[Frontiers in Bioscience 8, e235-244, January 1, 2003]

MOLECULAR EPIDEMIOLOGY OF *ESCHERICHIA COLI* MEDIATED URINARY TRACT INFECTIONS

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1. ABSTRACT

Urinary tract infection (UTI) is one of the most frequently acquired bacterial infections and *Escherichia coli* accounts for as many as 90% of all UTIs seen among ambulatory populations. Risk factors for UTIs include host behaviors, host characteristics and bacterial characteristics. Sexual activity and contraceptive method are the strongest determinant of a symptomatic UTI episode. The characteristics of cell receptors, anatomical differences and genetic predisposition in the host may be important determinants of increased risk for recurrent infections. Uropathogenic *E. coli* have special characteristics causing urovirulence. They most likely belong to phylogenic lineage B2. They usually possess specific adhesins such as P, S or Dr to facilitate their colonization in the urinary tract, and toxins such as hemolysin and cytotoxic necrotizing factor 1 to provoke inflammatory response that possibly are responsible for the development of UTI symptoms. Interestingly, virulence genes in uropathogenic *E. coli* are often co-located on pathogenicity islands. Currently, however, none of the known virulence genes or set of genes can clearly define the prototypic uropathogenic *E. coli*. Additional studies are needed to identify factors that promote uropathogen transmission and persistent colonization, and to investigate potential different modes of pathogenesis by *E. coli* strains with different compositions of virulence genes.

2. INTRODUCTION

Urinary tract infection (UTI) is one of the most commonly acquired bacterial infections in ambulatory and hospitalized populations (1). Women are at much higher risk of UTI than men because of differences in anatomy. In women, the moist peri-urethral areas and vagina enable the growth of uropathogens; the short distant of urethral opening to the anal opening and bladder increase the chance for infection from ascending uropathogens. Overall, approximately half of all women have had a UTI by their late 20s (2, 3). About 20-30 percent of women with first UTI will have two or more infections (4); and, for 5 percent, chronic recurring infections which greatly disrupt a woman's life (5). The large number of women affected by UTI each year creates a heavy burden on society. In the United States, the annual total direct and

indirect costs of UTI in 1995 were estimated to be $1.6 billion as the result of urinary infections suffered by an estimated 11.3 million women (3).

The family of bacteria that most frequently cause UTIs is the *Enterobacteriaceae*, gram-negative facultative anaerobic bacilli commonly found in the large intestine. The most common of these bacteria is *Escherichia coli*, which accounts for about 90% of all UTIs seen among ambulatory patients (6). Other *Enterobacteriaceae*, including *Klebsiella* and *Proteus*, as well as members of the *Pseudomonas* family, also cause UTIs, especially among women with complicated infections (7). Staphylococci may cause 5 to 10 percent of urinary tract infections in many populations (8).

Since uropathogens usually belong to species found in the residential bacteria of the normal intestinal microflora, UTIs are often regarded as opportunistic infections; that is, resulting from fecal organisms being mechanically moved into the lower urinary tract. Despite a significant element of opportunism, uropathogens are not random samples of the fecal isolates. This was recognized a long time ago. In the summary of the pyelonephritis conference in 1959, the first professional meeting on the UTI research, Edward Kass (9) noted that " It is apparent from the observations of many workers …, that individual bacterial strains differ with respect to capacity to produce manifest disease of the urinary tract." These early investigators knew that strains causing UTI must have special characteristics causing urovirulence. Since then, great advances have been made in understanding the molecular pathogenesis of UTI.

In this review, we will begin with a description of the epidemiology of UTI. Our focus then turns to the virulence features of uropathogenic *E. coli* and on what might distinguish them from avirulent *E. coli* that are part of normal human bowel flora.

3. EPIDEMIOLOGY OF URINARY TRACT INFECTIONS

3.1. Clinical manifestations

A UTI is defined as a significant number of pathogenic organisms in the urinary system. If symptoms, such as painful or frequent urination or blood in the urine, are present, as few as 100 uropathogenic bacteria per milliliter urine may be considered significant (8). UTIs occurring in otherwise healthy individuals with normal urinary tracts and without pre-disposing conditions are regarded as uncomplicated (10). Most community-acquired UTIs are of this type. Clinical manifestations of UTI by *E. coli* are very variable in extent and severity. Bacteria can be detected at high concentrations in the urinary tract in individuals during routine urine examination. However, many of these individuals experience no symptoms. This condition is termed asymptomatic bacteriuria (ABU). Cases of symptomatic bacteriuria are classified either as cystitis (CY) when infection is limited to bladder or pyelonephritis (PY) when the kidney is infected (7, 10). While cystitis in the otherwise healthy individual generally resolves without sequelae, pyelonephritis can cause serious morbidity and can be fatal. Patients with abnormal or obstructed urinary tracts or with compromised immune systems are at high risk of UTI. These infections are often referred as complicated UTIs (10). There is an increased risk in this group that a simple urinary tract infection may progress to systemic infection.

3.2. Behavioral risk factors

Sexual activity and contraceptive method are the best-described behavioral UTI risk factors. There is a marked increase in UTI diagnosis (2) or incidence (3) around the average age of first sexual intercourse. Foxman *et al.* estimated that initiating sexual activity was associated with 3.5 fold increase in UTI risk (11). Virtually all women become bacteriuric following sexual intercourse (12, 13) and sexual activity is the strongest determinant of a symptomatic UTI episode. Furthermore, various studies have associated UTI with frequent sexual activity (14, 15, 16). The hypothesized mechanism of increased UTI risk by sexual activity is trauma and movement of bacteria from the vagina and/or bowel to the urethral opening (7). In addition, sexual activity might also increase the risk of UTI by increasing exposure to uropathogens. After adjusting for frequency of vaginal intercourse, women who have a sex partner of a year or more compared to less than one year have half the risk of first UTI (17). Evidence of sexual transmission of uropathogens has been reported (18).

Contraceptive use is also associated with risk of UTI. The traumatic effects of vaginal intercourse on UTI risk may be increased by condom use (11, 14, 17). Oral contraceptives double UTI risk relative to using no birth control method (17), even after adjusting for frequency of vaginal intercourse. Diaphragm use and spermicide enhance vaginal colonization of uropathogens associated with recurrent infection (16, 19, 20).

Many personal hygiene behaviors that might facilitate the migration of uropathogen from the bowel to the peri-urethral area have previously been hypothesized as potential risk factors. However, none of these factors have been shown to increase risk of UTI in controlled studies (4, 21, 22).

3.3. Host characteristics

Four groups are at increased risk of UTI: school-age girls, men with prostate enlargement, the elderly, and young women in their sexually active years (5). Urinary tract abnormalities or a compromised host are major explanations for the increased risk in the first three groups. Host behavior is a major determinant among sexually active young women, however, not all individuals in these high risk groups become infected and only a small proportion go on to have recurrent infections. Some of these differences in risk may be explained by characteristics of cell receptors, anatomical differences and genetic predisposition.

The density and accessibility of receptors for uropathogenic *E. coli* adherence is an important host factor in determining UTI risk. The P1 blood phenotype has been associated with the carriage of pap$^+$ *E. coli* (23, 24, 25) presumably because the P1 antigen is identical to the receptor recognized by P fimbriae. The secretor status, determined by the secretor gene, influences the expression of host cell surface receptors as well as the presence or absence of these molecules in the mucosal secretions. Non secretors of blood group antigen are significantly more susceptible than secretors to be colonized by P- fimbriated uropathogenic *E. coli*, which is most likely due to the expression of globoseries glycolipid receptors found on the cells of nonsecretors (26). It is also likely that non secretors have fewer soluble receptors in their mucosal secretions and therefore a lower capacity for competitive interference with pathogen adherence (26, 27). Women with three or more UTI in the past 12 months are more likely to be non-secretors of blood group antigens (28, 29). Furthermore, secretion of cytokines or presence of immunoglobulins may limit the bacteria's ability to either colonize or invade the mucosa (30).

Anatomical differences in the urogenital tract may play a role in the development of recurring UTIs among healthy women. For example, in a study comparing women with history of recurrent UTI (cases) to women without a UTI history (controls), cases were more likely than controls to have a shorter distance between the urethra and anus (31). Because the rectum is a common uropathogen reservoir, urethral colonization may occur more frequently when the distance to the urethra is shorter (31).

There is some evidence suggesting that the frequency of asymptomatic bacteriuria varies by ethnic group (2, 32, 33). However, whether such variation exists for symptomatic UTI is not known. Finally, having a mother with a UTI history, and developing a first UTI at an early age are also associated with recurrence after adjusting for other important behavioral factors (19).

The other major determinant of UTI risk is the pathogen itself. In the next section we describe the characteristics of the most common uropathogen, *E. coli*.

4. *E. COLI* AS A UROPATHOGEN

4.1. Colonization of the colon, vagina and periurethral area

E. coli is a residential bacterium of the large intestinal in almost every individual, although it can be isolated from the upper respiratory tract and urogenital tract in some healthy individuals (34). Since UTIs usually begin with colonization of the urethra by *E. coli* strains from the colon, stable maintenance of a uropathogenic strain in the colon provides a constant source of bacteria and thus increases the chance for seeding the urethral opening. About 3/4 of the time the urinary isolate responsible for infection can also be isolated from a rectal specimen of the same individual (35). Further more, about half of recurrences are due to re-infection with the same strain coming from an internal or exogenous source (21, 36). The internal source may be in the rectal or fecal flora or vaginal flora or possibly even the bladder: it was hypothesized that an intracellular reservoir of *E. coli* in the urinary tract may seed recurrence (37).

E. coli colonization of the peri-urethral and vagina can also increase the opportunity for a uropathogen to enter the urethral opening. Periurethral colonization with a specific strain precedes episodes of significant bladder bacteriuria with the same organism (38). The infecting *E. coli* can be found in the vaginal cavity of most (88%) women with UTI caused by *E. coli* (35). Among women of child bearing age, the healthy vaginal tract microflora is usually dominated by lactobacilli. Any disruption of the resident microflora opens the way for colonization of the vaginal tract by *E. coli*. Spermicide inhibits growth of lactobacilli leading to overgrowth of *E. coli*; spermicide use is associated with increased UTI risk (16, 19). Antibiotic use also increases risk of UTI (11, 39), probably due to the same mechanism. *E. coli* can be occasionally found in the flora of the nasopharynx (34). The significance of such colonization on UTI risk is not clear. However, it may facilitate the successful colonization of the colon with the same strain because of constant seeding of the gastrointestinal tract.

4.2. *E. coli* population structure and uropathogenic clones

E. coli is a species of great genetic diversity by any measure. Over 250 serotypes have been identified based on O, H and K antigens (40). The DNA/DNA reassociation threshold and 16S rRNA sequence show extended intraspecies variation (41). There is also considerable variation in the DNA content of different *E. coli* strains. Differences up to one million base pairs (Mb) in chromosome size have been demonstrated in natural populations (42). Given the existence of a high degree of genetic diversity in *E. coli* species, a persistent question in the study of the etiology of UTI by *E. coli* is what, if any, are the genetic differences between pathogenic (disease origin) and nonpathogenic (commensal origin) strains. Studies, including ours, have demonstrated that UTI causing *E. coli* are not a random sample of the fecal flora (44, 43). There are measurable differences in two broad contexts: 1) phylogenic segregation between pathogenic and nonpathogenic strains; and 2) possession of specialized virulence genes that are often horizontally acquired and are usually absent in nonpathogenic strains (discussed in Section 4.3).

4.2.1. Phylogenic segregation

Despite obvious genetic diversity, *E. coli* species has a clonal population. Data supporting the clonality of *E. coli* populations are extensive: coefficients of linkage disequilibrium are near their theoretical maxima (45, 46) and are independent of map distance between the genes (47); strains of identical alloenzymic profile can be recovered from geographically and temporally unassociated hosts. Although horizontal gene transfers are often observed, the frequency of such transfer is too low to destroy linkage disequilibrium. It is apparent that, at the

population and the chromosomal level, *E. coli* are basically clonal. *E. coli* have been broadly classified into five major groups: phylogenetic lineages A, B1, B2 and D, and non-aligned group E (48).

Early observations of the association of particular serotypes with disease suggest that pathogenic strains of *E. coli* are from only a few evolutionary lineages, since O:K:H serotypes often correspond with clonal groups (40, 49). The first comprehensive study of the genetic diversity and relationships among *E. coli* strains from fecal and those causing UTI was conducted in the early 80's by Caugant and colleagues (43). Using multilocus enzyme electrophoresis (MLEE), they found that UTI causing *E. coli* are not a random sample of fecal flora. There are distinct genetic differences between MLEE types (ETs) of clones causing symptomatic UTI and those isolated from fecal samples, indicating a phylogenetic difference between pathogenic and nonpathogenic *E. coli* strains.

More recent studies suggest that extraintestinal pathogenic *E. coli* strains are mostly derived from phylogenetic group B2 (50, 51, 52, 53). In a study among 118 strains isolated from meningitis and other miscellaneous extraintestinal infections, Duriez *et al.* found that 85 (72%) of them belong to group B2 (54). In our study, 69% of UTI isolates were B2 strains (55), which is very similar to other studies. Based on this information, it may be safe to estimate that group B2 strains account for about two thirds of all extraintestinal *E. coli* infections.

In contrast to the dominance of B2 lineage among UTI causing *E. coli*, B2 strains are usually the rarest among commensal strain collections. Picard *et al*. found that carboxylesterase B2 type (which corresponds to phylogenetic group B2) strains accounted for only 9% of examined commensal human strains (56). In a recent examination of commensal *E. coli* isolates in Mali, France, and Croatia using the same PCR based phylogenetic grouping method, the frequencies of B2 strains were found to be 2% (1/55), 10.5% (6/56) and 19% (11/57), respectively (54). However, a much higher percentage (48%) of B2 strains were found in our recent examination on a sample of 88 commensal rectal *E. coli* from healthy young women (55). The sharp contrast between our and previous results may be due to geographic variation, difference in sample population or sampling method, or a combination of the three.

Not all studies support the notion that there is a phylogenetic difference between pathogenic and nonpathogenic strains. Pupo *et al.* (57) used MLEE and the sequence of the mdh gene of a small set of *E. coli* strains to study the relationship of pathogenic clones to commensal clones. They did not find that pathogenic strains clustered according to their mode of pathogenesis except for *Shigella* and enterohemorrhagic *E. coli*. Their results suggest that any *E. coli* strains acquiring the appropriate virulence factors may give rise to a pathogenic form. However, these conclusions are based on a very limited *E. coli* sample: only 7 UTI strains were examined.

4.3. Virulence factors

A hallmark of pathogenic *E. coli* isolates is their possession of specialized virulence factors, traits that confer pathogenic potential and are infrequent among commensal strains (58, 59, 60). The proposed virulence factors of uropathogenic *E. coli* include an array of adhesins including Type 1, P, and S fimbriae as well as adhesins of the Dr family and non-fimbrial adhesins. Toxins such as α-hemolysin and cytotoxic necrotizing factor 1 have been shown to be important in extra-intestinal *E. coli* infection. The siderophore aerobactin that helps *E. coli* overcome iron limitation, and polysaccharide capsules that confer resistance to host killing are also implicated.

4.3.1. Adhesins

Adherence factors facilitate the colonization of the urinary tract and promote *E. coli* colonization and persistence in the colon or vagina, which may serve as a reservoir for ascending infection in the urinary tract (58, 59). Various adhesins have been identified and studied. Type 1 fimbriae recognize mannose-containing receptors. The *fim* open reading frame encoding type 1 fimbriae exists in almost all *E. coli* isolates, urinary or fecal (61, 62). Although Type 1 fimbriae has been suggested to aid in the persistence of *E. coli* in the urinary tract in experimental UTI models (63, 64, 65), there has been little direct epidemiologic evidence for an association between Type 1 fimbriae and UTI infection. As Type 1 occurs in virtually all *E. coli* it is difficult to show an association outside an experimental setting. Allelic variation exists in *fimH*, the gene for lectin subunit of the type I fimbriae. Sokurenko *et al.* (66) have shown that type 1 fimbriae with different FimH alleles vary in their ability to recognize various mannosides and only those capable of mediating high levels of adhesion via monomannosyl residues are more capable of mediating *E. coli* adhesion to uroepithelial cells. Therefore, it seems that certain variants of type 1 fimbriae may contribute more than others to *E. coli* urovirulence (66). In addition, Type 1 fimbriae may contribute to colonization of the vaginal tract. The Type 1 mediated adherence to vaginal mucous is increased in patients with recurrent urinary tract infections (67).

The best-studied and perhaps the most important type of adhesin is P fimbriae, which recognizes the globoseries of glycolipids as receptors. A great many studies have confirmed that P fimbriae occurs more frequently, measured either by phenotype or genotype, among *E. coli* strains causing UTI than fecal isolates (for a review see Donnenberg, 1996 (58)). P fimbriae is the most dominant feature in strains causing pyelonephritis. It was estimated using pooled data from various studies that about 80% of the *E. coli* isolates from patients with pyelonephritis possess P fimbriae (58). Similarly, about 31% of the *E. coli* isolates from patients with cystitis possess P fimbriae. Using hybridization to a *pap* gene probe we found the percentage of probe positive isolates from pyelonephritis, recurring UTI, first UTI, and fecal samples to be 82.4%, 59.3%, 49.8%, and 34.2%, respectively (44). These data suggest that the prevalence of P fimbriae varies directly with the severity of UTI. Based on binding specificities, P fimbriae are grouped into three major classes (I, II, III).

Class II is more common in pyelonephritic than fecal isolates, but was equally common among our first UTI and fecal isolates from collage age women. Compared to Class II, Class III is less common in pyelonephritic isolates. However, Class III is more frequently found in cystitis strains than in fecal isolates (44). A new P fimbriae subtype, Class IV, was recently identified and is more frequently found in *E. coli* isolates from UTIs (68).

S fimbriae of *E. coli* bind to sialyl galactosides (69) and are implicated in experimental UTI in rats (70). In our studies, UTI isolates are at least two times more likely to carry S fimbriae genes than fecal isolates (44).

The Dr family of adhesins share a common receptor, the Dr blood group antigen component of decay-accelerating factor (71). This widely distributed receptor along the urinary tract may underline the potential importance of Dr adhesin-producing *E. coli* in ascending colonization of the urinary tract. Dr adhesins occur more frequently among *E. coli* cystitis isolates than fecal isolates (58, 59). We also found the presence of Dr at time of first UTI is associated with an increased risk of second UTI (61). However, many studies suggest no significant difference in the prevalence of Dr adhesins in pyelonephritic isolates when compared to fecal isolates (72, 73, 74). In our study, a *drb* probe hybridized to significantly more first time UTI (15.2%) than to fecal isolates (5.6%) and pyelonephritic isolates (5.9%) (44). In a more recent report, Goluszko *et al.* have found that 30 to 40% of *E. coli* isolates from pregnant women with pyelonephritis were associated with the presence of Dr operons (75).

4.3.2. Toxins

Toxins are important virulence factors in a variety of *E. coli* mediated diseases. Production of toxins by colonized *E. coli* may cause an inflammatory response, a possible pathway for UTI symptoms. Alpha hemolysin (HlyA) and cytotoxic necrotizing factor 1 (CNF1) are two toxins that have been associated with uropathogenic *E. coli*. In 1993, Ikaheimo *et al.* reported that *E. coli* isolated from women with cystitis were hemolytic 22.5% of the time, while only 10.8% of stool isolates were hemolytic (76). Using hybridization to an *hly* gene probe, we found a significant difference in the presence of *hly* between various UTI (31% to 48%) and fecal (15%) isolates (44). CNF1 is also found more often in UTI strains than in fecal strains. Caprioli *et al.* (77) examined 91 UTI isolates and determined that 37% produced both CNF1 and hemolysin, while among 114 isolates from normal stools only 1 (0.9) produced CNF1. Lockman and O'Brien reported (78) that a *cnf1* mutant had decreased virulence in mouse model of ascending UTI compared to the isogenic *cnf1*$^+$ strain. Using hybridization to a *cnf1* gene probe we found a significant difference in the presence of cnf1 between various UTI (27% to 41%) and fecal (9%) isolates (44).

Most recently, a new toxin, secreted autotransporter toxin (Sat), was identified as a virulence factor of uropathogenic *E. coli* (79). Sat, a vacuolating cytotoxin, elicits defined damage to kidney epithelium during upper urinary tract infection (80). Using a *sat* gene probe, Guyer *et al.* found 38 out of 67 (55%) pyelonephritis isolates but only six out of 27 (22%) fecal isolates carried the *sat* gene (79).

4.3.3. Siderophores

Iron is an essential nutrient for bacterial growth. While almost all *E. coli* can produce the siderophore enterobactin, production of the alternative siderophore aerobactin has been shown to increase virulence of strains causing bacteremia (81). Aerobactin is associated with some *E. coli* strains which cause pyelonephritis and cystitis (82). Interestingly, in our studies, we did not find a significant difference between various cystitis (40% to 46%) and fecal (42%) isolates in hybridization to an *aer* gene probe (44). However, we did observe that aer occurs more frequently in pyelonephritis than fecal isolates (70% vs. 42%). More recently, the IroN$_{E.\ coli}$, a siderophore receptor, was associated with UTI causing *E. coli* when compared to fecal isolates (83, 84, 85).

Other factors such as polysaccharide capsules (21, 44) and outer membrane proteases such as OmpT (21, 44, 86) also may be important in UTI pathogenesis. Studies, including ours, have shown uropathogenic *E. coli* carry various virulence factors, but are very heterogeneous (44, 58, 72). Certainly none of the known virulence genes or set of genes clearly define a uropathogen.

4.4. Pathogenicity islands and evolution of the uropathogen

Virulence genes may be located on mobile genetic elements. Genes encoding for α-hemolysin, Dr adhesin, and aerobactin can be found on plasmids as well as the chromosome (87). One of the important findings in recent years is that genes involved in virulence, the presence of which may distinguish pathogenic and nonpathogenic strains of a species, are often clustered in so-called pathogenicity islands (PAIs) (88, 89). PAIs are large blocks of chromosomally located DNA that can be inserted or deleted from the genome. PAIs were first described in uropathogenic *E. coli*. Genes encoding for hemolysin, CNF1, P pili, and S fimbriae have been found on various PAIs in different *E. coli* strains of UTI origin (88). While most PAIs are identified by physical mappings, our studies on the frequency of various virulence genes and the associations between them in a large collection of isolates provide indirect evidence for PAI being a wide spread phenomenon in *E. coli*. In a pairwise comparison of virulence factors, we found that virulence factors were not distributed at random and several gene combinations occurred together more frequently than predicted by chance alone (21, 44). For example, *cnf1*, *kpsMT*, *hly*, *prf*, and *sfa* are highly associated with each other, which is in agreement with these factors being a component of a PAIs. Using the combination of the presence or absence of all probed virulence factors, we were able to create a virulence signature for each *E. coli* isolate (21, 44). There are a large number of virulence signatures observed among *E. coli* isolates and certain signatures are more associated with UTI isolates while other are more associated with fecal isolates. However,

only a few virulence signatures made up at least 5% of *E. coli* collection (21, 44). The various combinations of those known to be PAI-born virulence genes indicate that the composition of potential PAIs in pathogenic *E. coli* population are very diverse.

Given the observed differences in phylogenetic lineage and virulence gene distribution between UTI causing *E. coli* and fecal *E. coli*, more insight into the nature of uropathogenic *E. coli* might be obtained by examining the relationship between the two. However, very limited efforts have been made to explore the link between strain phylogenetic lineage and the distribution of potential virulence genes. Goullet *et al.* (90) first reported that B2 group strains have numerous virulence determinants implicated in extraintestinal infections, indicating a potential link between a strain clonal frame and its possession of virulence genes. Recent studies by the same research group further demonstrated a similar association in *E. coli* strains of urinary tract infection and neonatal meningitis (50). Boyd and Hartl (51) also reported that chromosomal regions specific to pathogenic isolates of *E. coli* have a phylogenetically clustered distribution. A study by Johnson and Stell (52) on strains from patients with urosepsis showed that virulence genes are concentrated in group B2.

Picard *et al.* (53) used a mouse model to evaluate the virulence of bacterial strains of different phylogenetic lineages and thus provided new insights into the relationships between clonal origin, virulence genes, and virulence. These strains were further characterized by the distribution of known virulence genes. The study established a link between phylogeny and virulence in *E. coli*. As noted by the authors, the lethality was proportional to the number of virulence traits present. This is not a surprise since the virulence genes were defined mostly by the mouse model in the first place. How well in-mouse virulence can be translated to uropathogenicity in humans is still an open question.

Although the majority of uropathogenic *E. coli* belong to phylogenic lineage B2, *E. coli* uropathogens under this intraspecific subdivision show great genotype diversity. Further, the virulence of a strain is often driven by the presence of specific virulence factors that are often horizontally acquirable. Thus, uropathogens may not originate from a single ancestor but, instead, have arisen several times from several ancestors. However, the selective concentration of virulence factors in B2 group may indicate compatibility between virulence genes and B2 genetic background.

5. TREATMENT AND PREVENTION OF UTI

A considerable amount of effort has been made to study the treatment and prevention of UTI since it is one of the most common bacterial infections and can be fatal in compromised patients. For a review, see paper by Hooton and Stamm (91). Of concern from the molecular epidemiologic perspective, is the increasing antibiotic resistance in uropathogens causing both community- and nosocomially acquired UTIs (92). Resistance to TMP-SMX has increased from 8.1% in 1992 to 15.8% in 1999 among uropathogenic *E. coli* from women with UTI in Michigan (93), and from 9% in 1992 to 18% in 1996 among *E. coli* isolates from women with acute uncomplicated cystitis in Washington state (92). Ciprofloxacin resistance rates as high as 37% have been reported from some Europe countries (94), although fluoroquinolone resistance is still low in the U.S. (92, 93). In Michigan, we found a significant increase in the prevalence of resistance among uropathogenic *E. coli* to nitrofurantoin between 1992 and 1999; however the prevalence of resistance at the end of the study period remained low (2.4%) (93). This is consistent with previous findings in the U.S. (92). Of particular concern is a recent report suggesting a potential association between antibiotic resistance and virulence genes. Hart *et al.* reported that 75% of *E. coli* with Dr adhesin were ampicillin resistant compared to the average resistant rate of 45% without Dr among 78 pyelonephritis isolates (95).

For preventing UTIs, low dose antimicrobial prophylaxis has been an effective and safe way in patients with recurrent UTIs. However, increasing antimicrobial resistance may eventually limit its efficacy. Cranberry juice consumption may prevent bacteriuria (96) due to blocking or down regulating *E. coli* adherence factors by the constituents of cranberries (97). Regular cranberry juice also has reduced the incidence of recurring UTI among women with a history of recurrence (98), and a protective effect has been observed in some case-control studies (17, 99) and in one open randomized controlled clinical trial (100). The use of probiotics, such as Lactobacillus supplements, has been under investigation (101), but evidence of effectiveness among human populations has been limited to date.

The idea of creating a vaccine for *E. coli* UTIs has been pursued for many years. With increased understanding of adhesins in pathogenesis of UTI, anti-adhesin vaccines are being developed. The heterogeneous nature of uropathogenic *E. coli* has made choosing a vaccine target a challenge. Vaginal mucosal immunization with a multi-strain vaccine has been shown to reduce the risk for recurrent UTI infection (102). Protection against acute pyelonephritis was induced by immunization of baboons with purified P-fimbriae as vaccines (103). Recent focus on a Type 1 fimbriae based vaccine may provide a more universal vaccine since Type 1 is ubiquitous among *E. coli*. Cystitis due to Type 1 fimbriated *E. coli* has been prevented in a mouse model by vaccination with the FimH adhesin. In addition, passive administration of immune sera to FimH antigen led to reduced bladder colonization by Type-1 fimbriated *E. coli* (104, 105). Clinical trials are ongoing. One concern of using a Type 1 fimbriae based vaccine is the effect on the normal *E. coli* inhabiting in the gut. Since almost all *E. coli* isolates, including normal colon inhabitants, have Type 1 pili, there is legitimate concern about the potential risk of eliminating normal gut *E. coli* within a person. Changing the normal gut microbial ecology may lead to unforeseen harm to the human host.

6. PERSPECTIVE

Forty years after the pioneers in UTI research first speculated that bacterial stains differ with respect to the capacity to produce urinary tract infection, we know a great deal about the genetic factors underlying the urovirulence of a *E. coli* strain. Uropathogenic *E. coli* are most likely to belong to phylogenic lineage B2 and are heterogeneous in their genetic composition. They usually possess specific adhesins such as P, S or Dr to facilitate their colonization in the urinary tract. Toxins, hemolysin and cytotoxic necrotizing factor 1 in particular, are often carried by uropathogenic *E. coli* leading to an inflammatory response that possibly is responsible for the development of UTI symptoms. Virulence genes in uropathogenic *E. coli* are often co-located in pathogenicity islands.

Despite advancement in understanding of uropathogenic E. coli, many questions remain. While emphasis has been on identifying factors associated with virulence during an infection, little is known about factors that promote the transmission of uropathogens in the human population and persistent colonization among anatomic niches within a single host. With new molecular genetic technology such as DNA subtraction, coupled with epidemiological screening, we have begun to identify these additional factors (106).

The genetic diversity of uropathogenic *E. coli* is high. Currently, none of the known virulence genes or set of genes can clearly define the prototypic uropathogenic *E. coli*. It is likely that *E. coli* strains with different compositions of virulence genes have different modes of pathogenesis. It is well established that *E. coli* mediated diarrheal disease is caused by seven different groups (pathotypes) of *E. coli* strains that are characterized by a distinguishing set of virulence genes (107, 108). Additional studies are needed to investigate whether different uropathogenic *E. coli* can be linked to specific clinical or epidemiological features of the UTI. Defining different pathotypes of uropathogenic *E. coli* will further our understanding to the UTI pathogenesis.

7. ACKNOWLEDGMENTS

We appreciate and thank all the staff and students worked as part of research group under Drs Betsy Foxman and Carl F. Marrs in the last 10 years. Their contributions to our understanding toward *E. coli* mediated UTIs have been incorporated into this review. Our work was supported by the NIH grants R01 DK35368 (Betsy Foxman), DK 47519 (Betsy Foxman), and DK39434 (Carl F. Marrs).

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Key Words: *Escherichia coli*, Urinary Tract Infection, Virulence Factors, Review

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