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Review Article

Escherichia coli Sequence Type 131: A Review of Antimicrobial Resistance, Virulence and Metabolic Potential in Saudi Arabia

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Abstract

Extraintestinal pathogenic *E. coli* (ExPEC) strains are associated with causing a wide range of infections such as urinary tract infections and bacteraemia. Over the past two decades, the levels of antimicrobial resistance of ExPEC strains have increasingly been reported worldwide, and this is attributed to the global emergence and dissemination of a single ExPEC lineage, known as *E. coli* ST131. This review explored the current knowledge of *E. coli* ST131 in Saudi Arabia, focusing on its antimicrobial resistance, virulence capacity and metabolic potential. Many local reports have shown that the antimicrobial resistance levels of *E. coli* ST131 were higher than non-ST131, particularly to front-line agents used for the empirical treatment of infections caused by ExPEC. Furthermore, *E. coli* ST131 strains have been associated with high virulence capacity, which could drive the current success of this clone locally. The metabolic activity of ST131 was also found to be slightly higher than non-ST131 strains that obtained from blood population. Taken together, the future studies should focus on elucidating the factors that drive the success of ST131.

Keywords: *E. coli*, ST131, antimicrobial resistance, virulence capacity, metabolism.

INTRODUCTION

Extraintestinal pathogenic *E. coli* (ExPEC) are associated with causing a wide range of infections such as urinary tract infections (UTIs) and bloodstream infections (BSIs) (Russo & Johnson, 2003; Smith, Fratamico, & Gunther, 2007). These infections represent a major source of morbidity, mortality and increased economic and healthcare costs. On the basis of the type of infection they cause, ExPEC strains can be categorized into different pathotypes: uropathogenic *E. coli* (UPEC), sepsis-associated *E. coli* (SEPEC) and neonatal meningitis-associated *E. coli* (NMEC) (Johnson & Russo, 2002a, 2002b).

Over the past two decades, the level of antimicrobial resistance of ExPEC to many front-line antibiotics, such as cephalosporins and fluroquinolones, has increased (Lautenbach, Patel, Bilker, Edelstein, & Fishman, 2001; Tumbarello *et al.*, 2007). More recently, The spectrum of resistance to more powerful antibiotic families, such as carbapenems and polymyxins, has also been increasingly reported among ExPEC strains (Wang *et al.*, 2018). Additionally, there has been an increase in the prevalence of extended-spectrum β-lactamase (ESBL)-producing *E. coli*, and this represents a serious challenge to effective treatment of infections (Al-Agamy *et al.*, 2014).

The current elevated level of resistance among Gram-negative bacteria, particularly ExPEC, is attributed to the worldwide spread of a specific ExPEC lineage, known as *E. coli* sequence type 131 (*E. coli* ST131) (Alqasim, 2020). This review aimed to summarize the current knowledge of *E. coli* ST131 in Saudi Arabia, with a particular focus on the antimicrobial resistance, virulence capacity and metabolic potential of ST131 strains.

DEFINITION OF *E. COLI* ST131 CLONE

E. coli ST131 was first identified in 2008 using multilocus sequence typing (MLST) genotyping tool (Woodford *et al.*, 2009). It usually belongs to the phylogenetic group B2 and to serotype O25:H4 (Coque *et al.*, 2008; M. H. Nicolas-Chanoine *et al.*, 2008; Petty *et al.*, 2014). *E. coli* ST131 is often multidrug resistant (MDR), which can resist at least one antibiotic in three

or more antibiotic classes (Magiorakos *et al.,* 2012). Additionally, ST131 isolates possess the *fimH* gene which has a high level of allelic diversity, and *fimH30* is the most common *fimH* type (M.-H. Nicolas-Chanoine, Bertrand, & Madec, 2014). ST131 *H30* subclone includes two important subsets (*H30*R and *H3*0Rx) (Johnson *et al.,* 2013; Mathers, Peirano, & Pitout, 2015; M.-H. Nicolas-Chanoine *et al.,* 2014). The *H30* subclone comprises most of the fluroquinolone (FQ)-resistant ST131 isolates (Sauget *et al.,* 2016). Within the *H30* subclone, the *H30*Rx subset is strongly associated with carrying CTX-M ESBLs (M.-H. Nicolas-Chanoine *et al.,* 2014; Sauget *et al.,* 2016). Since its discovery, *E. coli* ST131 has been attracting the interest of researchers in the field of bacteriology due to its responsibility for causing widespread difficult-to-treat extraintestinal infections. The next part of this review will provide an update on the major traits of ST131 in Saudi Arabia.

Antimicrobial resistance of ST131

E. coli ST131 is often multidrug resistant (MDR), and is frequently associated with carrying a variety of other antimicrobial resistance determinants such as CTX-M, OXA, TEM, SHV, CMY-2 β-lactamases and the aminoglycosides/fluoroquinolone acetyltransferase AAC (6')-Ib-cr (Rogers, Sidjabat, & Paterson, 2011; Woodford *et al.,* 2009). It is commonly associated with carrying the $bla_{CTX\text{-}M\text{-}15}$ gene, encoding the CTX-M-15 ESBL, on the IncFII plasmids (Coque *et al.,* 2008).

In Saudi Arabia, previous studies have determined and compared the prevalence of antimicrobial resistance and ESBL carriage of *E. coli* ST131 and other major ExPEC clones. Alghoribi and colleagues have demonstrated high levels of resistance among ST131 strains. For instance, 33 of 35 (94.3%) ST131 strains showed resistance to ampicillin and piperacillin, whereas 25 of 33 (75.8%) ST131 strains were ciprofloxacin resistant (Alghoribi *et al.,* 2015). They also found that 21 of 33 (63.6%) ST131 strains were ESBL-producing. Moreover, a comparative study by Alqasim and co-authors has determined and compared the antimicrobial resistance characteristics of a collection of UPEC isolates belonging to ST131 and non ST131 from Riyadh city, and concluded that ciprofloxacin resistance was exhibited by 35 of 37 (94.6%) ST131 strains. They also found that 31 of 37 (83.7%) ST131 strains were MDR, and that 24 of 37 (64.9%) of ST131 strains were associated with ESBL carriage (Alqasim, Jaffal, & Alyousef, 2020). With regard to antimicrobial resistance of strains belonging to different ST131 subclones, *H30* ST131 isolates, including *H30*R and *H3*0Rx, were higher in their ESBL carriage and FQ resistance levels compared to non *H30* ST131 isolates. However, MDR phenotype was more predominant in non *H30* compared to *H30* isolates (Alqasim, Jaffal, & Alyousef, 2020).

Similarly, another study has explored the antimicrobial resistance patterns and ESBL carriage of ExPEC isolates from bacteraemia patients in Riyadh, and demonstrated that ST131 isolates were associated with very high resistance levels to front-line agents. For example, all tested ST131 isolates were insusceptible to ampicillin and ciprofloxacin, while 82% of isolates were resistant to amoxicillin-clavulanic acid (Alqasim, Jaffal, Almutairi, Arshad, & Alyousef, 2020). Additionally, it was found that all ST131 isolates were MDR, and that 15 of 17 (88.2%) ST131 isolates were ESBL-producing (Alqasim, Jaffal, Almutairi, *et al.,* 2020).

Virulence capacity of ST131

Since its discovery, the virulence potential of ST131 lineage has been explored by enormous number of studies. In contrast to previous reports showing ST131 strains with moderate virulence capacity compared to other major ExPEC STs such as ST73 and ST127 (Alghoribi *et al.,* 2015; Gibreel *et al.,* 2012), many local studies have shown that ST131 strains were of higher virulence associated gene (VAG) carriage compared to other ExPEC lineages. For instance, Alqasim and co-authors have concluded that *E. coli* ST131 urine isolates were higher in the VAG carriage (Alqasim, Jaffal, & Alyousef, 2020). They demonstrated that these isolates were significantly associated with carrying 8 VAGs, *papA*, *papC*, *papG* allele II, *fimH*, *iha*, *hlyA*, *PAI*, *ompT*, *usp* and *sat*, compared to non ST131 isolates. Additionally, testing the virulence potential of ST131 isolates belonging to various ST131 subclones found that *H30* subsets (*H30*Rx and non-Rx) were significantly associated with 5 VAGs, *iha*, *iutA*, *PAI*, *traT* and *usp*, compared to non *H30* (Alqasim, Jaffal, & Alyousef, 2020). Another study has evaluated the virulence capacity of ExPEC blood isolates obtained from bacteraemia patients in Riyadh (Alqasim, Jaffal, Almutairi, *et al.,* 2020). It has demonstrated that ST131 isolates had a higher VAG carriage in comparison to non-ST131 isolates, and that ST131 isolates were significantly associated with carrying 3 VAGs: *iha*, *hlyA* and *sat* (Alqasim, Jaffal, Almutairi, *et al.,* 2020).

Metabolic potential of ST131

Metabolism is a key factor that enhances bacterial colonization of human hosts (Rohmer, Hocquet, & Miller, 2011). With regard to the role of metabolism in triggering the virulence of ExPEC, a previous study demonstrated that the increased catabolism of the amino acid D-serine by the *E. coli* CFT073 strain during UTI can enhance its colonization and virulence gene expression (Anfora, Haugen, Roesch, Redford, & Welch, 2007). Additionally, many reports have proposed that sugar metabolism (Le Bouguénec & Schouler, 2011) and specific metabolic enzymes (Pancholi & Chhatwal, 2003) may enhance bacterial virulence.

In Saudi Arabia, the metabolic capacity of ExPEC isolates has not been assessed until 2021 when two comparative metabolic studies on ExPEC isolates, including ST131 and non ST131, from urine and blood samples were conducted (Alangari, Jaffal, Alyousef, & Alyousef, 2022; Alqasim, Jaffal, Almutairi, & Alyousef, 2021). The first study tested 40 UPEC isolates for their ability to utilize 35 biochemical substrates, and showed that non-ST131 isolates were more metabolically active than ST131 isolates, where non-ST131 were more able to utilize fifteen substrates. (Alqasim *et al.*, 2021). Moreover, it revealed that six biochemical substrates: salicin, arabitol, cellobiose, melezitose, xylitol and ONPG were only utilized by members of non-ST131 isolates, however, there was no substrate that was exclusively utilized by ST131 isolates. Furthermore, the same study compared the metabolic activity of ST131 isolates belonging to different subclones and found that all isolates had similar utilization patterns for 21 biochemical substrates (Alqasim *et al.*, 2021). However, there was variability between ST131 subclones in the ability to utilize 14 substrates. Generally, *H30* isolates were slightly higher in their utilization ability for some substrates, such as raffinose, citrate and sorbose, than non-*H30* isolates. Within *H30* subclone, *H30*Rx was of higher metabolic ability compared to *H30* non-Rx. Nevertheless, the study found that dulcitol was only utilized by non-*H30* isolates while adonitol was exclusively metabolized by members of *H30* non-Rx (Alqasim *et al.*, 2021).

Another study has tested the metabolic activity of ExPEC isolates, including ST131 and non ST131, from blood samples (Alangari *et al.*, 2022), and demonstrated that ST131 isolates were of high metabolic potential compared to non-ST131. It found that both isolate groups were similar in metabolising 16 carbohydrates. However, the ability of ST131 isolates in utilizing 13 substrates, such as fructose, was higher than non-ST131. ST131 members exclusively utilized rhamnose, and they were significantly associated with rhamnose utilization**.** Nonetheless, non-ST131 isolates were higher than ST131 in utilizing 6 substrates such as lactose and xylose, but this difference remained insignificant (Alangari *et al.*, 2022).

Concluding remarks

Since its emergence, *E. coli* ST131 has extensively been studied and many reports have explored its traits as an important pathogen. Nonetheless, little is known about the major characteristics of ST131 isolates in Saudi Arabia, and it is important to shed light on the factors that drive the success of ST131. This is the first review to discuss the antimicrobial resistance, virulence capacity and metabolic potential of ST131 locally. Over the past decade, the levels of antimicrobial resistance have been found to be higher than non-ST131, particularly to front-line agents that used for the empirical treatment of infections caused by ExPEC. This is alarming and highlights the need to revise the local guidelines used for efficient therapy. Moreover, ST131 isolates have been associated with high virulence capacity, which could drive the current success of this clone locally. In the future, performing large-scale molecular studies on various factors that give ST131 a competitive advantage over other potential ExPEC clones would be crucial to enhance our knowledge of ST131 in Saudi Arabia.

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