue, this study attempts to outline some of the primary molecular features of UPEC as well as its antimicrobial resistance patterns in Saudi Arabia during the last 5 years. This study also attempts to fill some of the present gaps, with the goal of improving awareness of UPEC in the region and influencing focused initiatives for successful UTI care and prevention.

2. Materials and Methods

2.1. Literature Review and Data Sources

A comprehensive literature search was conducted using different search engines including PubMed, Scopus, and Google Scholar databases. Keywords that were used included "Uropathogenic Escherichia coli", "UPEC", "Urinary tract infection", "UTI", "E. coli", "Saudi Arabia". Studies published between January 1, 2018, and December 18, 2023, were included and further analyzed for appropriate data extraction. Moreover, national journals such as Saudi Medical Journal, Annals of Saudi Medicine, etc. as well as the reference lists of included articles were further screened in order to identify additional published relevant studies.

2.2. Eligibility Criteria

All published studies that reported on (1) urinary tract infections, (2) were conducted in the Kingdom of Saudi Arabia, (3) reported on UPEC prevalence, (4) it's antimicrobial resistance patterns and (5) molecular characteristics were eligible and included in the review (i.e., inclusion criteria). Additionally, eligible studies had to report on the isolation and identification of UPEC based on standard bacteriological methods following the Clinical Standards Laboratory Institute (CSLI) guidelines. Publications that did not stem from primary research (e.g., opinion and letters to the editor), or were from conference proceedings or abstracts, were not included (i.e., exclusion criteria). The search was limited to English language publications and focused on studies reporting on the prevalence data on UPEC in Saudi Arabia.

2.3. Data Extraction Process and Analysis

Every included study was screened about the following data: (1) authors' names, (2) publication year, (3) study design, (4) sample age and size, (5) study population, (6) (7) UPEC prevalence, (8) UPEC antimicrobial resistance pattern, (9) UPEC ESBL production rate and (10) UPEC molecular characteristics. The main findings from the screened articles were categorized under broad themes.

3. Results

3.1. General Description of the Studies

A total of 19 relevant studies were identified, screened and extracted data for this review. Most of the studies reported the from patients attending healthcare facilities in Riyadh. The studies were either retrospective or cross sectional by design and included patient who were having UTI or were suspected to be having UTI.

3.2. UPEC prevalence

While analyzing the prevalence of UPECs across different studies, Ahmed et.al. reported the lowest prevalence of UPEC among all Uropathogenic Bacteria with a UPEC prevalence of 27%. Alamri et al. reported a slightly higher prevalence of 33.7% followed by slightly higher findings by Alsubaie et al. and, Altamimi et al. reporting 54.5% and 59% respectively (13,15,16). Alanazi et al.'s and Alsohaim et al. reported a UPEC prevalence of beyond 60% as they reported 62%, and 65% in their studies (6,16). Albalawi et.al. reported the highest prevalence of UPEC at 97% and included a

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fair sample size of 210 patients (17). In addition, three studies exclusively focused on EPEC reported a striking 100% prevalence. Notably, studies with larger sample sizes tended to reveal comparatively lower prevalences, particularly when the patient pool exceeded 1000 individuals. An expansive investigation by Alamri et.al. further emphasized this trend, as their large-scale study, spanning four years and encompassing 49,779 isolated uropathogens, disclosed a prevalence of 39.7% for UPEC. These findings highlight the nuanced relationship between study scale and reported prevalence, shedding light on the complex dynamics within the realm of uropathogenic bacteria research (18).

3.3. ESBL producing UPECs

The prevalence of ESBL production among *UPEC* varied greatly across all the studies included in this review. Hameed et.al reported the lowest ESBL production rate of 7.9% Alanazi et.al reported a slightly higher ESBL production rate among *UPEC* with a rate of 9% in a retrospective study conducted in Riyad (6). Moving upward, Bazaid et.al reported a rate of 14.7%, followed by Alghamdi et.al who reported a quite similar rate of 15% (19,20). The highest reported ESBL production rates were reported by Al Qasim et.al (33%), Abalkhail et.al (33.5%), and Emeka et.al (30%), all conducted in Riyadh, reflecting higher levels of antibiotic resistance in this region (13,21,22). It is noteworthy that the large-scale studies who included more than 1000 patients reported a relatively high prevalence of ESBL producing UPEC such as Balkhi et al (29%), followed by Abalkhail et.al (33.5%) (13,18,20,23–25). On the other hand, Alghamdi et.al reported a relatively lower prevalence of 15%. Even though they reported lower prevalence o ESBL producing UPEC on a larger sample size they reported from a different region Al Baha (20). It is noteworthy that some studies did not provide specific data on ESBL production rates among UPEC.

3.4. Antimicrobial Susceptibility:

Analyzing the antimicrobial profiles of UPEC across multiple studies, some antimicrobials consistently demonstrated lower resistance rates, while others demonstrated higher levels of resistance. Amikacin is a potent antimicrobe but is associated with several side effects and is not part of the first line therapies for UTI. However, it exhibited relatively lower resistance rates across multiple studies. For instance, the resistance rates varied from as low 0.5% to as high as 30%. However as mentioned earlier the studies varied greatly in sample size (15,16,19,23,26–28). It is noteworthy that the studies with a large sample size showed a relatively lower resistance, particularly Alamri et.al who reported a resistance rate of 13% out of a total 16,779 isolated UPEC (18).

Trimethoprim / Sulfamethoxazole (SXT) is an antibiotic combination that targets bacterial folate synthesis, and is reported to be effective in treating a wide range of infections by hindering bacterial growth and replication (29). SXT is among the first line choices for uncomplicated UTI with no urological abnormalities, stones or catheters according to the national Guidelines in KSA (30). UPEC has shown relatively and consistent high resistance rates against SXT ranging from 39% in the report of Alamri et.al (2021) to around 60% by Alamri (2018) et.al who had the largest sample size of 16,779 isolated UPEC (18,24). However, the guidelines state that in case there is allergy to sulfamethoxazole or there is resistance reported than nitrofurantoin is suggested as second line.

Nitrofurantoin belongs to the class of antibiotics known as nitrofuran derivatives and is used a second line after SXT or in case there is report of SXT resistance from UPEC. It is commonly used in the treatment UTI. It acts by inhibiting bacterial enzymes that are involved in the DNA synthesis, damaging microbial genetic material (31). In contrast to SXT, nitrofurantoin has been reported to have a quite lower resistance rate ranging between 2% to maximum 20% as reported by different studies. Alamri et.al. (2018) reported a resistance rate of 14.5% suggesting safe usage of nitrofurantoin as a first line (17,18,22,24,24–26,32).

Amixicillin/clavulanate and cefuroxime are part of the alternative therapy for uncomplicated UTI (30). Amoxicillin is a beta-lactam antibiotic, part of the penicillin class whereas cefuroxime is a cephalosporin antibiotic. They have similar mode of action as they act by inhibiting bacterial cell wall synthesis by binding to penicillin-binding proteins (33). The resistance rates varied greatly as the sample size but the study by Alamri et.al had the largest sample and reported a resistance rate for

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Amixicillin/clavulanate of 41% (18). Cefuroxime resistance was not reported by many studies as it is not widely used and the resistance rates varied greatly as the sample sizes. However the largest studies that reported the resistance rates of cefuroxime were Balkhi et.al. (23) with 771 samples and Altamimi et.al. (25) with 599 samples reported a resistance rate of 31% and 39% respectively.

In cases of severe and complicated UTI that results in acute pyelonephritis the national antibiotic prescription guidelines for out-patients suggest the usage of ceftriaxone and particularly ertapenem if ESBL were reported (30). In cases of acute pyelonephritis, the recommended method of administration is intravenous. Both antibiotics, ceftriaxone and ertapenem, were reported to have exhibited relatively low resistance rates against isolated UPEC. Studies from various regions indicate ceftriaxone resistance ranging from 17% to 54%. This underscores the importance of selecting antibiotics judiciously, considering regional variations in resistance patterns (17,21,25–27). However ertapenem was reported to be much more potent and effective against EPEC with resistance rates less than 5% with some particular studies like Balkhi et.al. reporting 0% resistance and Altamimi et.al reporting less than 1% resistance rate (18,23,25).

Complicated UTI that might end up in acute pyelonephritis guidelines suggest the usage of ceftazidime which is a third-generation cephalosporin antibiotic on hospitalized patients (34). The resistance rates were reported to be relatively low and ranging around 30% (21–26,28,35). In hospitalized patients with complicated UTI ceftazidime is suggested as a potent therapy. The preferred route of administration is intravenous, and the administration is every 8 hours.

Imipenem is a broad-spectrum carbapenem antibiotic that is used to treat severe bacterial infections. It is quite effective against both Gram-positive and Gram-negative bacteria (36). Imipenem inhibits the bacterial cell wall synthesis, similar to other beta-lactam antibiotics (20,33). It is combined with cilastatin, which helps prevent in the breaking down of imipenem in the kidneys (37). Imipenem is part of the guidelines for a very potent antibiotic and is advised to be used in acute pyelonephritis and among hospitalized patients. Several studies have reported a low resistance rate and suggested effectiveness in severe UTI cases. Alamri et.al. (2018) (18,21,22,24–26,32). Reported imipenem to have the lowest antimicrobial resistance rate among all tested antimicrobial drugs.

3.5. Multidrug resistance: and Biofilms

The antibiotic resistance patterns observed in various bacteria not only extend but also progressively evolve, eventually resulting to the emergence of multidrug resistance (MDR) patterns. Multidrug resistance is categorized as the ability of bacteria to resist the bactericidal effects of at least one antimicrobial agent in three or more distinct categories (11,13,22). This complex phenomenon underscores the adaptability of bacteria, as they can undergo genetic mutations or acquire resistance genes as a protective mechanism, resulting them resilient to a broader spectrum of antibiotics. The evolution of multidrug resistance poses a significant challenge in the field of medicine and public health, as it limits the effectiveness of traditional antimicrobial treatments and necessitates the development of innovative strategies to combat these resilient microbial strains (22). Abdulaziz Alqasim et al. reported UPEC isolates antibiotic resistance patterns and revealed a high prevalence of MDR, with 67% of isolates exhibiting MDR (22). They reported the distribution of resistance across various antimicrobials groups, ESBL-producing UPEC isolates showed a 100% association with MDR. This highlights a significant link between ESBL and MDR

Alanazi et.al reported that 22.77% of their UPEC isolates exhibited MDR, with varying resistance patterns observed for different types and categories of antibiotics (38). All their UPEC isolates that were resistant to augmentin and nitrofurantoin were also MRD. On the other hand 73 to and 82% of all isolates that were resistant to ciprofloxacin and cefazolin were MDR (39). MDR were reported to notably present in intensive care units according to Azim et.al. (38). Ibrahim et.al. reported that MDR rates were higher in KSA as compared to other regional countries (40).

Biofilm formation is a bacterial mechanism that contributes to antibiotic resistance, making infections difficult to treat. Arafa et.al tested the ability of UPEC to produce Biofilms (41). Firstly, it was reported that 56% of the UPEC isolates were unable to form biofilms. Moreover 84% exhibited a weak ability to form biofilms. They concluded that biofilm formation is not a universal trait that is

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found among all UPEC isolates and this suggests a significant heterogeneity between UPEC strains in KSA in their biofilm-forming capabilities. They also tried to find if there is any significant association between MDR and the ability for biofilm formation. However, their analysis revealed no significant correlation between MDR and biofilm formation.

3.6. Genomic Characteristics:

This comprehensive review highlights some of molecular characteristics and virulence factors of UPEC identified in different regions of KSA, to provide some insights into the genomic landscape of UPEC. Several studies conducted whole genome sequencing on UPEC isolates. Aljohani et al. reported diverse phylogroups, with the majority belonging to B2 Phylogenetic group (27). Sequence types of UPEC varied, with ST131 being the most prevalent across different studies such as Aljohani et.al., Alqasim et.al, and Alghoribi et.al (27,42,43). Serotyping and FimH typing conducted by Aljohani et.al. on different isolates revealed associations between STs and specific serotypes, highlighting the wide diversity of UPEC strains in the Kingdom (27). Alqasim et.al. reported that their ST131 isolates were prevalent in clade O25b, and they also identified subclones, further highlighting the genetic diversity within ST131 (43).

Hassan et.al. reported the presence of various virulence genes like kpsII, fimH, hly, and uidA among the isolated UPEC strains (44). Other studies such as Emeka et.al. reported that fimH virulence factors was more prevalent than papE/F (21). Further genetic testing in the efforts to identify antimicrobial resistance genes among isolates revealed the presence of various resistance genes identified in UPEC strains, including blaNDM, blaCTX-M, and blaTEM (21,44). It is noteworthy that some of the isolated strains carried multiple carbapenem-hydrolysing genes which enables the UPEC to break down and carbapenem antibiotics a widely used class of antimicrobials in the treatment of UTI. Moreover, fluoroquinolone and sulfonamide resistance genes were identified among several isolates (45). ESBL production was reported to be relatively high. Further genetic testing revealed that many of the UPEC isolates carried CTX-M genes encode beta-lactamase enzymes. The presence of CTX-M genes among pathogens particularly UPEC poses a significant threat for the public health as it is a major limitation factor for the effectiveness of commonly used antibiotics. Bacteria that carry the CTX-M genes are often resistant to multiple antibiotics, which results in a more complicated way to treat the UTI caused by these strains.

4. Discussion

The Enterobacteriaceae family continues to be the leading cause of UTIs in all types of patients, with E. coli being the most commonly isolated organism, and in some cases, the only organism detected. They exhibited a high incidence of antibiotic resistance; those isolated from inpatients were more likely to exhibit MDR and a high rate of ESBL production.(12,19,24,26,43). Antimicrobial resistance is spreading at an alarming rate. A continuing, more extensive, and inclusive investigation is required to understand the whole antimicrobial sensitivity pattern in KSA, both locally and nationally, and to establish an updated treatment strategy.

UPEC, pose a significant public health concern. The rise in community and hospital acquired UTIs is alarming. The increasing antibiotic resistance among UPEC is part of the risk factors contributing in such high prevalences. Several reports indicate alarmingly high resistance rates to many of the commonly used antibiotics as first line of treatment including antibiotics like nitrofurantoin and cephalexin, leaving healthcare professionals with limited treatment options. As mentioned earlier another concern is the MDR rates have kept growing and their genetic mutations which are associated with this widely spread resistance. The continuous emergence of different and dangerous mutations among UPEC strains circulating within the KSA enhances the virulence factors among UPEC, allowing them to evade the immune system and resist different antibiotics and colonize the urinary tract more efficiently. This is associated with an increased difficulty of effectively treating infections. It also raises the risk of complications like pyelonephritis, a potentially life-threatening kidney infection.

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Most investigations reporting resistance patterns of UPEC are retrospective in nature, and they do not have patient follow-up until the completion of treatment and full recovery from the infection. As a result, evidence on the efficacy of therapies is scarce and there is a gab in the available literature about the effectiveness of the therapies. A follow up of the patients will help in preventing untreated infections or improper usage of antimicrobial drugs that result in increased antimicrobial resistance rates. Furthermore, no information on the prescribed empirical therapy and its suitability for the microbiological report was provided. Future research should concentrate on these issues.

Table 1. Main findings of the studies.

#	First author (year)	Design	Location	Isolated microorganisms	Patient Type	Age range (years)/ sex (M/F)	UPEC prevalence n (%)	ESBL production rate among UPEC
1	Balkhi 2018 (23)	Retrospective	Riyadh	1245	Patients presenting with positive urine culture	All ages and (M/ F)	771 (62%)	226 (29%)
2	Al Qasim 2018 (22)	Cross sectional	Riyadh	100	Inpatients diagnosed with UPEC associated UTI	All ages and (M/ F)	100 (100%)	33 (33%)
3	Al Wutayd 2018 (28)	Cross-sectional	Buraidah	418	Patients presenting with UTI	All ages (M/F)	157 (37.6%)	N/A
4	Alanazi 2018 (39)	Retrospective	Riyadh	162	Patients admitted with UTI in emergency department	All ages (M/F)	101 (62%)	9 (9%)
5	Albalawi, 2018 (17)	Cross-sectional	Tabuk	210	Patients presenting with UTI	0-12 (M/F)	203 (97%)	N/A
6	Alamri, 2018 (18)	Retrospective	Aseer	49,779	Patients presenting with UTI	All ages (M/F)	16,478 (39.7%)	N/A
7	Taher, 2019 (26)	Retrospective	Aljouf	415	Patients presenting with UTI	All ages (M/F)	137 (33%)	57 (41.6%)
8	Alsohaim, 2019 (16)	Retrospective	Buraidah	133	Patients presenting with UTI	All ages (M/F)	86 (65%)	N/A
9	Ahmed, 2019 (35)	Retrospective	Buraidah, Qassim	89	Patients presenting with UTI	All ages (M/F)	24 (27%)	N/A
10	Hameed 2019 (32)	Retrospective	Riyadh	202	Patients admitted with UTI	Pediatric patients 0–14 (M/ F)	153 (75.7%)	12 (7.9%)
11	Bazaid, 2021 (19)	Retrospective	Ha'il	428	Patients presenting with UTI	All ages (M/F)	156 (36%)	23 (14.7%)
12	Alamri, 2021 (24)	Retrospective	Abha	1506	Patients presenting with UTI	All ages and (M/ F)	507 (33.7%)	N/A

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13	Alzahrani 2021 (46)	Retrospective	Al-Baha	118	Patients presenting with UTI	0-14 years (M/ F)	52 (44%)	14 (27%)
14	Abalkhail, 2022 (13)	Experimental study	Riyadh	2250	Patients presenting with UTI	All ages (M/F)	1523 (67.68%)	510 (33.5%)
15	Emeka 2022 (21)	Retrospective	Riyadh	170	Patients presenting with UTI	All ages (M/F)	170 (100%)	48 (30%)
16	Alsubaie 2023 (15)	Retrospective	Jeddah	510	Pediatric patients presenting with UTI	0-14 years (M/F)	278 (54.5%)	75 (26.8%)
17	Aljohani 2023 (27)	Retrospective	Riyadh	165	Patients presenting with UTI	All ages (M/F)	165 (100%)	56 (34%)
18	Altamimi 2023 (25)	Retrospective	Riyadh	1022	Patients presenting with UTI	All ages (M/F)	599 (59%)	N/A
19	Alghamdi 2023 (20)	Retrospective	Al Baha	4406	Patients presenting with UTI	All ages (M/F)	1644 (37.3%)	246 (15%)

Table 2. Antimicrobial resistance profiles of UPEC.

Study	UPEC (n)	Amikacin	Amox/ Cla	Ampicillin	Ceftazidime	Cefepime	Cefoxitin	Ceftriaxone	Cephalothin	Cefazolin	Cefotetan	Cefuroxime	Ciproflox acin	Co-trimoxazole	Ertapenem	Imipenem	Fosfomycin	Gentamicin	Levoflox acin	Nitrofurantoin	SXT	Tobramycin
Balkhi 2018 (13)	771	1%	22%	65%	30%	29%	10%			30%	29%	31%	34%		0%			15%	28%	3%	47%	11%
Al Qasim 2018 (22)	100		55%	92%	29%		13%						40%			0%		12%		15%	54%	

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Al Wutayd 2018 (28)	157	10%	72%	93%	31%	31%	16%				16%	86%	56%					14%		15%	49%	48%
Albalawi, 2018 (17)	203			87%				12%						82%				19%		10%		
Alamri, 2018 (18)	16779	13%	41%	88%	67%	64%	27.5%		92%				76%		5%	1.6%	6.3%	36%	76%	14.4%	60%	60%
Taher, 2019 (26)	137	9.5%	30%	86%	37.5%	38%		46%	62%				37.5%			16%	58%	18%	44.5%	32%		
Alsohaim, 2019 (16)	86	30%					71%					69%						60%				
Ahmed, 2019 (35)	24	17%	54%	92%	8.3%	8%	8.3%					25%	33%					4.2%		8.3%	58%	21%
Hameed 2019 (32)	153		29.5%	66%						22%			15%	57%		0%		9.6%		2.2%		
Alamri 2021 (24)	507		42%	88%			18%		92%				72%				6.5%		85%	15%	61%	
Bazaid, 2021 (19)	156	7.7%		13.5%			1.3%						17%			5%		33%		21%	41%	
Emeka 2022 (21)	170		73%	88%	27%	15%	38%	27%	100%	100%			70.5%			4.5%		53%	76.5%		84%	
Alsubaie 2023 (15)	278	0.5%		73%				35%		55.5%				46%		0.8%						

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Aljohani 2023 (27)	165	0.6%	8%	66%	17%	8%	4.2%	54%	41%			36%				10%		3.6%	45.5 %	
Altamimi 2023 (25)	599		54%	72%	35%	35%	8%	35%	65%		39%	28%		1%	5%	11%	17%	3%	53%	

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5. Conclusions

Urinary tract infections are a very common infection and remain a major challenge for the healthcare system. E. coli remains the major causative pathogen and is continuously developing new resistance rates. Continuous surveillance is crucial to combat this rising antimicrobial resistance among UPEC strains in the Kingdom of Saudi Arabia and worldwide.

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Conflicts of Interest: Not Applicable.

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