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Pathogenesis of urinary tract infections: an update

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The pathogenesis of uncomplicated urinary tract infection (UTI) is complex and influenced by many host biological and behavioural factors and by properties of the infecting uropathogens. Most uncomplicated UTIs in women are not associated with underlying functional or anatomical abnormalities of the urinary tract, whereas sexual intercourse, spermicide use, a history of recurrent UTI and recent antimicrobial chemotherapy are important risk factors. A maternal history of UTI and young age at first UTI, as well as sexual intercourse and spermicide use, are risk factors for recurrent UTI in young women. In some young healthy women, especially those with 'low UTI risk' behaviour, features of pelvic anatomy appear to be associated with UTI risk. In postmenopausal women, anatomical and functional characteristics of the genitourinary tract are more strongly associated with UTI risk than in younger women. A genetic predisposition to recurrent UTI is suggested by the association of recurrent UTI in certain age groups with the ABH blood group non-secretor phenotype, a maternal history of UTI and early age at onset of UTI. Virulence determinants of uropathogens are much more important in the normal host than in the host who has a functional or anatomical abnormality of the genitourinary tract.

Background

Acute uncomplicated urinary tract infections (UTIs) are among the most common conditions causing individuals to seek medical care. In the USA, it is estimated from surveys of office practices, hospital-based clinics and emergency departments that there are over eight million episodes of urinary tract infection annually.[1] The incidence of cystitis in young sexually active women in the USA is approximately 0.5 per person-year;[2] Kunin has stated that about 40–50% of adult women report that they have had a UTI at some time in their life.[3] Recurrent UTI occurs in 27–48% of healthy women, even though they generally have anatomically normal urinary tracts.[4,5] UTIs in healthy postmenopausal women are probably less common than in premenopausal women, but incidence data are lacking. UTIs in young healthy men are very uncommon.

Although there are few data on the incidence of pyelonephritis, a recent population-based study in Canada showed that the overall rate of hospitalization for pyelonephritis in women was about one case per 1000 population.[6] This rate is almost certainly an underestimate since up to 75% of patients presenting to emergency departments with acute pyelonephritis do not require hospitalization.[7,8]

Differentiation between uncomplicated and complicated UTIs has implications regarding pre- and post-treatment evaluation, type and duration of antimicrobial treatment and extent of evaluation of the urinary tract. A complicated infection is an infection associated with a condition that increases the risk of therapy failure. Acute cystitis is generally considered uncomplicated but may, in some cases, be complicated. Likewise, acute pyelonephritis should be considered uncomplicated in the healthy host even though it involves the upper urinary tract. Factors associated with complicated UTI include: the presence of anatomical or functional abnormalities of the urinary tract that compromise urine flow, such as a renal stone or neurogenic bladder; the presence of foreign bodies, such as an indwelling urethral catheter; multidrug-resistant uropathogens; immunosuppression; and settings that compromise antibiotic delivery, such as prostatitis. It is reasonable to assume that cystitis or pyelonephritis occurring in a premenopausal, sexually active, non-pregnant woman who has not had recent genitourinary tract instrumentation or been treated with antimicrobial agents and who has no history of

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a genitourinary tract abnormality is an uncomplicated infection. Although not as well studied, it is likely that most UTIs in healthy postmenopausal women are also uncomplicated. Infections in men have generally been considered complicated, but it has become clear that a small number of 15–50 year old men suffer acute uncomplicated UTIs.[9]

The availability of potent oral fluoroquinolones has reduced the need to distinguish between uncomplicated and complicated UTIs since most so-called 'complicated' infections not requiring surgical intervention respond rapidly to therapy with these agents.

The discussion that follows will focus on the pathogenesis of UTI in women.

Pathogenesis

In the healthy woman, most uropathogens originate in the rectal flora and enter the bladder via the urethra with an interim phase of periurethral and distal urethral colonization. Vaginal acquisition of uropathogens from a woman's male sexual partner has been reported but is probably only rarely the underlying cause of UTI. Vaginal colonization is a prerequisite to bladder infection; factors that increase the risk of UTI generally do so at least in part by facilitating vaginal colonization. Such factors are discussed below. Whether subsequent UTI occurs is the result of a dynamic interaction between the host and uropathogen. Symptomatic UTIs develop when uropathogens in the bladder or kidney stimulate cytokine release, resulting in an inflammatory response and symptoms.

The large difference in UTI prevalence between men and women is thought to result from a variety of factors, including: the greater distance between the anus (the usual source of uropathogens) and the urethral meatus; the drier environment surrounding the male urethra; the greater length of the male urethra; and the antibacterial activity of prostatic fluid.[10] Risk factors associated with UTI in healthy men include intercourse with an infected female partner, homosexuality and lack of circumcision, although often none of these factors is present in men with UTI.[9] Uropathogenic strains infecting healthy young men tend to be highly urovirulent.[9]

Haematogenous seeding of the urinary tract by potential uropathogens such as *Staphylococcus aureus* is the source of some UTIs, but this is more likely to occur in the setting of persistent bloodstream infection or urinary tract obstruction. The importance of lymphatic spread of uropathogens to the urinary tract in the pathogenesis of UTI is not known.

Vaginal microecology

Alterations in vaginal microflora are thought to play a critical role in facilitating vaginal colonization with coliforms and, thus, UTI.[11] In particular, alterations in the presence or concentrations of lactobacilli, especially hydrogen peroxide-producing strains, have been postulated to have a major role in vaginal colonization with uropathogens. Generally, the factors that predispose to vaginal colonization also predispose to bladder colonization and infection. Vaginal colonization with uropathogens, however, does not inevitably lead to UTI. It remains to be determined why vaginal colonization progresses to UTI in some women and not in others. It is likely that vaginal colonization is usually a necessary predeterminant to UTI, but that other events, such as sexual intercourse, generally must occur to allow infection to occur.

Host risk factors

Several host factors have been identified that are associated with an increased risk of uncomplicated UTI. All of these factors predispose to UTI by facilitating vaginal colonization with uropathogens or by facilitating entry of colonizing uropathogens into the bladder. Risk factors for recurrent UTI are discussed separately below, but it seems logical to assume that factors that predispose to recurrent infection also predispose to sporadic infection, although the reverse is not necessarily true. The behavioural and anatomical characteristics discussed below have not been evaluated as risk factors for pyelonephritis. Such studies are in progress.

Healthy premenopausal women and UTI. Most uncomplicated UTIs in women cannot be explained by underlying functional or anatomical abnormalities of the urinary tract. However, several host biological and behavioural characteristics that appear to predispose women to uncomplicated cystitis have been identified and are discussed below. Not surprisingly, having a history of previous recurrent UTI is a strong risk factor for having a subsequent UTI.[2] This could reflect a biological or behavioural predisposition of the host or a predisposition for persistent or recurrent colonization with a uropathogenic strain. Antibacterial characteristics of urine and other host defence mechanisms may be important factors associated with UTI risk, but have not been clearly shown to be associated with UTI in healthy persons.

Sexual intercourse and spermicide use, especially in conjunction with diaphragm use, are the factors most clearly demonstrated to predispose young healthy women to UTI.[2] One study of sexually active university students predicted that the average 24 year old woman who had sexual intercourse on 3 days in a given week would have a risk of UTI 2.6 times greater than that of a similar student who had not had intercourse during that week.[2] Daily intercourse over the course of the week increased the relative risk nine-fold. The increased risk caused by sexual intercourse appears to operate through a mechanical effect of introducing uropathogens into the bladder[12] and possibly through a trauma effect.[13]

Use of spermicides greatly increases the risk of vaginal

colonization with uropathogens and UTI, independently of sexual intercourse.[2] Nonoxynol-9, a non-ionic surfactant, is the active ingredient in most spermicidal compounds marketed in the USA. *In vitro* studies have shown that it is markedly less active against uropathogenic bacteria than against *Lactobacillus* spp.[14,15] Moreover, hydrogen peroxide-producing strains of lactobacilli appear to be more susceptible to nonoxynol-9 than non-producers.[15] It appears, therefore, that the effect of spermicide on vaginal flora may result, at least in part, from the effect of nonoxynol-9 on vaginal colonization by lactobacilli. The production of hydrogen peroxide by vaginal strains of lactobacilli may be important in colonization resistance.[16] Thus, vaginal colonization with hydrogen peroxide-producing lactobacilli appears to have a protective effect against bacterial vaginosis and symptomatic candidosis, and against vaginal colonization by some genital pathogens.[17,18] Given the differential effects of nonoxynol-9 on lactobacilli, especially hydrogen peroxide-producing strains, and uropathogens described above, it is possible that the adverse effects of spermicide on vaginal flora may, in part, result from a decrease in lactobacilli, especially protective hydrogen peroxide-producing species, after spermicide use. In support of this argument, it has recently been found in a case–control study that vaginal *Escherichia coli* colonization was significantly more frequent in women without hydrogen peroxide-producing lactobacilli than in women with such strains [odds ratio (OR) 4.0; $P = 0.01$].[19] Spermicide use was associated with greater risk of vaginal *E. coli* colonization (OR 12.5; $P < 0.001$) and with absence of hydrogen peroxide-producing lactobacilli (OR 2.9; $P = 0.04$). The inverse association between vaginal hydrogen peroxide-producing lactobacilli and *E. coli* colonization remained in case patients after controlling for spermicide use (OR 6.5; $P = 0.02$). Another recent study showed an increase in vaginal coliforms and decrease in vaginal lactobacilli after nonoxynol-9 instillation in the absence of sexual activity or diaphragm use.[20] Women in whom the number of lactobacilli was decreased were less likely to regain normal flora than were those whose lactobacilli were unaffected. However, coliform colonization occurred whether lactobacilli produced hydrogen peroxide or not.

Based on these *in vitro* and clinical studies, it seems likely that the differential antimicrobial activity of spermicides may alter the vaginal ecosystem, provide an environment conducive to the growth of uropathogens and, thus, predispose women who use these products to vaginal colonization with uropathogens and to UTI. Even the relatively small amounts of nonoxynol-9 coating condoms increase the risk of UTI, independent of sexual intercourse,[21,22] presumably by altering vaginal flora as described above. However, some clinical studies, as noted above, have not demonstrated that nonoxynol-9 significantly affects hydrogen peroxide-producing lactobacilli, so the mechanism whereby spermicide alters vaginal flora and predisposes to UTI warrants further investigation.

Animal and human data suggest that use of certain antimicrobial agents may predispose women to UTI, apparently through their adverse effects on vaginal ecology.[11,23–29] Data from studies in monkeys suggest that facilitation of vaginal *E. coli* colonization by β-lactam antimicrobial agents may result from alterations in the indigenous anaerobic flora of the vagina and, thus, altered colonization resistance. Trimethoprim and nitrofurantoin, which have much less effect on the periurethral anaerobic flora than does amoxycillin, did not result in enhanced vaginal colonization with *E. coli* in similar monkey experiments. Studies have shown that administration of β-lactam antibiotics induces marked changes in the indigenous genital flora of girls and a concomitant increase in genital uropathogen colonization.[11] Administration of co-trimoxazole or a fluoroquinolone, on the other hand, results in less vaginal colonization with uropathogens than β-lactams. In a recent prospective study of premenopausal college women, it was found that the women were at increased risk for UTI if antimicrobial agents had been taken during the previous 15–28 days but not during the previous 3, 7 or 14 days (when they may be protective).[30] The increased risks were noted both for women whose antimicrobial use was for treatment of a previous UTI and for women who received antimicrobial agents for other illnesses.

The role of oestrogens in predisposing premenopausal women to UTI is unclear. *In vitro* studies have demonstrated that oestrogens facilitate adherence of uropathogens to human vaginal or uroepithelial cells.[11] Moreover, several studies have shown that oestrogen treatment facilitates experimental UTI in animals.[11] We recently demonstrated a strong association between the time at which young women present with acute uncomplicated cystitis and the time from the onset of their last menstrual period, but we were not able to determine whether this association was caused by a hormonal mechanism or by changes in sexual behaviour associated with the menstrual cycle.[31] On the other hand, as noted below, oestrogen deficiency in postmenopausal women appears to increase the risk of UTI, and the risk can be greatly diminished by topical application of oestrogen, apparently by normalizing vaginal flora.[32] The effects of oestrogen on vaginal flora and UTI, therefore, appear to vary by age group; this topic warrants further study.

Healthy premenopausal women and recurrent UTI. Risk factors for recurrent UTI have received relatively little study. In a recent large case–control study of women with and without a history of recurrent UTI, the strongest risk factor for recurrent UTI in a multivariate analysis was the frequency of sexual intercourse.[33] Other risk factors were: spermicide use during the past year; having a new sexual partner during the past year; having a first UTI at ≤15 years of age; and having a mother with a history of UTIs. As is true of most previous studies, no associations were found between history of recurrent UTI and pre- and post-coital

voiding patterns; frequency of urination; delayed voiding; wiping patterns; douching; use of hot tubs; frequent wearing of tights; or body mass index.[33] It should be pointed out, however, that these behavioural factors have never been evaluated in prospective randomized trials.

Having a first UTI at an early age and having a mother with a history of UTIs were associated with two- to four-fold increases in risk and were the most strongly associated variables after sexual intercourse.[33] These findings suggest that inherited factors may be important in some women with recurrent UTIs. In this regard, it has been shown that women with a history of recurrent UTIs are several times more likely to be non-secretors of histo-blood group antigens than are women without such a history; women with the P_1 blood group phenotype have an increased risk for recurrent pyelonephritis; children with febrile UTIs caused by *E. coli* have a significantly higher prevalence of the non-secretor phenotype than control subjects.[11,34,35] Further, uropathogenic *E. coli* adhere better to uroepithelial cells from women who are non-secretors than to cells from secretors.[36] Recent data suggest that the biochemical explanation for the increased adherence of *E. coli* to non-secretors' uroepithelial cells and for the propensity of non-secretors to develop recurrent UTI is the presence of unique globoseries glycolipid receptors that bind uropathogenic *E. coli*.[37] These glycolipids are selectively expressed by epithelial cells of non-secretors, but not secretors, presumably as a result of sialylation of the gal-globoside precursor glycolipid, which in secretors is fucosylated and processed to ABH antigens.[37]

It is noteworthy that in the large case–control study mentioned above,[33] no association was found between blood group phenotype or non-secretor phenotype and history of recurrent UTI. It is possible, however, that non-secretor status may not figure prominently as a risk factor for recurrent UTIs in young women in whom sexual intercourse and spermicide exposure are more important. The mean age of the populations in whom an association between secretor status and recurrent UTI has been demonstrated is >35 years,[34,35] much older than the student population.

The interleukin-8 receptor (IL-8R), CXCR1, is another factor with genetic variability that may influence the development of UTI. IL-8 is an inflammatory cytokine that promotes neutrophil migration across the infected uroepithelial cells.[38,39] It has recently been demonstrated that knockout mice lacking CXCR1 were unable to clear bacteria from the kidney and eventually developed bacteraemia.[40] In addition, a preliminary analysis of IL-8R expression on the neutrophils of children with a history of recurrent pyelonephritis has demonstrated a defective version of CXCR1 which the authors suggest may explain the susceptibility of these children to recurrent pyelonephritis.[40]

Pelvic anatomy may play a role in some women with recurrent UTI. One hundred women with a history of recurrent UTI (cases) and 113 women with no such history (controls) were recently studied to determine whether there were differences in perineal anatomical measurements, post-void residual urine volume or urine voiding characteristics.[41] The urethra and anus were significantly closer together in cases (4.8 ± 0.6 cm) than in controls (5.0 ± 0.7 cm; $P = 0.03$). Among non-spermicide users, after controlling for sexual intercourse frequency, cases were more likely than controls to have a urethra-to-anus distance of <4.5 cm [odds ratio (OR) 5.7; 95% confidence interval 2.0–16.6] ($P = 0.0013$). No such difference was found among spermicide users. There were no differences between cases and controls in urethral length, post-void residual urine volume or urine voiding characteristics (e.g. peak flow rate or time to peak flow). These data suggest that pelvic anatomy may predispose some young women to recurrent UTI, especially those who do not have exogenous risk factors for UTI.

Healthy postmenopausal women. The reduced levels of oestrogenic hormones present after menopause appear to contribute to the occurrence of recurrent UTI in healthy postmenopausal women. In a double-blind, placebo-controlled intervention study, Raz & Stamm[32] demonstrated that topically applied intravaginal oestrogen markedly reduced the incidence of recurrent UTI. They demonstrated that *E. coli* vaginal colonization was halved, lactobacillus colonization was re-established in most women and vaginal pH fell significantly in the intervention group. In a more recent case–control study of healthy postmenopausal women by these investigators, mechanical and/or physiological factors that affect bladder emptying were found to be strongly associated with recurrent UTIs, in contrast to the predominantly behavioural risk factors described above for premenopausal women.[42] In this study, three urological factors were found to be strongly associated with recurrent UTI: urinary incontinence (41% of cases and 9% of controls; $P < 0.001$); presence of a cystocele (19% and 0%, respectively; $P < 0.001$); and post-voiding residual urine (28% and 2%, respectively; $P = 0.00008$). Multivariate analysis showed that urinary incontinence (OR 5.79), a history of UTI before menopause (OR 4.85) and non-secretor status (OR 2.9) (presence of a cystocele or post-voiding residual urine were excluded because of low frequency in the controls) were most strongly associated with recurrent UTI.

For older institutionalized women, obstructive uropathy, adverse effects on bladder emptying caused by uterine prolapse and cystocele, perineal soiling from faecal incontinence in demented individuals, and frequent instrumentation and bladder catheter use are the most imporant risk factors associated with UTI.[43]

Complicated UTI. The pathogenesis of complicated UTI is multifactorial. The many factors that predispose individu-

als to complicated UTI generally do so by causing stasis of urine flow, facilitating entry of uropathogens into the urinary tract by bypassing normal host defence mechanisms, providing a nidus for infection that is not readily treatable with antimicrobial agents or compromising the host immune system.[44] Obstruction, the most important factor leading to complicated UTI, interferes with local mucosal defence mechanisms by causing overdistension; the resulting residual urine pool provides a continuous medium for bacterial growth. Urinary catheters allow easy access to the urinary tract either through or around the catheter by uropathogens, whereas fistulae provide direct access of uropathogens in the bowel to the urinary tract. Renal and bladder stones and biofilms on urinary cathethers and other foreign bodies appear to provide a nidus from which it is difficult or impossible to eradicate uropathogens with antimicrobial agents.

UTIs are more likely to occur and/or to have serious consequences in certain conditions that impair host defences. Diabetes in particular is associated with several syndromes of complicated UTI, including intrarenal and perirenal abscess, emphysematous pyelonephritis and cystitis, papillary necrosis and xanthogranulomatous pyelonephritis.[45]

Uropathogen virulence determinants appear to be of much less importance in the pathogenesis of complicated UTIs than in uncomplicated UTIs. Infection with multiple-drug resistant uropathogens is more likely than with uncomplicated UTI, especially in those infections which develop in institutional settings and in patients who require frequent courses of antimicrobial agents.

Virulence determinants of uropathogens

Certain virulence determinants of uropathogens provide a selective advantage to those strains possessing them with regard to colonization and infection.[46,47] Paradoxically, bacteria causing complicated UTI often lack these virulence factors, while the majority of uropathogens causing uncomplicated UTI, especially pyelonephritis, express such virulence determinants. Among the most important of these virulence characteristics are surface glycoprotein projections called fimbriae or pili which serve as ligands for glycoprotein and glycolipid receptors on uroepithelial cells. Fimbriated *E. coli* can be categorized as either mannose sensitive or mannose resistant, based on their ability to agglutinate erythrocytes in the presence of mannose. P-fimbriated (mannose-resistant) strains of *E. coli* are strongly associated with acute uncomplicated pyelonephritis, probably because the major glycolipid component of renal cell membranes is the receptor for P fimbriae.[47]

The pathogenesis of cystitis is less well understood; there are no bacterial properties that identify 'cystitogenic' *E. coli* clones or distinguish them from strains that cause acute pyelonephritis. However, haemolysin, type 1 fimbriae and the *prs*G$_{J96}$ type of P fimbriae may occur more often in acute cystitis strains than in other *E. coli* strains.[46]

Other bacterial virulence factors include K or capsular antigens, which inhibit phagocytosis, and the aerobactin system, which chelates urinary iron (the release of which is facilitated by haemolysin), and offers a growth advantage to the organism.[47] Although patients with asymptomatic bacteriuria may have pyuria, the magnitude of the inflammatory response is not sufficient to make them symptomatic. Asymptomatic bacteriuria may be either the consequence of bacterial attenuation by the host or a primary condition in which bacteria of low virulence stably colonize the urinary tract without causing a symptomatic response. The bacterial and host factors responsible for this phenomenon are unknown.[46]

Summary

UTIs are very common in women, are associated with considerable morbidity and recur frequently. The pathogenesis of UTI is complex and influenced by many host biological and behavioural factors as well as characteristics of the infecting uropathogens. We now have a much better understanding of the factors that influence the risk for acquiring sporadic and recurrent UTI in both premenopausal and postmenopausal women. However, there remains much to learn about this very common disorder. A better understanding of the pathogenesis and risk factors associated with UTI is necessary in order to develop optimal preventive strategies for this very common syndrome.

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