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# Extended Characterization of Human Uropathogenic *Escherichia coli* Isolates from Slovenia

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## 1. Introduction

*Escherichia coli* (*E. coli*) is a very diverse bacterial species found naturally in the intestinal tract of humans and many other animal species. Even though *E. coli* is known to be part of the normal gut microbiota, some strains – that are pathogenic – cause a wide variety of different intestinal and extraintestinal diseases (Marrs et al., 2005). Typical extraintestinal infections due to *E. coli* include urinary tract infections (UTI), diverse intra-abdominal infections, pneumonia, surgical-site infection, meningitis, osteomyelitis, soft-tissue infections, bacteremia (Russo & Johnson, 2006).

UTIs are one of the most frequently acquired bacterial infections and *E. coli* accounts for as many as 90% of all community-acquired UTIs. Approximately 50% of all women have had a UTI by their late 20s. About 20–30% of women with first UTI will have two or more infections; while 5%, will develop chronic recurring infections which greatly disrupt a woman's life (Marrs et al., 2005). In Slovenia *E. coli* is the causative agent of approximately 80% of uncomplicated UTIs (Lindič, 2005).

*E. coli* isolates that cause UTI exhibit a number of specific characteristics and are classified, as uropathogenic *E. coli* (UPEC), a subgroup of extraintestinal pathogenic *E. coli* (ExPEC) (Russo & Johnson, 2000). UPEC strains mainly belong to the B2 phylogenetic group and to a lesser extent to the D group, while commensal strains belong to groups A and B1 (Picard et al., 1999). Further, some O-antigens (O1, O2, O4, O6, O7, O18 and O83) are more prevalent among uropathogenic *E. coli* strains and are therefore associated with UTI (Moreno et al. 2006). In comparison to commensal *E. coli* strains, UPEC possess an array of virulence factors namely, adhesins, toxins, polysaccharide coatings, invasins, iron uptake systems and systems to evade host immune responses (Oelschlaeger et al., 2002).

Of serious concern and an increasing health problem, on a global scale, is the appearance and spread of antimicrobial resistance. One of the major health care concerns is emergence of multidrug resistant bacteria and clinical microbiologists increasingly agree that multidrug resistant Gram-negative bacteria pose the greatest risk to public health (Kumarasamy et al., 2010). Therefore, it is essential to determine susceptibility of pathogenic strains for antimicrobial agents and association of antimicrobial resistance with virulence genes.

One of the means for acquiring specific virulence factor genes and antimicrobial resistance genes, is via mobile DNA (e. g. conjugal plasmids, transposons/integrations) (Aleksun &

Levy, 2007; Boerlin & Reid-Smith, 2008; Dobrindt et al., 2010). Hence, determining the prevalence of mobile elements and examining the correlation of antimicrobial resistance/virulence factor genes with mobile elements among UPEC is of great significance.

The search for alternative antibacterial agents is of great importance and colicins, toxic, narrow killing spectrum exhibiting proteins produced by colicinogenic *E. coli*, exhibit great potential as an alternative approach in the battle against microbes. It has been reported that colicins are effective against intestinal and UPEC strains (Rijavec et al., 2007; Schamberger et al., 2004; Stahl et al., 2004), and that they prevent colonization of urinary catheters (Trautner et al., 2005). To evaluate the potential of colicins as antimicrobial agents, studies on the prevalence of colicins and colicin resistance are needed.

In summary, to diminish the burden of UPEC, using effective preventive measures, data on phylogenetic groups, serogroups, virulence factor prevalence, antimicrobial resistance, presence of mobile DNA, colicin production and colicin resistance among *E. coli* isolates from different geographic regions must be assessed.

In Slovenia in 2002, we collected 110 *E. coli* isolates from humans with community-acquired urinary tract infections at the Institute of Microbiology and Immunology, Medical Faculty, Ljubljana, Slovenia. Isolation was performed according to standard laboratory protocols and UPEC were isolates from  $> 10^5$  colony-forming units (CFU) (Rijavec et al., 2006). These isolates were studied in order to obtain an extended characterisation, including phylogenetic groups, serogroups, virulence factor prevalence, antimicrobial resistance, presence of mobile DNA and colicinogeny and colicin resistance (Rijavec et al., 2006; Starčič Erjavec et al., 2006; Starčič Erjavec et al., 2007; Starčič Erjavec & Žgur-Bertok, 2008; Starčič Erjavec et al., 2008; Starčič Erjavec et al., 2009; Starčič Erjavec et al., 2010).

## 2. Phylogenetic groups and subgroups

*E. coli* strains can be assigned to one of four main phylogenetic groups: A, B1, B2, and D. The four groups were identified on the basis of allelic variation at enzyme-encoding genes detected by multilocus enzyme electrophoresis (Ochman et al., 1983, Whittam et al., 1983). Clermont et al. (2000) established the method of rapid and simple determination of the *E. coli* phylogenetic groups by a triplex PCR. This genotyping method is based on the amplification of a 279 bp fragment of the *chuA* gene; a 211 bp fragment of the *yjaA* gene; and a 152 bp fragment of TSPE4.C2, a noncoding region of the genome. The presence or absence of combinations of these three amplicons is used to assign *E. coli* to one of the four phylogenetic groups. However, to increase the discriminative power of phylogenetic group analysis, Escobar-Paramo et al. (2004) proposed the introduction of phylogenetic subgroups. They defined (Figure 1), apart from the phylogenetic group B1 (lacking *chuA* and *yjaA* and having Tspe4.C2), the following six subgroups: in the phylogenetic group A, subgroup A<sub>0</sub> (lacking *chuA*, *yjaA*, and Tspe4.C2) and subgroup A<sub>1</sub> (lacking *chuA*, having *yjaA*, and lacking Tspe4.C2); in the phylogenetic group B2, subgroup B2<sub>2</sub> (having *chuA* and *yjaA* and lacking Tspe4.C2) and subgroup B2<sub>3</sub> (having *chuA*, *yjaA*, and Tspe4.C2); in the phylogenetic group D, subgroup D<sub>1</sub> (having *chuA* and lacking *yjaA* and Tspe4.C2) and subgroup D<sub>2</sub> (having *chuA*, lacking *yjaA*, and having Tspe4.C2), Fig. 1.

Analysis of our collection of 110 UPEC isolates showed that 55 (50%) belonged to group B2, 28 (25%) to A, 21 (19%) to D, and 6 (5%) to the B1 group (Rijavec et al., 2006). When subgroups were considered the distribution of the isolates was: 4 (4%) of the studied isolates

belonged to the subgroup A<sub>0</sub>, 24 (22%) to A<sub>1</sub>, 6 (5%) to B<sub>2</sub><sub>2</sub>, 49 (45%) to B<sub>2</sub><sub>3</sub>, 16 (15%) to D<sub>1</sub> and 5 (5%) to D<sub>2</sub> (our unpublished data).

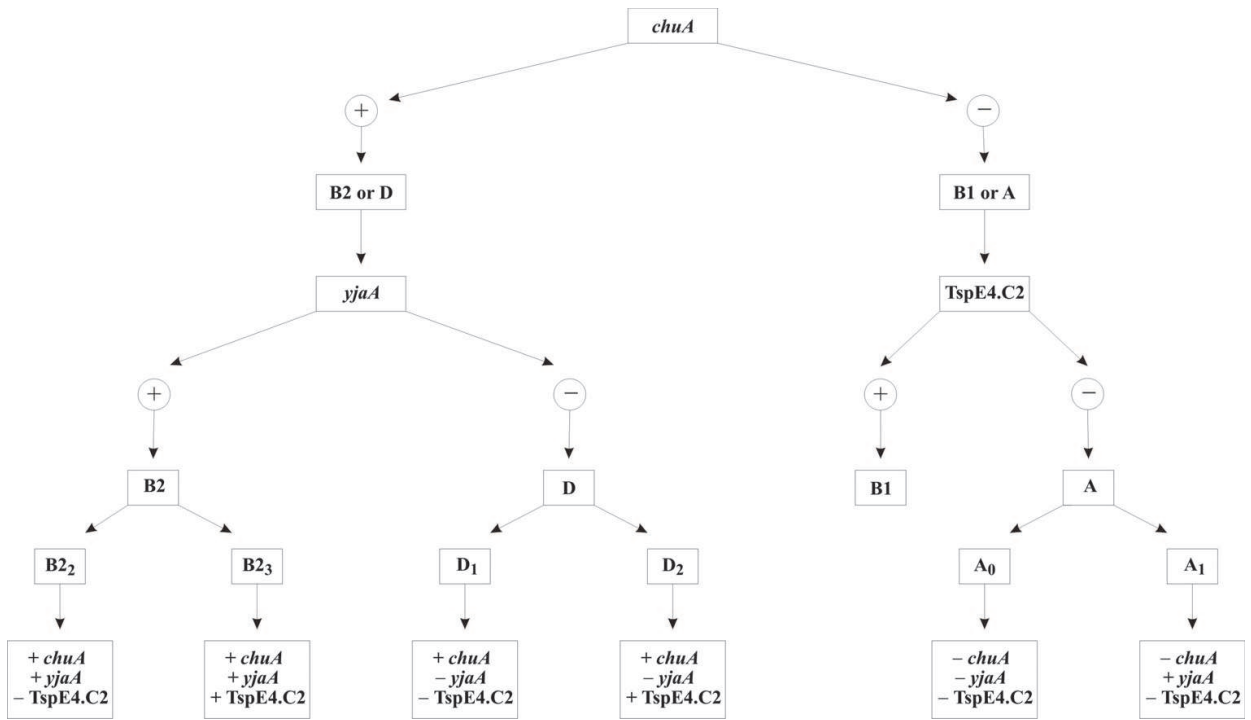


Fig. 1. Diagram of phylogenetic (sub)group determination.

The obtained distribution of the studied isolates into the phylogenetic groups, with the large majority classifying to the B2 group was expected since, it is known that ExPEC isolates mainly belong to the B2 phylogenetic group (Picard et al., 1999) however, the disproportionate distribution into the B<sub>2</sub><sub>2</sub> (5%) and B<sub>2</sub><sub>3</sub> (45%), and A<sub>0</sub> (4%) and A<sub>1</sub> (22%) subgroups was surprising.

3. Serogroups

Serotyping of *E. coli* isolates is an often used method for distinguishing possible pathogenic *E. coli* from commensal *E. coli*. It is complex since among *E. coli* 173 O-antigens, 80 K-antigens, and 56 H-antigens can be found. The O-, K-, and H-antigens can occur in many possible combinations therefore, the final number of *E. coli* serotypes is very high, 50,000-100,000 or more. However, the number of frequent pathogenic serotypes is limited. Two main groups of frequent serotypes are: (i) serotypes from diarrhoeal disease and (ii) serotypes from extraintestinal disease (Orskov & Orskov, 1992). Serotyping of the 110 uropathogenic strains revealed that 77 (70%) were O-antigen typable, 19 (17%) were O-nontypable, and 14 (12.7%) were rough. Sixty-three (57%) of the examined strains were H-antigen typable, 41 (37%) were H-antigen negative, and 6 (5%) were H-antigen nontypable. The O-typable strains were distributed into 31 serogroups. Nevertheless, the most frequent were O2 (9 isolates) and serotype O6:H1 (10 isolates). Five common serotypes were identified in three or more strains: O2:HNT (n = 3), O2:H6 (n = 3), O6:H1 (n = 10), O7:HNT (n = 3), and O74:H39 (n = 4) accounting for 30% of the serotypable isolates. A number of other serotypes were detected in one or two strains (Rijavec et al., 2006).

Serotype analysis of the studied strains revealed that they belonged to diverse serogroups. However, the most frequent were O2 and O6, which are well established as associated with urinary tract infections. The large majority, 96%, of the O2 and O6 isolates were assigned to the B2 phylogenetic group (Rijavec et al., 2006).

## 4. Virulence factors

Any component of a microbe that is required for, or potentiates its ability to cause disease is designated as a virulence factor. Many different virulence factors exist however, they can all be placed in one of the four major groups of virulence factors: adhesins, toxins, iron uptake systems and host immunity evading systems. Hence, virulence factors facilitate colonization and invasion of the host, avoidance or disruption of host defence mechanisms, injury to host tissue, and/or stimulation of a noxious host inflammatory response (Johnson and Steel, 2000).

### 4.1 Adhesins

Among the first virulence factors that come into play during establishment of an infection are adhesins. Besides their primary role as adhesin molecules, they can also function as invasins, promoters of biofilm formation and transmitters of signals to epithelial cells resulting in inflammation. Various adhesins have been identified and studied (Zhang & Foxman, 2003). In our analysis we focused on the four mostly studied: type 1 fimbriae, P fimbriae, S fimbriae and the Afa/Dr family of adhesins (Starčič Erjavec & Žgur-Bertok, 2008).

Type 1 fimbriae are the most common adhesive organelles of *E. coli* strains. They are encoded by the vast majority of uropathogenic *E. coli* (UPEC) isolates and many other pathogenic and commensal isolates (Bower et al., 2005). Receptors for type 1 fimbriae are present on erythrocytes, buccal epithelial cells, intestinal cells, vaginal cells and uroepithelial cells (Johnson, 1991). The *fimH* gene that was tested in our study (Starčič Erjavec & Žgur-Bertok, 2008), encodes the minor subunit protein FimH that mediates binding to the receptor. FimH has several variants: UPEC strains have a FimH that binds both monomannose and trimannose containing glycoprotein receptors, while commensal *E. coli* isolates typically show high affinity binding to only trimannose residues (Bower et al., 2005). Type 1 fimbriae function not just as adhesins, but also as invasins for bladder epithelial cells (Martinez et al., 2000).

P fimbriae are among the best studied fimbrial adhesive fibres of UPEC strains. The P fimbrial adhesin molecule (PapG) recognizes globoseries of glycolipids as receptors (Zhang & Foxman, 2003). In our study the *papC*, *papGII* and *papGIII* genes were included (Starčič Erjavec & Žgur-Bertok, 2008). The *papC* gene encodes the outer membrane usher protein that is required for ordered P fimbriae assembly (Thanassi et al., 1998). Many studies showed that P fimbriae occur more frequently among UPEC than fecal isolates. Based on binding specificities, P fimbriae are grouped into three major classes: I, II and III (Zhang & Foxman, 2003).

S fimbriae bind to sialyl galactosides. Studies showed that *E. coli* UTI isolates were at least two times more likely to carry S fimbriae genes (*sfa* operon) than fecal strains (Zhang & Foxman, 2003). In our study the fimbriae typical gene sequence *sfa/foc* was investigated (Starčič Erjavec & Žgur-Bertok, 2008).

The Afa/Dr family consists of 13 known adhesins that all bind to the Dra blood group antigen present on the complement regulatory molecule CD55, also known as decay-



accelerating factor (DAF) (Bower et al., 2005). The *E. coli* strains harbouring these adhesins have been found to be associated with UTIs and also with various enteric infections (Servin, 2005).

Among the tested adhesin genes in the studied UPEC isolates (Table 1), the type 1 fimbriae were the most prevalent - the *fimH* gene nucleotide sequences were detected in 107 strains (97%). The P fimbriae were also abundant, the *papC* encoding gene sequence was found in 54 strains (49%), 37 strains (34%) harboured the class II *papG* adhesin sequence and 14 strains (13%) harboured the class III *papG* adhesin. Twenty-six (24%) possessed the S fimbriae typical gene sequence *sfa/foc*. Only 2 strains (2%) harbored *afa/dra* sequences (Starčič Erjavec & Žgur-Bertok, 2008).

Analysis of the distribution of adhesin gene sequences among phylogenetic groups revealed that adhesin gene sequences were differently distributed (Table 1): *fimH* sequences were found with similar prevalence in strains of all four phylogenetic groups, *papC* sequences were found in all phylogenetic groups, but they were most prevalent (65%) among B2 group strains. The association of *papC* with the B2 group was statistically significant. Nevertheless, *papGII* sequences were found in all phylogenetic groups, in contrast, *papGIII* adhesin sequences were exclusively found among strains of the B2 group.

Further, a very high, statistically significant, prevalence of S fimbriae in the B2 group was detected, 45% of the strains belonging to the B2 group harboured *sfa/foc* sequences (Starčič Erjavec & Žgur-Bertok, 2008).

## 4.2 Toxins

Toxins affect an astonishing variety of fundamental eukaryotic processes and thereby harm the host (Kaper, 2004) and are important virulence factors in a variety of *E. coli* mediated diseases - in UTI the production of toxins by colonized *E. coli* may cause an inflammatory response that leads to the UTI symptoms (Zhang & Foxman, 2003).

In pathogenic *E. coli* strains several important toxins have been identified, the best known, associated with UPEC strains, are alpha hemolysin (HlyA) and cytotoxic necrotizing factor 1 (CNF1) (Zhang & Foxman, 2003).

Well known toxins are also invasins, the Ibe proteins that help *E. coli* strains to invade the human brain microvascular endothelial cells (Xie et al., 2004). The presence of IbeA protein is statistically significantly higher in strains causing cystitis and/or pyelonephritis (Johnson et al., 2005). The gene for the uropathogenic specific protein (USP) that was found as a homologue of the *Vibrio cholerae* zonula occludens toxin encoding gene (Kurazono et al., 2000), has been significantly more often detected in UPEC strains than in fecal strains from healthy individuals (Bauer et al., 2002).

Among the screened toxin encoding genes in the studied UPEC isolates (Table 1), the *usp* gene had the highest prevalence as *usp* specific nucleotide sequences were detected in 48 strains (44%). The prevalence of *hlyA* and *cnf1* was similar, 28 (25%) and 25 strains (23%), respectively, possessed the tested nucleotide sequences. Only 10 strains (9%) harboured *ibeA* sequences (Starčič Erjavec et al., 2008).

Analysis of the distribution of toxin encoding genes among the determined phylogenetic groups of studied strains (Table 1) revealed that the tested toxin encoding genes *hlyA*, *cnf1*, *ibeA* and *usp* were mostly harboured by UPEC strains belonging to the B2 phylogenetic group, as 26 (93%) of the strains harbouring *hlyA* belonged to the B2 group, 25 (100%) harbouring *cnf1*, 9 (90%) harbouring *ibeA* and 42 (88%) harbouring *usp* belonged to the B2 phylogenetic group (Starčič Erjavec et al., 2008).

	Prevalence (N, [%])				
		Phylogenetic group			
Trait	Total (N=110)	A (N=28)	B1 (N=6)	B2 (N=55)	D (N=21)
Virulence factors					
Adhesins					
<i>fimH</i>	107 (97)	28 (26)	5 (5)	53 (50)	21 (20)
<i>papC</i>	54 (49)	8 (15)	1 (2)	35 (65)	10 (19)
<i>papGII</i>	37 (34)	5 (14)	1 (3)	21 (57)	10 (27)
<i>papGIII</i>	14 (13)	0 (0)	0 (0)	14 (100)	0 (0)
<i>sfa/foc</i>	26 (24)	1 (4)	0 (0)	25 (96)	0 (0)
<i>afa/dra</i>	2 (2)	1 (50)	0 (0)	1 (50)	0 (0)
Toxins					
<i>hlyA</i>	28 (25)	1 (4)	0 (0)	26 (93)	1 (4)
<i>cnf</i>	25 (23)	0 (0)	0 (0)	25 (100)	0 (0)
<i>ibeA</i>	10 (9)	0 (0)	0 (0)	9 (90)	1 (10)
<i>usp</i>	48 (44)	1 (2)	0 (0)	42 (88)	5 (10)
Iron uptake systems					
<i>iucD</i>	46 (42)	8 (17)	0 (0)	27 (59)	11 (24)
<i>iroCD</i> (=iroN)	51 (46)	9 (18)	0 (0)	41 (80)	1 (2)
<i>ireA</i>	22 (20)	4 (18)	0 (0)	12 (55)	6 (27)
<i>fyuA</i>	84 (76)	17 (20)	3 (4)	49 (58)	15 (18)
Host immunity evading systems					
K1	6 (5)	1 (17)	1 (17)	4 (67)	0 (0)
K5	11 (10)	2 (18)	1 (9)	8 (73)	0 (0)
<i>traT</i>	63 (57)	20 (32)	4 (6)	29 (46)	10 (16)
<i>tcpC</i>	23 (21)	0 (0)	0 (0)	23 (100)	0 (0)
Antimicrobial susceptibility					
Ampicillin	57 (52)	12 (21)	5 (9)	32 (56)	18 (32)
Ciprofloxacin	99 (90)	23 (23)	5 (5)	52 (53)	19 (19)
Chloramphenicol	50 (45)	7 (14)	3 (6)	32 (64)	8 (16)
Kanamycin	95 (86)	20 (21)	5 (5)	51 (54)	19 (20)
Mezlocillin	59 (54)	12 (20)	5 (8)	34 (58)	8 (14)
Nalidixic acid	64 (58)	12 (19)	3 (5)	38 (59)	11 (17)
Norfloxacin	99 (90)	23 (23)	5 (5)	52 (52)	19 (19)
Streptomycin	69 (63)	15 (22)	5 (7)	40 (60)	9 (13)
Sulfamethoxazole-Trimethoprim	87 (79)	18 (21)	6 (7)	49 (56)	14 (16)
Tetracycline	47 (43)	6 (13)	4 (9)	33 (70)	4 (9)
Trimethoprim	72 (65)	14 (19)	6 (8)	41 (57)	11 (15)
Mobile genetic elements					
RepFIA	20 (18)	7 (35)	0 (0)	10 (50)	3 (15)
RepFIB	57 (52)	18 (32)	2 (4)	26 (46)	11 (19)
RepFIIA	24 (22)	7 (29)	0 (0)	15 (63)	2 (8)
Integron	34 (31)	12 (35)	1 (3)	12 (35)	9 (26)
Colicinogenity	42 (38)	12 (29)	3 (7)	20 (48)	7 (17)

Table 1. Characterized traits in studied UPEC isolates – prevalence and distribution among phylogenetic groups.

### 4.3 Iron uptake systems

Iron is an essential cofactor for many basic metabolic pathways and bacteria have developed specialized iron uptake systems to capture iron. The most prominent are the siderophores, iron-binding molecules that are taken up by special siderophore receptors and ATP-consuming porin-like transporters in the bacterial outer membrane (Schaible & Kaufmann, 2004). Siderophores can be classified into three groups: (i) the catecholate type (enterobactin, salmochelin = enterochelin), (ii) hydroxamate type (aerobactin) and (iii) a mixed type - a combination of both (yersiniabactin) (Grass, 2006; Schaible & Kaufmann, 2004). In addition to siderophore synthesis strains can use siderophores produced and released into the extracellular medium by other bacteria and even fungi. In the host, bacteria may use iron sources such as heme, hemoglobin, hemopexin, and iron bound to transferrin and lactoferrin (Braun & Braun, 2002). Apart from the siderophores and their receptors, autotransporters, virulence-associated proteins in gram-negative bacteria, can also play a role in obtaining iron for example, the hemoglobin protease Hbp (Otto et al., 2002). All autotransporter proteins are energy-independent secreted via a type 5 secretion system and possess an overall unifying structure, comprising (i) an amino-terminal leader peptide (for secretion across the inner membrane), (ii) the secreted mature protein (or passenger domain), and (iii) a dedicated C-terminal domain, which forms a pore in the outer membrane through which the passenger domain passes to the cell surface (Henderson & Nataro, 2001).

In our study the following iron uptake systems genes were investigated (Table 1): *iucD* for aerobactin, *iroCD* and *iroN* for salmochelin, *fyuA* for yersiniabactin and *ireA* of a putative TonB-dependent siderophore receptor. The iron uptake system with the highest prevalence was yersiniabactin, the *fyuA* gene coding for the ferric yersiniabactin receptor was found in 84 strains (76%). The salmochelin uptake system genes *iroN*, coding for the catecholate siderophore receptor, and *iroCD* coding for proteins needed in salmochelin transport, were found in 51 (46%) of studied strains. The aerobactin iron uptake system gene *iucD*, coding for lysine:N6-hydroxylase needed in aerobactin biosynthesis, was detected in 46 strains (42%) and the *ireA* gene was harboured by 22 studied strains (20%) (our unpublished data). Analysis of the distribution of iron uptake systems encoding genes among the determined phylogenetic groups of studied strains (Table 1) revealed that all of the studied iron uptake systems were mostly harboured by UPEC strains belonging to the B2 phylogenetic group, as 41 (80%) of the strains harbouring *iroCD* and *iroN* belonged to the B2 group, 49 (58%) harbouring *fyuA*, 27 (59%) harbouring *iucD* and 12 (55%) harbouring *ireA* belonged to the B2 phylogenetic group (our unpublished data).

### 4.4 Host immunity evading systems

Pathogenic microbes avoid host defences using a wide array of virulence factors, ranging from polysaccharide capsules, serum resistance proteins to immune system modulating agents (Kaper et al., 2004).

Capsules are the discrete structural layers of extracellular polysaccharides that envelope the cell and allow the bacteria to evade or counteract the host immune system (Roberts, 1996). Capsules protect pathogens from assaults such as opsonophagocytosis and complement-mediated killing (Roberts, 1995); and in case of acidic capsules they can act as “sponges” to sequester and neutralize antimicrobial peptides (Llobet et al., 2008). Virtually all UPEC have a K-type polysaccharide capsule. Most UPEC express Group 2 or 3 capsules on their surfaces (Goller and Seed, 2010) and the K-antigens K1, K5, K30 and K92 are the most prevalent among UPEC (Johnson, 1991).



TraT, the surface exclusion protein of the plasmid transfer system, has been implicated in increased serum resistance (Binns et al., 1979). TraT is one of the most prevalent virulence factors in pathogenic *E. coli* isolates, as *traT* sequences have been found in 50% of *E. coli* isolates from sepsis (Ananias & Yano, 2008), in 68% of uroseptic *E. coli* (Johnson & Stell, 2000), and in 65% of UPEC isolates from cystitis, pyelonephritis, prostatitis (Johnsons et al., 2005a).

Recently, TcpC, a Toll/interleukin-1 receptor (TIR) domain-containing protein of uropathogenic *E. coli* inhibiting Toll-like receptor (TIR) and MyD88-specific signaling, impairing the innate immune response was described (Cirl et al., 2008). The *tcpC* homologous sequences were found in about 40% of *E. coli* isolates from individuals with pyelonephritis, in 21% cystitis isolates, in 16% asymptomatic bacteriuria and in only 8% of commensal isolates therefore, TcpC is implicated in the severity of urinary tract infections (UTI) in humans (Cirl et al., 2008).

Among the 110 studied UPEC isolates (Table 1) 6 (5%) had the K1-capsule and 11 (10%) had the K5-capsule (Starčič Erjavec et al., 2007). The *traT* sequences were found in 63 (57%) (Rijavec et al., 2006) and the *tcpC* sequences were found in 23 (21%) (Starčič Erjavec et al., 2010) of studied UPEC isolates.

Analysis of the distribution of the studied immune system evading characteristics among the determined phylogenetic groups (Table 1) showed that, isolates with K1- and K5-capsules were the most prevalent in the B2 group, 4 (67%) and 8 (73%), respectively however, capsule possessing isolates also belonged to the A and B1 group, albeit at low prevalence. One (17%) K1-capsule coated strain was found in the A and one in the B1 group and 2 (18%) K5-capsule coated strains in the A group and one (9%) in the B1 group. The *traT* sequence was more evenly distributed among all four phylogenetic groups A, B1, B2 and D – the prevalence was 20 (32%), 4 (6%), 29 (46%) and 10 (16%), respectively. On the other hand, the *tcpC*-encoding strains were found only in the B2 group.

## 5. Antimicrobial susceptibility

An important task in clinical microbiology is the performance of antimicrobial susceptibility testing in order to detect possible drug resistance in common pathogens and to assure susceptibility to drugs of choice for particular infections (Jorgensen & Ferraro, 2009). Therefore, several studies on the subject of antimicrobial susceptibility and *E. coli* isolates from UTI have been performed (e. g. Karlowsky et al., 2003; Kahlmeter & Mendeny, 2003; Yilmaz et al., 2009).

In the year 2002, when the studied isolates were collected, treatment of UTI in outpatients in Slovenia was as follows: a course of antibiotics (therapy of choice - trimethoprim 160 mg or trimethoprim/sulfamethoxazole 160 mg/800 mg twice daily for 3 days) and advice to consume sufficient quantities of liquids (2-3 l per day) (Car et al., 2003).

The studied uropathogenic strains were screened for susceptibility to the following antibiotics: ampicillin, chloramphenicol, kanamycin, streptomycin, tetracycline, trimethoprim, trimethoprim-sulfamethoxazole, ciprofloxacin, norfloxacin, nalidixic acid, mezlocillin, amikacin, cefotaxime, cefotiam, cefoxitin, ceftazidime, and gentamicin. Susceptibilities to the tested antibiotics ranged from 109 (99%) susceptible to amikacin, cefotaxime, ceftazidime, to 47 (43%) susceptible to tetracycline. Antibiotics with the highest prevalence of susceptibility, apart from amikacin, cefotaxime, ceftazidime, were to cefotiam, cefoxitin, and gentamicin as 108 (98%), 103 (94%), and 101 (92%) of the studied

strains, respectively, were susceptible. Antibiotics with the lowest prevalence of susceptibility, apart from tetracycline, were to chloramphenicol, ampicillin, mezlocillin and nalidixic acid, as 50 (45%), 57 (52%), 59 (54%) and 64 (58%), respectively, were susceptible (Rijavec et al., 2006).

Forty-six (42%) of the studied strains were resistant to more than three classes of the tested antimicrobial agents—beta lactams, quinolone/fluoroquinolone, trimethoprim/trimethoprim-sulfamethoxazole, tetracycline, chloramphenicol, aminoglycosides (streptomycin, kanamycin)—and were designated as multidrug resistant (MDR). Subsequently, the association between MDR and the phylogenetic group was examined. A statistically significant correlation between non-MDR and the B2 group was determined and a significant correlation between MDR and the D phylogenetic group was found. On the other hand, there were no statistically significant correlations between MDR or non-MDR strains and the A or B1 groups (Rijavec et al., 2006).

## 6. Mobile genetic elements

The loss and gain of mobile genetic elements has a pivotal role in shaping the genomes of pathogenic bacteria. Horizontal gene transfer is an important mechanism that rapidly disseminates new traits to recipient organisms. Acquiring these new traits is crucial in promoting the fitness and survival of a pathogen while it coevolves with its host (Croxen & Finlay, 2010).

Bacterial plasmids, self-replicating, extrachromosomal elements are key agents of change in microbial populations. They promote the dissemination of a variety of traits, including virulence, enhanced fitness, resistance to antimicrobial agents, and metabolism of rare substances (Johnson & Nolan, 2009). *E. coli* strains possess a variety of plasmid types, of different sizes, usually ranging in size from approximately 300 bp to 2400 kbp nevertheless, each plasmid must harbour a replication region (Kado, 1998). Plasmids are classified into incompatibility groups mostly on the basis of the replication region (Couturier et al., 1988). Integrons are assembly platforms that incorporate exogenous open reading frames by site-specific recombination and convert them to functional genes by ensuring their correct expression. Integrons are composed of three key elements necessary for the capture of exogenous genes: a gene (*intl*) encoding an integrase belonging to the tyrosine-recombinase family; a primary recombination site (*attI*); and an outward-orientated promoter (Pc) that directs transcription of the captured genes. At present, five classes of mobile integrons are distinguished. These classes have been historically defined based on the sequence of the encoded integrases, which show 40–58% identity. All five classes are physically linked to mobile DNA elements, such as insertion sequences, transposons and conjugative plasmids, all of which can serve as vehicles for intraspecies and interspecies transmission of genetic material. Class 1 integrons are associated with functional and non-functional transposons derived from Tn402 that can be embedded in larger transposons, such as Tn21. Class 2 integrons are exclusively associated with Tn7 derivatives and class 3 integrons are thought to be located in a transposon inserted in a plasmid. The other two classes of mobile integrons, class 4 and class 5, have been associated only with *Vibrio* species; class 4 is a component of a subset of SXT elements found in *Vibrio cholerae*, and class 5 is located in a compound transposon carried on a plasmid in *Vibrio salmonicida* (Mazel, 2006).

The studied UTI strains were screened for replication regions of IncFI and IncFII plasmids. We found (Table 1) a high (62 strains, 56%) incidence of *rep* IncF sequences among the

examined UPEC strains. Particularly prevalent were RepFIB sequences that were detected in 57 (52%) of the strains while RepFIA and RepFIIA were found in 20 (18%) and 24 (22%) strains, respectively. *rep* sequences were found in all four phylogenetic groups. Of the 62 isolates harbouring at least one of the tested IncF replicons, 20 belonged to group A, 2 to B1, 27 to B2, and 13 to group D (Rijavec et al., 2006).

Since only class 1, 2 and 3 of integrons were shown to be associated with pathogenic *E. coli* in our study we focused only on these three classes. Analysis (Table 1) revealed that 29 (26%) of the strains harboured a class 1 integron, 1 strain (1%) contained a class 1 and a class 2 integron, and 4 strains (4%) a class 2 integron. Analysis of the distribution of integrons with regard to the phylogenetic group showed that integron sequences were found in all four groups. Of the 34 isolates harbouring integron sequences, 12 belonged to group A, 1 to B1, 12 to B2, and 9 to group D (Rijavec et al., 2006).

## 7. Colicins

Colicins are bacteriocins produced by *E. coli* strains. As other bacteriocins, colicins are extracellular bacterial toxic proteins that are active against the same, or closely related species as the producer cell (Daw & Falkner, 1996). The mechanism of action of these compounds involves adsorption to specific receptors located on the external surface of sensitive bacteria followed by killing via one of three primary mechanisms: i) formation of channels in the cytoplasmic membrane, ii) degradation of cellular DNA or iii) inhibition of protein synthesis (Riley & Gordon, 1999). Because of their narrow range of activity, it has been proposed that the primary role of bacteriocins is to mediate intraspecific, or population level, interactions (Riley, 1998) however, bacteriocins have also been implicated in virulence determination, since many pathogenic strains harbour plasmid-encoded bacteriocins, for example the ColV plasmid of UPEC isolates (Johnson & Nolan, 2009). Typically, 25–50% of *E. coli* isolates are colicinogenic and usually, the percentages are higher among pathogenic than commensal strains (Riley & Gordon, 1996). Due to high levels of colicinogenity in natural *E. coli* populations, high levels of colicin resistance are known to occur (Feldgarden & Riley, 1998).

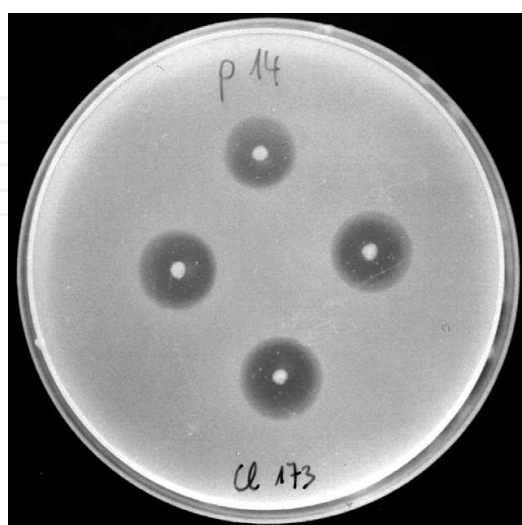


Fig. 2. A colicinogenic uropathogenic strain was stab inoculated on 4 points on an agar plate and overlaid with a sensitive *E. coli* strain.

Among the studied UPEC isolates 42 (38%) exhibited colicinogenic activity (Starčič Erjavec et al., 2006). Each of the 110 UPEC strains was resistant to at least 3 colicinogenic strains from Pugsley's collection of colicinogenic strains (Pugsley & Oudega, 1987), 23 UPEC strains (21%) were resistant to all 20 tested Pugsley's strains (our unpublished data). Colicinogenic strains were found in all four phylogenetic groups (Table 1) however, most colicinogenic strains, 20 (48%) belonged to the B2 group (our unpublished data).

## 8. Conclusion

Our investigation of UPEC isolates from Slovenia revealed a high prevalence of drug resistance and multidrug resistance. The virulence profile of the examined strains was comparable to that of strains from other geographic regions.

## 9. Acknowledgment

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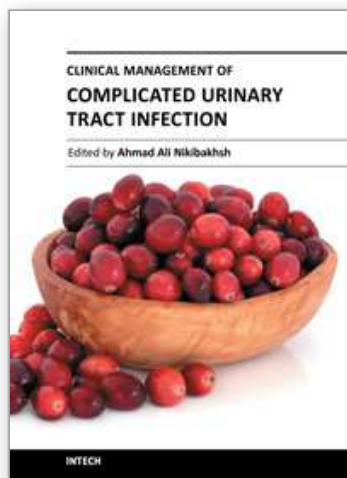
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## **Clinical Management of Complicated Urinary Tract Infection**

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Complicated urinary tract infections (cUTIs) are a major cause of hospital admissions and are associated with significant morbidity and health care costs. Knowledge of baseline risk of urinary tract infection can help clinicians make informed diagnostic and therapeutic decisions. Prevalence rates of UTI vary by age, gender, race, and other predisposing risk factors. In this regard, this book provides comprehensive information on etiology, epidemiology, immunology, pathology, pathogenic mechanisms, symptomatology, investigation and management of urinary tract infection. Chapters cover common problems in urinary tract infection and put emphasis on the importance of making a correct clinical decision and choosing the appropriate therapeutic approach. Topics are organized to address all of the major complicated conditions frequently seen in urinary tract infection. The authors have paid particular attention to urological problems like the outcome of patients with vesicoureteric reflux, the factors affecting renal scarring, obstructive uropathy, voiding dysfunction and catheter associated problems. This book will be indispensable for all professionals involved in the medical care of patients with urinary tract infection.

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