Distribution and virulence properties of extra-intestinal pathogenic *Escherichia coli* in Turkey

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**Summary**

Extrainestinal pathogenic *Escherichia coli* (ExPEC) is a universal pathogen which causes variety of diseases that impact on people of all ages. ExPEC strains are genetically diverse and associated virulence factors contribute to the wide spectrum of infections, ranging from urinary tract infections to fatal bacteraemia. During the last decade, ExPEC strains have been increasingly reported in Turkey. The development of antibiotic resistance by ExPEC strains, such as extended spectrum beta-lactamase, has important clinical consequences. Studying the distribution and virulence factors of various ExPEC strains will be enhancing our understanding of ExPEC epidemiology and prevalence.

**The bad side of the two-faced *Escherichia coli*: extraintestinal pathogenic *E. coli***

*Escherichia coli* is one of the most common Gram negative bacteria of the human gastrointestinal tract (GIT) (9,36,61). Certain *E. coli* strains live in intestine without causing any infection disease (10). However, a small percentage of *E. coli* strains are capable of causing various infections outside the GIT. These organisms called Extraintestinal pathogenic *Escherichia coli* (ExPEC) (45). ExPEC strains generally can be grouped based on infection site and can be divided into four following groups: Uropathogenic *E. coli* (UPEC), neonatal-meningitis causing *E. coli* (NMEC), Avian pathogenic *E. coli* (APEC), and sepsis causing *E. coli* (SPEC) (46). Among these strains, APEC causes systemic infection in poultry, whereas the other pathogenic ExPEC subsets cause human diseases (29). Even though ExPEC strains are frequently associated with urinary tract infections (UTIs), they are also a major cause of sepsis, meningitis, pneumonia, bacteremia, lower respiratory and skin, soft tissue and central nervous system infections (17,21,48,49). For instance, *E. coli* related to necrotizing fasciitis after renal transplantation was found in a 39-year-old male patient in Istanbul (65). ExPEC is also known as *colibacillas*; in new-borns and adults, it may lead to sepsis and have a mortality rate of approximately 80% (58). Occasionally, these bacteria are found in the bloodstream, suggesting that these ExPEC strains can remain alive in a non-ferrous environment and are resistant to bactericidal activity present in blood (45).

ExPEC pathogenicity is multifactorial and involves multiple processes, including colonization, host invasion, and bacterial fitness. ExPEC pathogenicity is the result of genes that encode virulence factors (VFs) and are grouped as follows: i) adhesins, ii) toxins, iii) iron acquisition systems, iv) capsule production, and v) protectins and invasins (22,46). Genes for VFs are usually located within pathogenicity islands (PAIs) on plasmids and/or chromosomes.

UTIs associated with ExPEC derived from a fecal reservoir. After urethral colonization, ExPEC strains reach bladder and kidneys where tissue invasion result in serious clinical syndromes. During infection stages, UTIs associated with ExPEC strains use Type I fimbriae to bind uroepithelial cells (41,60). Other VFs important for adhesion are S. fimbriae/FIC fimbriae and P. fimbriae. Furthermore, ExPEC strains acquire ferric iron to grow and then disseminate bloodstream. These processes involve siderophores such as yersiniabactin and aerobactin (15,26,50). To induce uroepithelial injury, ExPEC strains produce toxins such as hemolysin (68). To overcome immune responses, ExPEC strains produce conjugal transfer surface exclusion protein (TraT) which is associated with serum resistance (19). In contrast to UTIs associated with ExPEC, Neonatal meningitis-causing *E. coli* (NMEC) has particular virulence mechanisms that contribute to invasion of the blood-brain barrier invasion (38). NMEC strains frequently produce a capsule that inhibits phagocytosis. Additionally, bacterial serum resistance is associated with outer membrane proteins (*e.g.*, OmpA) and cytotoxic necrotizing factor 1 (CNF1) is required to develop a high titre bacteremia (30,53,67).

With regards to APEC, important VFs are adhesins such as F1 and P fimbriae, K1 capsule and temperature-dependent hemagglutinin (Tsh) (54). ExPEC strains are distributed throughout the entire world and are
the most common Gram negative bacteria in humans (63). In Turkey, ExPEC strains are frequently isolated from blood cultures of hospitalized patients (31,32). In 2006, 214,340 blood samples were collected from 43,254 patients in 16 Turkish University hospitals. The most frequent pathogen cultured from these blood samples was identified as _E. coli_ (22.45%) (3). ExPEC (approximately 28% of samples) also was detected in Kayseri (63). This ratio increased by 44% when the blood of patients in the Internal Medicine Department were examined (24). Moreover, ExPEC strains were detected from blood cultures of 34% of neutropenic patients in Izmir, which is located in western Turkey (74). Furthermore, 55 _E. coli_ strains were detected in total of 10,168 blood cultures from patients reported in Samsun in 2006 (69).

Each year, 1.6 million new-borns die due to the bacterial infections including sepsis. Neonatal sepsis, which is characterized by infection during the first month of life, is responsible for 1 to 8 of these deaths. This rate is much higher in developing countries (64). Sepsis-causing _E. coli_ (SPEC) strains are reported frequently in new-borns and generally the main cause of septicaemia (31,71). The source of contamination is usually originates from mother's vagina and rectum microbiota and is designated ExPEC (4,5). Fifty-eight Gram negative bacteria were detected in 6116 blood cultures from the new-born intensive care unit in Kayseri; 21 of these 58 strains were reported as _E. coli_ (36.02%) (59). A study was performed to determine of demographic characteristics of new-borns diagnosed with late-onset sepsis and to characterize the bacteria. The reported to increase more than three-fold in both SPEC and between 2004 and 2008 (71). Of the 148 patients with bloodstream infections, _E. coli_ was reported as the sepsis-causing agent in 8 of them (5.4%) at the Neonatal Intensive Care Unit in Diyarbakir, Turkey (39). Further, SPEC was detected in transsectial prostate biopsy. Quinolone-resistant _E. coli_ was reported in Istanbul in a patient with sepsis; _E. coli_ was presented in the prostate needle biopsy (33).

ExPEC associated with neonatal meningitis (NMEC) has a mortality rate of 40% (22). Neonatal meningitis is inflammation of meninges that within the first 30 days of life (23). NMEC can lead to neurological disorders including hydrocephalus and encephalopathy (42). ExPEC-related NMEC studies are rare and the ratio of NMEC has not been determined high risk. A study was performed to examine neonatal bacterial meningitis in Turkey the authors studied risk factors and prognosis of NMEC patients between January 2003 and June 2010. Of the 118, 091 neonates born in a hospital, 38,023 neonates were hospitalized due to various clinical problems. Among them, 344 patients were diagnosed with meningitis. Regarding these data, maternal risk was evaluated and _E. coli_ (23%) was reported as most common pathogen (45). Avian pathogenic _Escherichia coli_ (APEC) lead to aerosacculitis, polyserositis, septicaemia and other extraintestinal diseases of many avian species (25). Although, numerous of studies from many locations throughout the world have been reported on APEC, there is no study examining the distribution of APEC in Turkey. ExPEC associated with UTIs are among the most common community-acquired infection all over the world. UTIs are mainly composed of catheter-associated urinary tract infection (CAUTIs), pyelonephritis and simple cystitis (56). Generally, when we examine of the UTIs related to ExPEC strains in Turkey, the reliable detection rate is approximately 70%. For example, Azap et al. reported that the percentage of UTIs associated _E. coli_ was 57.8% in Ankara (6). Three years later, Yilmaz et al. stated that most commonly detected bacteria from urine samples was _E. coli_ (68.5%) in Kars, which is located eastern Turkey (72). This incidence rate was similar with that observed in Izmir, located in the western part of Turkey. In Izmir, UTIs associated with _E. coli_ were detected in 8975 (67%) of 13,821 urine samples (70).

Approximately 15 years ago, 371 of 2083 patients (17.8%) patients were diagnosed with UTIs out in Samsun (14). During the last 15 years, ExPEC related infections have increased from 17.8% to 65.3% (47). ExPEC strains that lead to UTIs generally have Extended Spectrum β-lactamases (ESBLs) resistance. The incidence of community-acquired UTIs due to ESBLs producing _E. coli_ has increased worldwide (37,44,52,66). One of the most significant ESBL is CTX-M-15. The emergence of an intercontinental clone of an _E. coli_ strain, producing CTX-M-15 has gained much interest recently (8,28,57). CTX-M-15-producing _E. coli_ strain was reported in 2005 in Turkey and it was first isolated from a hospitalized patient’s urine (2). Azap et al. stated that 6.3% of _E. coli_ isolated form urine samples from patients (aged 18 to 65) who had undergone an operation because of urolithiasis or bladder disservice were ESBL positive (7). Furthermore, for nearly 10 months in Adana, Turkey, the presence of ESBL-positive _E. coli_ was determined in cases of community-acquired UTIs. ESBL-positive _E. coli_ was detected in 77 of the 310 (24.8%) samples (34) (Table 1).

ExPEC strains can be grouped based on clonal variation using multilocus sequence typing (MLST) analysis (27,51,55). With respect to clonal variation, sequence type (ST) 131 strains has drawn much attention in recent years (1,11,12). An _E. coli_ ST131 clone, also classified as a ExPEC strain, is significant human pathogen throughout and is known as a pandemic clone, (16,35). Recent studies reported that variety of ST131 clonal groups are associated with antimicrobial resistance profiles including CTX-M-15 type ESBLs. Recently, Johnson et al. described a subclone within ST131, called H30 (40). ST131 comprises approximately 25% of ExPEC strains in Turkey. Clinical risk factors associated with this subclone within ST131 were studied by Can et al. in Istanbul and the percentage of the _E. coli_ that were ST131 was 24.3% (13). Similarly, Yumuk et al. reported one CTX-M-15 producing _E. coli_ ST131 strain in Kocaeli (73). Another study that examine urosepsis pathogenic _E. coli_ in the Aegean Region of Turkey reported that 4 of the 30 _E. coli_ strains were ST131 (29).

In conclusion, ExPEC has been reported at high rates in Turkey and this constitutes a major threat to public health. Why ExPEC is significant for the public? It can be explained following reasons; ExPEC has a complicated phylogeny and has a broad range of VFs that conduce to simple urinary tract infections to fatal bacteremia and sepsis (18,20,22). On the other hand, ESBL-producing resistant ExPEC strains are draw attention in recent years. For this reason, actual diagnose strategies are necessary to overcome ExPEC infections. Large scale epidemiological studies are essential to understand transmission dynamics and therapeutic strategies.

### Table 1. Distribution of extra-intestinal pathogenic _Escherichia coli_ strains according to the provinces of Turkey.

<table>
<thead>
<tr>
<th>Province</th>
<th>Infection</th>
<th>ExPEC %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kars</td>
<td>UTIs</td>
<td>68.5</td>
<td>72</td>
</tr>
<tr>
<td>Samsun-1</td>
<td>UTIs</td>
<td>65.3</td>
<td>47</td>
</tr>
<tr>
<td>Samsun-2</td>
<td>UTIs</td>
<td>17.8</td>
<td>14</td>
</tr>
<tr>
<td>Izmir</td>
<td>UTIs</td>
<td>67.0</td>
<td>70</td>
</tr>
<tr>
<td>Ankara-1</td>
<td>UTIs</td>
<td>57.8</td>
<td>6</td>
</tr>
<tr>
<td>Ankara-2</td>
<td>UTIs-ESBL</td>
<td>6.3</td>
<td>7</td>
</tr>
<tr>
<td>Istanbul</td>
<td>UTIs-ESBL</td>
<td>55.1</td>
<td>13</td>
</tr>
<tr>
<td>Trakya</td>
<td>UTIs-ESBL</td>
<td>36.7</td>
<td>16</td>
</tr>
<tr>
<td>Adana</td>
<td>UTIs-ESBL</td>
<td>24.87</td>
<td>33</td>
</tr>
<tr>
<td>Kocaeli</td>
<td>UTIs-ESBL</td>
<td>53.0</td>
<td>73</td>
</tr>
<tr>
<td>Isparta</td>
<td>UTIs-ESBL</td>
<td>29.0</td>
<td>43</td>
</tr>
</tbody>
</table>

References


Escherichia coli strain able to colonize the human gut in the intestinal microbiota of pigs. Vet Res 2016;47:12.


