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Case Report

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First Report of Escherichia coli Sequence Type 1193 a Multidrug-Resistant Clone Isolated in Ha'il, Saudi Arabia

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ABSTRACT

Escherichia coli is a significant source of morbidity and mortality in humans due to their enhanced virulence and colonization capacities, which enable them to cause a range of extraintestinal manifestations, including wound infection, neonatal meningitis, urosepsis, and urinary tract infection. In the recent past, globally, fluoroquinolone-resistant (FQr) E. coli sequence type ST1193 has emerged as a major causative agent of E. coli infections in humans. Here, we present a case report of a 54-year-old male who was presented with urethral strictures as well as an overactive bladder (OAB). The patient got a recurrent urinary tract infection (UTI) five times (during the timespan from 31/12/2018 to 18/06/2019). The causative agent was identified as extended-spectrum beta-lactamase (ESBL) positive; AmpC beta-lactamase positive, and ciprofloxacin-resistant E. coli ST1193. This is the first case of recurrent UTI caused by ESBL & AmpC beta-lactamase generating ST1193 E. coli in Ha'il, Saudi Arabia, to our knowledge. The ST1193 ESBL-producing E. coli isolates cultured in this study were resistant to ciprofloxacin and belonged to serogroup H5. Further regional studies are needed to assess the relevance of ESBL-producing E. coli ST1193 which could turn into a nosocomial pathogen in Saudi Arabia. For this recently emerged E. coli ST1193 clone, strategic surveillance, and control techniques will be required in the future.

Key words: *Escherichia coli, PCR, ST1193, Antimicrobial resistance, Fluoroquinolone resistance*

INTRODUCTION

Lactose fermenting *Escherichia coli* can be identified quickly using traditional methods in clinical microbiology laboratories. However, it is reported that up to 10% of *E. coli* strains do not ferment lactose and are therefore considered "atypical" [1]. These atypical non-lactose fermenting strains of *E. coli* carry several virulence factors and are resistant to antibiotics. Furthermore, these non-fermenting *E. coli* strains are strikingly similar to Shigella species, making them difficult to distinguish [2]. Because these strains differ in phenotypic traits such as motility, gas generation, and lactose-fermenting capacities, and because several facilities lack a comprehensive battery of biochemical testing, an accurate identification technique, as well as proper sample collection and transport, are required.

E. coli strains are the commensals of the human alimentary tract, and in the cases, where these bacteria colonize the human body beyond the alimentary tract become opportunistic pathogens [3, 4]. In numerous countries, sequence type 1193 (ST1193) has emerged as a fluoroquinolone-resistant *Escherichia coli* clone [5, 6]. In eastern Australia in 2008, the first report of ST1193 describes its significant contribution to the clinical population of fluoroquinolone (FQ)-resistant (FQ-R) human *E. coli* and transmission to canines [7]. Fluoroquinolones are the most widely used antimicrobials for treating a variety of infections [8]. The significant incidence of fluoroquinolone resistance in *E. coli* has been recognized as a hallmark of clinical bacteriology in the last ten

years [8, 9]. ST1193 was discovered in clinical isolates of ESBL-producing *E. coli* in Germany in 2019 [10]. *E. coli* is a significant source of morbidity and mortality in humans due to their enhanced virulence and colonization abilities, which enable them to cause a range of extraintestinal manifestations, including wound infection, neonatal meningitis, urosepsis and UTI [11]. UTIs are common and affect a substantial percentage of the population. UTIs affect over 150 million people worldwide each year, resulting in considerable social costs of $5 billion in the United States alone. With an estimated incidence of 80-90 percent, Uropathogenic *Escherichia coli* (UPEC) is the most common cause of community-acquired UTIs [12].

The risk factors that enhance the likelihood of UTIs are behavioral, anatomical, or genetic in character, and they vary based on the type of UTI and the type of individual. Furthermore, the risk factors can also be, transient conditions such as pregnancy, or permanent conditions such as neurogenic bladder dysfunction [13]. Many of these factors which cause recurrent urinary tract infections (rUTIs) can be corrected by surgical interventions. These risk factors could be congenital such as, vesicoureteric reflux and pelvi-ureteric junction obstruction, etc., or they can be acquired such as bladder dysfunction and bladder outflow obstruction [14].

Recently fluoroquinolone-resistant (FQr) *E. coli* sequence type ST1193 was found to be the major causative agent of *E. coli* infections in humans [15]. Several nations, including Australia, China, Korea, Norway, and the United States, have identified a novel virulent clone of FQr *E. coli* ST1193 [16]. In 2019, G. For the first time in Germany, Valenza *et al*. discovered the presence of ST1193 among clinical isolates of ESBL-producing *E. coli* [17].

Case report

A 54-year-old male presented with urethral strictures as well as an overactive bladder (OAB). The patient suffered from rUTIs five times (during the duration from 31/12/2018 to 18/06/2019). On cysteine lactose electrolyte deficient (CLED) agar media, urine samples were inoculated with a standard loop and incubated at 37°C overnight. The next day, pure colonies formed with colony-forming units $>10^5$ per milliliter (CFU/mL), indicating that they were *E. coli* by Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Germany) [18]. All five isolates were found to be the lactose non-fermenting and the identification was confirmed during antimicrobial susceptibility testing for all isolates in parallel by using a VITEK2 system (bioMérieux, Marcy-l'Étoile, France) and Microscan (Walk Away 40 plus System-Instrument, Indianapolis, United States). All isolates were found to have identical susceptibility patterns. ESBL-producing *E. coli* were initially screened using a phenotypic confirmatory method described by Almogbel *et al*. [19]. Whole-genome sequencing was performed using MiSeq, and the data were analyzed for serogroup, plasmids, virulence factor genes, and mutations defining quinolone resistance utilizing the Center for Genomic Epidemiology's online tools. The sequencing result confirmed the identification of bacteria like *Escherichia coli* sequence type ST1193 **(Table 1)**, with ESBL type CTX-M-15. Further, the isolates were positive for DHA-1 AmpC beta-lactamase. Cefoxitin resistance is considered screen positive for AmpC beta-lactamase which was confirmed by a genomic study **(Table 2)**.

The treatment protocol for the first infections was trimethoprim/sulfamethoxazole for one week, and for the last infection on 18th June, the same antibiotic was used but the course was extended for 4 months followed by surgery to correct the urethral strictures. Furthermore, after the surgery, the patient was also put on tolterodine to control OAB. After this treatment, the UTI did not relapse.

Table 1. Whole-genome sequencing results showing MLST type ST1193

Gene	%Identity	Alignment Length	DB Allele Length	Gaps	Best Match
adk-14	100	536	536	0	adk-14
fumc-14	100	469	469	0	fumc-14
gyrb-10	100	460	460	0	gyrb-10
icd-200	100	255	255	0	icd-200
mdh-17	100	452	452	0	mdh-17
pura-7	100	478	478	0	pura-7
reca-10	100	510	510	0	reca-10

Table 2. Characteristics of extended-spectrum β-lactamase (ESBL)- *E. coli* ST1193 isolated in this study (n = 5)[a]

Source	Urine
Infection	UTI
Serotype	H5
ESBL type Amp C beta-lactamase	CTX-M-15 DHA-1
Antibiotic-Resistant	Ciprofloxacin, Levofloxacin, Norfloxacin, Aztreonam, Ampicillin, Ampicillin/Clavulanic acid, Cefazolin, Cefepime, Cefotaxime, Cefoxitin, Ceftazidime, Cefuroxime, Moxifloxacin, Nitrofurantoin and Piperacillin.
Antibiotic Sensitive	Amikacin, Gentamicin, Imipenem, Meropenem, Colistin, Tobramycin, Tigecycline, Cefotaxime/Clavulanic acid, Ceftazidime/Clavulanic acid, Piperacillin/Tazobactam and Trimethoprim/Sulfamethoxazole.
Resistance Genes Aminoglycoside resistant genes Macrolide resistant genes Sulphonamide resistant genes Quinolone resistant genes Beta-lactam resistant genes	 *strA, strB* *mph(A)* *sul2, sul1* *QnrB4* *blaCTX-M-15, blaDHA-1, blaTEM-1B*
Plasmids	*IncFIA, IncFIB IncQ1, Col(MG828), Col(BS512), Col(MG828), Col156, IncB/O/K/Z, ColRNAI*
Virulence factor genes [b]	*iha, gad, vat, senB*

[a] The bacteria strains were isolated on 31/12/2018, 16/02/2019, 02/04/2019, 29/04/2019 and 18/06/2019

[b] *iha*, adherence protein; *gad*, glutamate decarboxylase; *vat*, vacuolating autotransporter toxin; *senB*, plasmid-encoded enterotoxin.

RESULTS AND DISCUSSION

Among normal individuals, the flushing of urine removes most of the invading bacteria, along with UPEC-filled exfoliated bladder epithelium cells [20]. However, among the patients with urethral strictures and overactive bladder, the flushing of urine is very weak, so it does not help to remove the bacteria. Targeted antibiotic treatment based on urine culture should be augmented with fast drainage in patients with UTIs and urinary tract obstructions, and definitive surgery to remove the source of blockage or stasis should be undertaken after the infection is under control [21]. Corrective therapy and long-term UTI prophylaxis may eradicate bacteria in the intracellular bacterial community (IBC) [22]. In the current case, a similar treatment regime for eradication of the causative bacterial strain to prevent the rUTIs was adopted.

From the current report, all the isolates obtained at different intervals were lactose non-fermenting, ciprofloxacin-resistant *E. coli*. These results were similar to that of a study by Jing Wu *et al*. 96.1% (49/51) of the ST1193 isolates were found to be the lactose non-fermenters [23]. Additionally, Johnson *et al*. examined the lac operon for possible deletions or mutations, because ST1193 isolates displayed a lactose-negative phonotype. They found a deletion of thymine at nucleotide position 239 in ST1193 isolates that resulted in a frameshift mutation and disruption of lacY. This deletion was consistent across ST1193 isolates [11]. The results of our case showed that "atypical" lactose non-fermenting *E. coli* isolates were resistant to levofloxacin, norfloxacin, augmentin, ampicillin, aztreonam, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, cefuroxime, moxifloxacin, nitrofurantoin, and piperacillin.

301 (23.2 percent) of 1314 FQr clinical isolates of *E. coli* belonged to ST1193, 24 (8.0 percent) of which were ESBL-producers, according to a multicenter surveillance study done in the United States. In a Chinese investigation, 22 (43.1%) of 51 *E. coli* ST1193 FQr clinical isolates were also resistant to cefotaxime and/or ceftazidime and had ESBL genes. Twelve of the ESBL-positive isolates carried blaCTX-M-14, while six carried blaCTX-M-15 [17]. Nguyen *et al*. [24] study showed that most isolates carried diverse AMR genes conferring resistance to co-trimoxazole (dfrA +sulI/sulII/sulIII) (36/46, 78 %), streptomycin (strAB) (33/46, 72 %), tetracyclines (tetA/B/M) (29/46, 63 %), and ampicillin (blaTEM- 1- D, blaOXA- 1, blaDHA- 1, blaCMY- 42) (31/46, 67 %). These results demonstrate the highest-level resistance of ST1193 *E. coli*. The results of our study also highlighted a high level of resistance patterns in ST1193 *E. coli* strains as shown in **(Table 2)**.

To the best of our knowledge, this is the first report of rUTIs caused by ESBL & AmpC beta-lactamase-producing ST1193 *E. coli* in Ha'il, Saudi Arabia. The ST1193 ESBL-producing *E. coli* isolates cultured in this study were resistant to ciprofloxacin and belonged to serogroup H5. Further regional studies are needed to assess the relevance of ESBL-producing *E. coli* ST1193 which could turn into a nosocomial pathogen in Saudi Arabia. Strategic surveillance and control schemes are needed in the future for this newly emerging clone of *E. coli* ST1193.

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