Urinary Tract Infections

Uncomplicated urinary tract infections

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Epidemiology and definitions

Uncomplicated urinary tract infections (UTIs) [1,2] in adults include episodes of acute cystitis and acute pyelonephritis occurring mostly in women without underlying risk factors, predisposing to infection. Approximately 7 million episodes of acute cystitis and >250,000 episodes of acute pyelonephritis occur annually in the USA, while 25–35% of women between 20 and 40 years have had an episode of UTI. In a recent study of college women with their first UTI, 27% experienced at least one culture-confirmed recurrence within the 6 months following the initial infection, while in a Finnish study, 44% of women aged 17–82 years with *Escherichia coli* cystitis, had a recurrence within 1 year. It is also estimated that 10–15% of women over age 60 have frequent recurrences. Because of persistent infection despite therapy, recurrences in women are due to relapse in 5%; the remaining are episodes of re-infection, the latter being determined by biotyping.

Acute cystitis is associated with considerable morbidity. It has been found that each episode is associated with 6.1 days of symptoms, 2.4 days of restricted activity, 1.2 days of abstaining from classes or work, and 0.4 of bed days, while >1 billion dollars are spent annually for the evaluation and therapy of ambulatory women with dysuria in the USA. It is generally safe for the clinician to assume that a pre-menopausal, sexually active, non-pregnant woman, with recent onset of dysuria, frequency and urgency and without a history of previous urinary tract instrumentation, or history of a genitourinary tract abnormality and/or treatment with antimicrobials, is suffering from an uncomplicated lower (cystitis) or upper urinary tract infection (pyelonephritis). Based on localization tests, it seems that ~15 to over 50% of women with symptoms of acute cystitis also have evidence of occult infection of the upper urinary tract. Such infections, although uncomplicated, are certainly more extensive, partly explaining why single-dose therapy could fail.

Acute pyelonephritis is expressed by flank pain, nausea and vomiting, fever (>38°C), and costovertebral angle tenderness and can occur in the absence of cystitis symptoms. The presentation varies from a mild to moderate illness to a life-threatening infection with full-blown sepsis syndrome with or without shock.

It is likely that most UTIs in post-menopausal women without genitourinary abnormalities are uncomplicated. Data on UTIs in healthy ambulatory adult men are sparse; however, it is considered that <3% represent uncomplicated UTIs.

Pathogenesis

In healthy women, most uropathogens originate from the rectal flora and enter the bladder via the urethra with a phase of prolonged periurethral and vaginal colonization [1,3,4]. It has been demonstrated that *E. coli*, *Proteus mirabilis*, Klebsiella and *Enterococcus faecalis* are present in 56% of vaginal cultures of women with recurrent UTIs, but only in 24% of those without a history of recurrence. This difference between women with and without recurrent UTIs appears to result from a greater propensity for uropathogenic coliforms to adhere to the uroepithelial cells of recurrently infected women as compared to cells from women without recurrent infection. The underlying reason appears to be genetically determined. In this regard, the non-secretor phenotype and the P1 phenotype are over-represented among girls and women with recurrent UTI and recurrent pyelonephritis, respectively. Further, uroepithelial cells from women who are non-secretors show enhanced adherence of uropathogenic *E. coli* compared to cells from secretors.

Recent data suggest that the biochemical explanation for the increased adherence of *E. coli* to non-secretors’ uroepithelial cells and propensity to develop recurrent UTI may be the presence of unique globoseries of glycolipid receptors that bind uropathogenic *E. coli* and which are selectively expressed on epithelial cells of non-secretors.

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Certain determinants of virulence have also been demonstrated to provide a selective advantage to those strains of uropathogens possessing them with regard to colonization and infection. For example, colonization with P-fimbriated strains of \textit{E. coli} is a strong risk factor for acute uncomplicated pyelonephritis. Whether vaginal colonization and subsequent UTI occur, will be the result of a dynamic interaction between the host defence characteristics, host behavioural characteristics, and uropathogen virulence determinants. There are no bacterial properties that identify ‘cystitogenic’ \textit{E. coli} clones or distinguish them from strains that cause acute pyelonephritis, although haemolysin, type 1 fimbriae and the \textit{prsG}_{396} type of P fimbriae may occur more often in strains providing acute cystitis than in other \textit{E. coli} strains.

**Risk factors**

In healthy pre-menopausal women, sexual intercourse, diaphragm–spermicide use, and a history of recurrent UTI have been shown to be strong and independent risk factors for UTIs \cite{1,2,5}. Even recent antimicrobial use, by adversely effecting vaginal flora is considered as a potent risk factor. However, the strongest risk factor in case of recurrent UTIs is the frequency of sexual intercourse. Other risk factors are spermicide use during the past year, having a new sexual partner during the past year, having a first UTI at/or before 15 years of age, or having a mother with a history of UTIs. The latter findings suggest the possibility that inherited factors may be important in some women with recurrent UTI. On the other hand, no association between history of recurrent UTI and pre- and post-coital voiding patterns, frequency of urination, delayed voiding habits, wiping patterns, showering, use of hot tubs, frequent use of pantyhose or tights, or body mass index have been found.

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. It has recently been demonstrated that knockout mice lacking CXCR1 were unable to clear bacteria from the kidney and eventually developed bacteraemia.

It seems that pelvic anatomy may play a role in some women with recurrent UTIs. The distance from the urethra to anus was significantly shorter in cases than in controls, while urethral length, post-void urine residual and urine voiding characteristics did not differ. The reduced levels of oestrogens in healthy menopausal women contribute to recurrent UTIs, as proved by the fact that topical application of intravaginal oestrogen normalized to acidic the pH of vagina with reappearance of Lactobacilli, reducing simultaneously the incidence of recurrent UTIs. In addition, mechanical and/or physiological factors that affect bladder emptying (i.e. urinary incontinence, presence of a cystocele and post-voiding residual urine) are strongly associated with recurrent UTIs.

**Diagnosis**

\textit{Escherichia coli} is the causative pathogen in 70–90\% and \textit{Staphylococcus saprophyticus} in 5–20\% of cases with other Enterobacteriaceae rarely isolated \cite{1,2}. Pyuria defined by $\geq 10$ leukocytes per mm$^3$ in unspun voided midstream urine, always follows bacteriuria and its absence strongly suggests an alternative diagnosis. The traditional standard for significant bacteriuria is $\geq 10^5$ c.f.u./ml of voided midstream urine. However after it was realized that $1/3$–$1/2$ of acute cystitis cases have $<10^5$ c.f.u./ml, a definition of $\geq 10^5$ c.f.u./ml for cystitis (sensitivity 80\% and specificity 90\%) and of $\geq 10^4$ c.f.u./ml (sensitivity 90–95\%) for pyelonephritis was recommended by the Infectious Diseases Society of America (IDSA).

Acute dysuria in sexually active women requires differential diagnosis from acute urethritis (caused by \textit{Chlamydia trachomatis}, \textit{Neisseria gonorrhoeae} and herpes simplex) and vaginitis caused by Candida spp. and \textit{Trichomonas vaginalis}.

Routine evaluation of recurrent cystitis with excretory urography or other invasive techniques is not recommended as significant abnormalities are very uncommon ($\leq 4\%$). In young women who suffer from acute pyelonephritis, excretory urography or ultrasound are recommended after two recurrences or if any complicating factor coexists in order to rule out nephrolithiasis or obstructive uropathy.

**Treatment strategies**

\textit{Escherichia coli} strains, representing the common pathogen in uncomplicated UTIs are usually susceptible to most of the commonly used oral agents \cite{1,2,5,6}. Worldwide, almost one-third of community-isolated \textit{E. coli} are resistant to ampicillin and sulfanamides while $\geq 15$–$20\%$ of \textit{E. coli} strains are nowadays resistant to trimethoprim (TMP) and/or trimethoprim–sulfamethoxazole (TMP-SMX). Resistance to nitrofurantoin is $<5\%$; resistance to fluoroquinolones, because of their overuse and misuse in the community is, however, increasing. Therefore, knowledge of the antimicrobial susceptibility profile of uropathogens in the community should guide therapeutic decisions.

Because of better compliance, lower cost, lower frequency of adverse reactions, and decreased possibility to induce resistance, 3-day short course regimens with TMP, TMP–SMX or a fluoroquinolone are generally applied in uncomplicated cystitis. \textit{β}-lactams should be given for $\sim 5$ days and nitrofurantoin for $\sim 7$ days while single-dose regimens (with the exception of fosfomycin–trimethamine), being less effective, have been abandoned. According to IDSA guidelines, TMP–SMX is the drug of first choice.
empiric therapy whenever there is no history of allergy, the patient has not been given antibiotics in the past 3–6 months, and if the resistance prevalence in the community is \( \leq 15\% \).

Acute pyelonephritis therapy should start parenterally with a switch of i.v. to oral therapy as soon as oral intake is feasible with antimicrobials obtaining adequate levels not only in urine, but also in renal tissue. Nowadays duration of therapy is reduced to 7 days.

**Prevention strategies and conclusions**

Women with two or more symptomatic UTIs over a 6-month period (or three or more over a year) should receive antimicrobial prophylaxis [2]. Continuous prophylaxis and post-coital prophylaxis have all been demonstrated to be effective. Experts advocate either 6 months of prophylaxis, given at night, or a longer period of \( \geq 2 \) years with either 40/200 mg of TMP–SMX or TMP 100 mg, nitrofurantoin 50 or 100 mg, cefaclor 250 mg, cephalexin 125–250 mg, cinoxacin 250 mg, norfloxacin 200 mg, ciprofloxacin 125 mg, and ofloxacin 100 mg. However, most women revert back to recurrent infections once prophylaxis is stopped. In post-menopausal women, topical oestrogen normalizes the vaginal flora and greatly reduces relapses. The application in humans of a promising vaccine based on *E.coli* type-1 fimbrial components is currently investigated.

**References**