Urinary Tract Infections in Women

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ABSTRACT

Urinary tract infections (UTIs) are one of the most common bacterial infections seen in primary care, second only to infections of the respiratory tract. Women are particularly at risk of developing UTIs because of their short urethra, and certain behavioral factors which include delay in micturition, sexual activity and the use of diaphragms and spermicides. Uncomplicated UTIs are usually treated empirically with antibiotics. However, not everyone diagnosed with a UTI and treated with an antibiotic will necessarily have a bacterial infection. At least one-half of women who suspect that they have UTI actually do. Studies have shown that one in 7 patients given an antibiotic for UTI symptoms will return within 28 days for a further prescription of antibiotic. Also, many UTIs are self-limiting, improving without treatment even when culture is positive. Symptomatic treatment of uncomplicated UTI may be an option which merits further research. Phenazopyridine is a time-tested urinary tract antiseptic and analgesic that provide symptomatic relief of the pain, burning, frequency and urgency associated with UTI.

Keywords: Urinary tract infections, symptomatic treatment, phenazopyridine, analgesic

PREDISPOSING FACTORS

Women are particularly at risk of developing UTIs because of their short urethra, and certain behavioral factors which include delay in micturition, sexual activity and the use of diaphragms and spermicides which promote colonization of the periurethral area with coliform bacteria. Infection in women most often results from perineal or periurethral bacteria that enter the urethra and ascend into the bladder, often in association with sexual activity, or due to mechanical instrumentation such as catheterization. Rates of infection are high in postmenopausal women because of bladder or uterine prolapse causing incomplete bladder emptying; loss of estrogen with attendant changes in vaginal flora (notably, loss of lactobacilli), which allows periurethral colonization with gram-negative aerobes, such as Escherichia coli; and higher likelihood of concomitant medical illness, such as diabetes.

Reports worldwide suggest a significant peak in the incidence of UTI for a few months each year in the post summer season. Anderson et al reported a rise in the incidence of UTI in August. They attribute this...
to hot and humid conditions during these months. In a study by Hasan et al, in a tertiary Indian hospital in New Delhi, rise in the incidence of UTI was reported during the monsoon months i.e. from July to September.8

CLINICAL PRESENTATION

The characteristic symptoms of UTI in the adult are primarily dysuria with irritating voiding symptoms like urinary urgency, frequency, nocturia, painful voiding, bladder discomfort or stranguria which greatly distress the patient. A sensation of bladder fullness or lower abdominal discomfort is usually present. Pain occurring at the beginning of or during urination suggests a urethral site of disease, whereas pain after voiding implies pathology within the bladder or prostate area. Sometimes a patient will relate a history of pain in the suprapubic area.9

Because of the referred pain pathways, even simple lower UTI may be accompanied by flank pain and costovertebral angle tenderness. In the emergency department, however, it is assumed that the presence of these symptoms represents upper UTI.

Bloody urine is reported in as many as 10% of cases of UTI in otherwise healthy women; this condition is called hemorrhagic cystitis. Fevers, chills and malaise may be noted in patients with cystitis, though these findings are associated more frequently with upper UTI (i.e. pyelonephritis).

CAUSATIVE ORGANISMS

E. coli is by far the commonest cause of uncomplicated community-acquired UTIs in both outpatient and inpatient settings. Other common uropathogens are Enterococcus faecalis, Enterobacter species, Staphylococcus saprophyticus, Klebsiella pneumoniae, Proteus mirabilis and Pseudomonas species.10

DIAGNOSIS

Urinalysis is mandatory in all patients who present with dysuria. The gold standard is evaluation of a spun midstream clean-catch urine specimen. Bacteria or pyuria (or both) are usually found in patients with UTI. Leukocyte esterase is 75% sensitive for detection of UTI (although studies done in the emergency department have demonstrated only 48% sensitivity), but 98% specific. Positive nitrite is highly suggestive of a UTI (90% specific), but a negative result does not rule it out (sensitivity is only 30%).8 Urine culture is unnecessary for most patients with consistent symptoms and a positive dipstick test, unless any predisposing factors for upper tract or complicated infection (hydronephrosis or atonic bladder) are present.11

MANAGEMENT

UTIs can be classified into acute uncomplicated cystitis, acute uncomplicated pyelonephritis, complicated UTI and acute complicated pyelonephritis. Uncomplicated UTIs are usually treated empirically with antibiotics as recommended by primary care guidelines. Antibiotics for empiric treatment of uncomplicated UTI include.9

- First-line antibiotic. Trimethoprim/sulfamethoxazole in communities with resistance rates for E. coli <20%. Avoid in women who have been treated within six months, as they are more likely to have resistant organisms.
- Second-line antibiotics or first-line in resistant communities: Fluoroquinolones, such as ciprofloxacin, levofloxacin, norfloxacin and ofloxacin.

Although, antibiotic treatment supports clinical cure in individual patients but also leads to emerging resistance rates in the population. Resistance has increased to various antimicrobials and more than one-quarter of E. coli strains causing acute cystitis are resistant to amoxicillin, sulfa drugs and cephalaxin and resistance to co-trimoxazole is now approaching these levels. Resistance to fluoroquinolones is also rising. Akram et al reported ciprofloxacin resistance rates ranging from 47 to 69% among the gram-negative organisms in their study in India.12 High levels of extended-spectrum beta-lactamase (ESBL) producers among gram-negative community-acquired uropathogens is seen in our country. This, along with the alarming rate of resistance to ciprofloxacin, sulfamethoxazole-trimethoprim and amoxicillin, precludes the use of these commonly used antibiotics for empiric treatment of community-acquired UTI in India.13

To prevent resistance, antibiotics should be used judiciously; they should be prescribed for as short a period as possible. Milo and colleagues reviewed 32 randomized controlled trials (with a total of 9,605 patients) comparing three days of oral antibiotic therapy with longer courses for women 18-65 years of age.14 Pregnant women and women with symptoms that suggest upper UTI (e.g., fever, flank pain, vomiting, positive blood cultures) were excluded. For short- and long-term resolution of symptoms, the reviewers found no difference between a 3-day antibiotic course and a course lasting 5-10 days. Longer courses were more
effective at clearing the bacteria on follow-up culture but also caused more adverse effects, and it was not clear that bacterial clearance resulted in improved patient-oriented outcomes.  

However, not everyone diagnosed by a general practitioner with a UTI and treated with an antibiotic will necessarily have a bacterial infection. At least one-half of women who suspect that they have UTI actually do. Fifty percent of patients consulting with urinary tract symptoms may not have a clinically important infection on culture. In a study by Eshwarappa et al in a South Indian population, only 510 of the 5,564 suspected cases (9.17%) were proved by culture. Studies have shown that one in 7 patients given an antibiotic for UTI symptoms will return within 28 days for a further prescription of antibiotic.

In many patients without additional risk factors, UTI seems to be a self-limiting condition. Studies have shown that many UTIs are self-limiting, improving without treatment even when culture is positive. One trial in Belgium has shown that half of the patients were free of symptoms after three days of placebo. If the volume of antibiotic prescribing is to be reduced and the increasing problem of resistant organisms addressed, alternative diagnostic and treatment strategies in primary care are needed. Symptomatic treatment of uncomplicated UTI may be an option which merits further research.

**SYMPTOMATIC TREATMENT OF UNCOMPPLICATED UTI**

Symptomatic UTIs are among the most common of bacterial infections. Though relatively benign and self-limiting, these irritating voiding symptoms like urinary urgency, frequency, nocturia, painful voiding, bladder discomfort or stranguria greatly distress the patient and have a detrimental influence on patient quality-of-life. Symptomatic treatment allows time for microbiological investigation and helps to reduce unnecessary prescribing of antibiotics. A urinary tract analgesic would have an immense reassuring effect on the patient. Phenazopyridine is a urinary tract antiseptic and analgesic that has for long been used to provide symptomatic relief of the pain, burning, frequency and urgency associated with UTI during the first 24-48 hours of therapy.

**PHENAZOPYRIDINE**

Phenazopyridine hydrochloride is an azo dye with local analgesic and anesthetic effects on the urinary tract. Chemically, phenazopyridine is 2,6-Pyridinediamine, 3-(phenylazo)-, monohydrochloride. It is used as a urinary tract antiseptic and analgesic as brief adjuvant therapy for treatment of UTI. Additionally, the drug is used for many urologic problems involving dysuria.

**Mechanism of Action**

The precise mechanism of action of phenazopyridine hydrochloride is not known. It is excreted in the urine, where it acts as a topical analgesic on the mucosal lining of the urinary tract thus relieving pain, burning, urgency and frequency. However, it does not possess any antimicrobial properties.

In a study undertaken recently, it was demonstrated that phenazopyridine directly inhibits the mechanosensitive Aδ-fibers in the normal rat bladder. In this study, the effect of phenazopyridine on afferent nerve activity was evaluated by direct measurement of both Aδ- and C-fibers, and compared the outcome with the effects of a local anesthetic (lidocaine) and of an analgesic (acetaminophen). Intravenous administration of phenazopyridine significantly decreased dose-dependently only the Aδ-fibers but not the C-fiber activity. According to the researchers, phenazopyridine exerts its clinical effect in conditions of urinary bladder hypersensitivity by direct inhibition of the mechanosensitive Aδ-fibers.

**Clinical Efficacy**

**Analgesic Properties**

A study was undertaken by Kirwin et al to evaluate the effects of phenazopyridine 500 mg (two tablets thrice-daily) administration in urogenital infections in 118 patients. It was seen that in 65 (55.1%) cases, all the characteristic symptoms of urogenital infections were relieved: Pain on urination was alleviated or abolished in 95.3%; burning on urination was relieved in 93.6%; frequency decreased in 85%, nocturia was eliminated or reduced in 83.7%, with reduction the organized sediment. In the remaining 53 cases, symptomatic relief was also observed in all but a few, although, there was no concomitant reduction in the organized urinary sediment. Phenazopyridine was very well-tolerated with no toxic effects observed during the two weeks of its administration.

**Adjuvant to Antimicrobial Therapy in Uncomplicated UTIs**

Phenazopyridine is compatible with antibacterial therapy and can help to relieve pain and discomfort during the interval before antibacterial therapy controls the infection. Treatment of UTI with
phenazopyridine hydrochloride should not exceed two days because there is a lack of evidence that the combined administration of phenazopyridine hydrochloride and an antibacterial provides greater benefit than administration of the antibacterial alone after two days.\textsuperscript{28}

Efficacy of phenazopyridine when administered along with antibiotics as a short-term analgesic in the treatment of uncomplicated UTIs was demonstrated in a randomized, open label study. It was seen that phenazopyridine, when given with antibiotics such as ciprofloxacin, doxycycline within 48 hours of diagnosis, resulted in marked reduction in urinary symptoms of burning micturition (91%) and pain during voiding of urine (89%).\textsuperscript{29}

Phenazopyridine is widely used as an adjunct to sulfonamides in the treatment of bacterial infections of the urinary tract because of its proven analgesic effect on the mucosa of the urinary tract. It does not alter the effectiveness of sulfonamides against uropathogenic bacterial species in mice.\textsuperscript{23} The combined bacteriostatic activity of sulfonamide compounds and phenazopyridine upon \textit{Balantidium coli} has been demonstrated \textit{in vitro}.\textsuperscript{30,31}

Another study demonstrated that bioavailability of ciprofloxacin is enhanced by oral co-administration with phenazopyridine. This study compared the pharmacokinetic behavior of ciprofloxacin administered alone versus ciprofloxacin plus phenazopyridine. While there were no differences between the two treatments in terms of peak plasma concentration ($C_{\text{max}}$) and elimination constant ($k_e$), area under the concentration-time curve to last measurable concentration (AUC$_t$) and area under the concentration-time curve extrapolated to infinity (AUC$_\infty$) were 35% and 29% higher, respectively, in the combined treatment arm. In addition, a significant delay in $t_{\text{max}}$ (from 1 to 1.5 hours) and a statistical increase of 29% in mean residence time (MRT) were also observed in the combination group. The study concluded that phenazopyridine, when given together with antibiotic (ciprofloxacin) enhances its bioavailability with regard to the amount absorbed and MRT in the body, which is beneficial during treatment.\textsuperscript{32}

Pain due to Bladder Spasms

Indwelling urinary catheter is a foreign body and its presence may trigger spasms, or detrusor contractions due to irritation of the trigone area.\textsuperscript{33} This complication is distressing for the patient. Phenazopyridine hydrochloride helps relieve the pain caused by catheters.\textsuperscript{34}

Chronic Radiation Cystitis

Radiation therapy is an integral part of adjunctive treatment in approximately 66% of cancer patients and its use has increased cancer survival. However, it is associated with chronic cystitis which impairs the cancer survivor’s quality-of-life. Phenazopyridine provides symptomatic relief for chronic cystitis associated with radiation therapy.\textsuperscript{35}

Autonomic Dysreflexia

Phenazopyridine may be useful in the management of autonomic dysreflexia (AD) associated with UTI. Paola et al have reported a case of a 36-year-old man with tetraplegia and AD triggered by cystitis, who improved both subjectively and objectively following the institution of a 2-day course of phenazopyridine.\textsuperscript{36}

Phenazopyridine vs Other Antispasmodics

Urinary antispasmodics such as oxybutynin and flavoxate are muscarinic receptor antagonists and exert beneficial direct relaxant effect on smooth muscle of the urinary tract, with local analgesic and anesthetic effects on the urinary tract.\textsuperscript{16} However, flavoxate and oxybutynin have anticholinergic effects such as dry mouth, constipation and other anticholinergic effects. Phenazopyridine has a different mechanism of action; it has both local analgesic and anesthetic effects on the urinary tract. Anticholinergics like oxybutynin and flavoxate alter the absorption of some concomitantly administered antimicrobials due to anticholinergic effects on gastrointestinal motility.\textsuperscript{37} On the other hand, the bioavailability of ciprofloxacin has been shown to be enhanced by oral co-administration with phenazopyridine. Hence, the major limitation in the use of non selective drugs like flavoxate and oxybutynin is often failure to obtain desired therapeutic responses without concomitant side effects. The anticholinergic side effects, though usually not serious, are sufficiently disturbing to decrease patient compliance, particularly during long-term administration.\textsuperscript{38} Also, the lack of demonstrated effect of flavoxate in placebo-controlled studies makes it difficult to recommend the use of flavoxate and it is definitely not a first-line treatment.\textsuperscript{39}

Safety in Pregnancy

Phenazopyridine is currently classified in pregnancy category B. The Collaborative Perinatal Project monitored 50,282 mother-child pairs in which 1,109 exposures anytime during pregnancy and 219 exposures during the first-trimester were documented. Results indicated no increase in the rates of major malformations or any
other adverse effects. On the other hand, there are no well-controlled studies on use of flavoxate in pregnant women, so it should be used during pregnancy only if clearly needed.

CONCLUSIONS

UTIs are a significant clinical problem. The associated symptoms of burning micturition, pain during voiding and increased frequency of urination can be a source of great discomfort and can greatly affect patients’ quality-of-life. Uncomplicated UTIs are usually treated empirically with antibiotics. However, antibiotics should not be prescribed excessively, particularly in view of the increasing prevalence of antibiotic resistance. Symptomatic treatment is an option which allows time for microbiological investigation and helps to reduce unnecessary prescribing of antibiotics. Phenazopyridine is a urinary tract antiseptic and analgesic that provides symptomatic relief of the pain, burning, frequency and urgency associated with UTI during the first 24-48 hours of therapy and is safe in pregnancy. Other urinary antispasmodics such as oxybutynin and flavoxate are useful but the bothersome anticholinergic side effects, limits their use.

REFERENCES


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