Pathogenesis of urinary tract infections with normal female anatomy

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Recurrent urinary tract infections (UTIs) are common among girls and young women who are healthy and have anatomically normal urinary tracts. These infections are a main source of morbidity and health-care costs in this population. The interaction between specific infecting bacteria and urinary tract epithelium characteristics underlies the pathogenesis of this disease. Several pathogen-related factors predispose people to recurrent UTI, including periurethral bacterial colonisation and *Escherichia coli* virulence. Host behavioural risk factors include voiding dysfunction, high intercourse frequency, and oral contraceptive and spermicide use. The role of vesicoureteral reflux in recurrent childhood UTI is probably overestimated in the medical literature and is important only in a small group of children with high-grade reflux. Family pedigree analysis suggests a familial genetic predisposition for UTI among young females. Animal models show the multigenic nature of recurrent UTI. Putative candidate genes for the disease include ABH blood groups, interleukin-8 receptor (CXCR1), the human leucocyte antigen locus, toll-like receptors, tumour necrosis factor, and Tamm-Horsfall protein.

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Recurrent urinary tract infections (UTIs) are common among young, healthy women even though they generally have anatomically and physiologically normal urinary tracts.[1,2] Most of these episodes are cystitis-like, but some of them may become complicated by acute pyelonephritis. The frequency of acute cystitis among young women is 0·5–0·7 episodes per person per year,[3] representing a main source of morbidity and health-care costs in this population. Approximately 25% of women who have had an episode of acute cystitis develop recurrent UTI,[4,5] but no large population-based studies have yet been done.

UTI affects up to 10% of the childhood population and is an important cause of morbidity.[6] The recurrence rate for UTI in children is estimated at between 30% and 40%, with most recurrences occurring in the first 12 months after a primary infection.[7,8] Most recurrent UTIs in children older than 6 months of age are in girls.[9]

Pathogenesis

Most uncomplicated UTIs in women cannot be explained by underlying functional or anatomic abnormalities of the urinary tract, but instead seem to result from the interaction between the infecting *Escherichia coli* strains and the urinary tract epithelium (figure). Colonisation of the vaginal introitus with *E coli* seems to be one of the critical initial steps in the pathogenesis of both acute and recurrent UTI. In healthy individuals, most uropathogens originate in the rectal flora and enter the bladder via the urethra with an interim phase of periurethral and distal urethral colonisation.[10] Many host genetic, biological, and behavioural factors seem to predispose young, healthy women to uncomplicated UTI. Women with recurrent UTI have been shown to have an increased susceptibility to vaginal colonisation with uropathogens[10,11] and colonisation with Gram-negative bacilli was heavier and longer-lasting compared with women without a history of recurrent UTI.[12–15] This difference between women with and without recurrent UTI seems to result from a greater propensity for uropathogenic coliforms to adhere to the uroepithelial cells of women with recurrent infection. The underlying cause of this difference has not been determined although, in some cases, this may be genetically determined.

Bacterial factors

In a prospective, community-based study of 131 episodes of recurrent UTI during 1 year, *E coli* was the cause of 78% of the recurrent episodes. Uropathogenic *E coli* have several virulence factors that increase their ability to colonise and persist in the urogenital tract.[16] Binding to the urothelial surface is one factor that prevents bacterial washout by micturition and initiates bacterial invasion. This binding is mediated by the FimH adhesion located at the tip of the bacterial type 1 fimbrium, a filamentous attachment apparatus.[17] Type 1 fimbriated and P fimbriated strains of *E coli* have been associated with cystitis and pyelonephritis. There is experimental and clinical evidence for the pathogenic role of P fimbriae and type 1 fimbrium of *E coli* strains in both persistent bladder colonisation and recruitment of inflammatory response.[18,19] Phenotypic and genotypic analysis of *E coli* strains showed that two-thirds of UTI recurrences in infants were caused by the index-episode strain and thus could have represented endogenous relapses rather than re-infection from new organisms.[20] However, the possibility of de novo infection with the same strain—ie, re-introduction of the strain from a persisting vaginal or faecal

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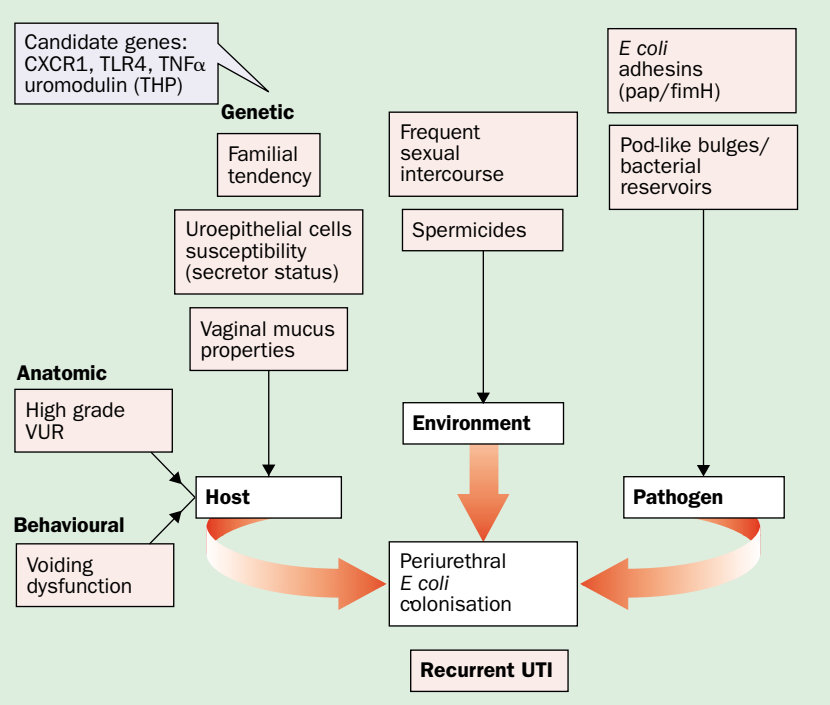

Pathophysiology model for recurrent UTI. CXCR1=interleukin-8 receptor; THP=Tamm Horsfall protein; TLR4=toll-like receptor-4; VUR=vesicoureteric reflux

reservoir, or from the environment, through a household member or pet—could also provide an explanation for this finding.[21] Since in many women with UTI, persistent vaginal or faecal colonisation with the initial UTI strain can be shown, even with appropriate antimicrobial therapy for the index UTI episode, same-strain re-infection is probable. Recently, Anderson and colleagues[22] reported that the intracellular bacteria mature into biofilms, creating pod-like bulges on the bladder surface. This bacterial organisation may explain the persistence of bladder infections despite robust host defences. Whether this pod phenomenon occurs in humans beings with spontaneously occurring UTI is unknown and remains to be shown. The findings of Elliott and co-workers[23] suggest there are bladder bacterial reservoirs; using bladder biopsies such bacteria were identified in 14 of 16 patients with a history of recurrent UTI but sterile urine.

Child risk factors for recurrent UTI

Voiding dysfunction

Voiding dysfunction is defined as a voiding pattern that is abnormal for age. The symptoms of voiding dysfunction include urinary urgency, frequency, and incontinence as well as infrequent voiding. Voiding disorders are common in paediatric patients who have neither neurological nor anatomic abnormalities of the urinary tract, and usually result from detrussor muscle instability. Children with detrussor instability who use various posturing manoeuvres to avoid urinary incontinence have a significantly higher incidence of UTIs than those who do not attempt to obstruct urine flow. Constipation is the main clinical condition associated with detrussor instability.[24] In another study of children with a history of recurrent UTI, 74% had abnormal functioning of the lower urinary tract, most commonly detrussor instability.[25] The aetiology of voiding dysfunction in children is unknown. It seems to be part of the "urge syndrome", which affects 10–15% of adult men and women with urgency, frequency, incontinence, and bladder over-activity and hypertrophy, with no known cause. Interestingly, bladder abnormalities in knockout mice for neuronal nitric oxide synthase gene (*nNOS*) have been described. The mice had hypertrophic dilated bladders and dysfunctional urinary outlets.[26]

Congenital anomalies: vesicoureteral reflux

Whereas children without vesicoureteral reflux (VUR) and children with grade 1–2 VUR do not differ in their recurrence rate, children with VUR grades 3–5 do; low grade VUR is not a risk factor for recurrent UTI.[7] VUR has been implicated in only 30% of all cases of recurrent UTIs in childhood.[27,28] Several studies have shown that children treated for VUR by ureteric re-implantation remain prone to recurrent UTI.[29,30] Additional evidence for the overestimation of VUR as a risk factor for recurrent UTI comes from studies on women with VUR who underwent antireflux surgery for recurrent UTIs during childhood. These patients continued to have a significant number of UTIs during the intervening years.[31,32]

Young adult risk factors for recurrent UTI

Behavioural risk factors

The genital flora surrounding the urethral orifice have a strong resistance to infection from uropathogens. In normal women who never experience UTI, the main introital, vaginal, and urethral microbial flora consists of lactobacilli and staphylococci.[12] Previous antibiotic use profoundly disturbs the normal vaginal microflora, reduces its adherence to vaginal epithelial cells in vivo and promotes a persistent vaginal *E coli* colonisation.[33] Vaginal fluid from women with recurrent UTIs more avidly binds *E coli* than fluid from healthy women.[34] Secretory-IgA in vaginal fluid may change during the menstrual cycle,[35] and potentially affect vaginal colonisation by *E coli*. A case-controlled study of women with and without a history of recurrent UTIs found with a multivariate analysis that the strongest risk factor for recurrent UTI was the frequency of sexual intercourse.[36] Any lifetime sexual activity and any sexual activity during the past year were the variables most strongly associated with risk of recurrence. More than four episodes of intercourse during the month preceding the reference

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date was more commonly reported by women with recurrent UTIs than by women without such infection. Substantially higher proportions of women in the case group also reported having a new sex partner during the preceding 12 months. Use of spermicides and oral contraceptives during the preceding year was more typically reported by patients with recurrent UTIs.[14,37] Because the sexual and contraceptive activities associated with sporadic UTI were also associated with recurrent UTI, young women experiencing recurrent UTI may not be as distinct from women with sporadic infections as the literature on recurrence might suggest.

Uropathogenic bacterial strains are that subset of clones with varying virulence for the urinary tract.[18] Uropathogenic *E coli* are more typically shared with a current heterosexual sex partner than commensal *E coli* (ie, *E coli* strains isolated from the vaginal or rectal flora).[37] Both intercourse and spermicide exposure increase periurethral *E coli* colonisation,[38] and such colonisation is more typical and for prolonged periods in women with recurrent UTI.[12]

Genetic risk factors

Hopkins and colleagues[39] reported the increased incidence of UTIs in the immediate, female, family members of women with recurrent UTI and suggested that this finding supports a model of genetic predisposition to disease. Additional studies support this observation.[40] In a case control study of more than 450 women with recurrent UTI, 47% had a maternal history of UTI and 22% had a first UTI episode before they were 15 years of age; these variables were associated with two–four fold increase in risk for recurrent UTIs and they were the most strongly associated with recurrent UTIs after sexual intercourse.[36] Both maternal history and childhood onset of cystitis suggest that inherited factors may be important in some women with recurrent infections, especially those with onset before first sexual intercourse or spermicide exposure. Alternatively, these observations could reflect other shared environmental factors or behaviours present in both mothers and daughters. These findings are supported by other studies of the long-term natural history of recurrent bacteriuria and symptomatic UTI in childhood.[41] A follow-up study of school-aged girls found that those who experienced these infections during childhood were also more prone to bacteriuria and symptomatic infections as adults.[42]

Animal models of UTI have contributed to the understanding of host-bacterial interaction during the infectious process.[43–45] Mouse models of induced, unobstructed UTI have been important in showing the influence of genetic factors on host susceptibility and resistance to bladder and kidney infections.[46,47] Studies of induced UTI in C3H/HeJ female mice have shown that resistance to infection is diminished in this mouse strain, which is genetically unresponsive to the biological effect of *E coli* lipopolysaccharide.[48] Other research shows the multigenic nature of increased susceptibility to UTI. Hopkins and colleagues[49] inbred UTI-resistant (BALB/c) and UTI-susceptible (C3H/HeJ) mouse strains and found that the increased UTI susceptibility is a complex heritable trait influenced by several genes. This susceptibility is very probably a recessive trait for bladder and kidney infections. Results suggested that host traits for defence mechanisms are different in bladder and kidney infections. Unlike a defence mechanism for kidney infection, a defence mechanism for bladder infection may be redundant because most animals are able to resolve infections and only those mice with deficiencies in several mechanisms develop severe infections.[49]

Candidate genes

Additional evidence for the genetically determined predisposition for recurrent UTI comes from studies on ABH blood groups. Women with recurrent UTI are three–four times more probable to be non-secretors of ABH blood-group antigens than are women without recurrent UTI.[50–51] The secretor gene encodes for one of the many glycosyltransferases that determine the carbohydrate composition of cell-surface glycoproteins and glycosphingolipids, some of which are also a binding site for uropathogenic *E coli*.[50] The vaginal epithelium of non-secretors expresses two extended-chain glycosphingolipids that bind uropathogenic *E coli* more avidly than do other sphingolipids, contrary to the condition among secretors. In this regard, the non-secretor phenotype is over-represented among girls and women with recurrent UTI.[50]

The interleukin-8 receptor, CXCR1, is another factor with genetic variability that may predispose to the development of UTI. Interleukin-8 is an inflammatory cytokine that promotes neutrophil migration across the infected uroepithelial cells.[52–53] Knockout mice lacking CXCR1 were unable to clear bacteria from the kidney and eventually developed bacteraemia. In addition, a preliminary analysis of interleukin-8 expression on the neutrophils of children with a history of recurrent pyelonephritis has shown a defective version of CXCR1, which may explain their susceptibility to recurrent pyelonephritis.[54]

Hopkins and colleagues[55] studied a possible association between MHC or red blood cell antigen phenotype (ABO and Lewis) and a predisposition to recurrent UTIs. In that study, however, no statistically significant differences in the proportions of HLA-A or HLA-B antigen types were observed between patients with and without recurrent UTI. Later, the same research group reported that specific HLA phenotypes were associated with a better response to a mucosal vaginal vaccine, containing multiple bacterial antigens, for control of UTI. Women who received the vaccine and had HLA-DR phenotypes other than DR2, had significantly delayed times to re-infection compared with women receiving a placebo.[56]

The innate immune system involves the toll-like receptor (TLR) family of receptors in microbial recognition. This recognition is through bacterial-specific common antigens, such as the lipopolysaccharide that is the specific ligand for TLR4.[57] Recent studies have identified genetic polymorphisms of the TLR4 molecule.[58] Such genetically determined structural variations could affect innate immune responses to uropathogenic *E coli* by increasing or decreasing the affinity of TLR4 for lipopolysaccharide.

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In human beings, variations in tumour necrosis factor production are attributable to polymorphisms in its promoter[59] and it is possible that differences in the amount of tumour necrosis factor synthesised in response to a UTI could affect host resistance to infection.

Women with recurrent UTIs were shown to have lower levels of urinary secretory IgA (an important component of mucosal immunity) compared with other antibodies.[60] However, the contribution of secretory IgA to the local protection against UTI is probably not key, since even a complete failure of the secretory IgA system does not lead to an increased UTI rate. Furthermore, no association of recurrent UTIs with disturbances of the urinary secretory IgA excretion were found.[61] Bates and colleagues[62] showed that knockout mice for Tamm-Horsfall protein (THP) inoculated with type 1 fimbriated *E coli* had a longer duration of bacteriuria and more intense colonisation of the urinary bladder compared with THP+/+ mice. This finding is probably attributable to the capacity of urinary THP and urothelial cell receptors to compete efficiently in adhering to type 1 fimbriated *E coli*.[63] This property supports the notion that abundant THP excretion in urine is promoted in the host by selective pressure to obtain an efficient defence against UTIs caused by uropathogenic bacteria. THP involvement in tubulointerstitial nephritis has strengthened its clinical relevance.[64] However, in past studies, urinary THP concentration was not significantly decreased in women[65] or children[66] with recurrent UTI compared with controls.

Search strategy and selection criteria

Data for this review were identified by searches of Medline and references from relevant articles; several articles were identified through searches of the extensive files of the authors. Search terms were included in the Medical Subject Heading (MeSH) system and included "urinary tract infections" and "recurrence". The search was then limited to clinical studies including "female" and "human", and excluding "pregnancy" and "post menopause". Only English language papers were reviewed.

In summary, the pathogenesis of recurrent UTI is composed of the three classic components of any infection: host, pathogen, and environment. Treatments for recurrent UTIs include conventional antibiotic treatment for each episode of UTI, long-term low-dose antibiotics, postcoital antibiotic prophylaxis,[67] behavioural modification for voiding dysfunction,[68] and avoidance of spermicides.[67] Advances in the study of the immunological response to uropathogenic *E coli* are leading to the development of new approaches to this problem. Novel methods of preventing UTI under development include vaccine development,[69–71] restoration of the normal flora using lactobacillus-based probiotic preparations,[72] and use of cranberry products.[73,74]

Conflicts of interest

We declare that we have no conflicts of interest.

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