REVIEW ARTICLE

Dysuria: A Focus on Urinary Tract Infections

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Urinary tract infections are one of the most common infections faced by the primary care physician with nearly half of all women being diagnosed during their lifetime. Although easily treated with anti-microbial agents, urinary tract infections typically recur or are often incompletely resolved. New strategies are being developed for both treatment and prophylaxis of the disease process. In this review, the epidemiology, pathogenesis, treatment recommendations, and emerging research surrounding urinary tract infections will be discussed.

INTRODUCTION

Urinary tract infections (UTIs) are the most commonly encountered bacterial infection in the outpatient setting and are estimated to account for over eight million infections in the United States annually.[1] The majority of patients diagnosed with an acute UTI are prescribed antibiotics and 1% requires hospitalization.[2] This in turn results in over two billion dollars being spent every year for evaluation and treatment.[3] Therefore, a true understanding in the management and evaluation of these infections is vital for the primary care physician. This review will discuss the epidemiology, pathogenesis, treatment recommendations, and emerging research surrounding UTIs.

EPIDEMIOLOGY

Infections involving any section of the urinary tract are considered to be urinary tract infections (UTI). This includes urethritis, cystitis, ureteritis, and pyelonephritis.[2] In 2007, there were 10.5 million ambulatory visits for UTI with one fifth of these visits being to the emergency department.[4] UTIs are the most common primary diagnosis in women who present to the emergency department with more than 50% of having at least one UTI in their lifetime, and 11% of women being diagnosed with a UTI every year.[1,5,6] The higher incidence of UTIs in women can be related to the anatomy of the lower genital urinary tract. The shorter urethra in women in conjunction with colonization of the vaginal introitus with gastrointestinal pathogens can place women at higher risk of UTIs as compared to men.[7,8]

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While numerous risk factors have been defined for the development of UTIs, the majority of UTIs occur in individuals without any of the defined risk factors. The greatest risk populations are sexually active women aged 20-40 years and postmenopausal women over the age of 60 years.[9] The incidence of UTI in young sexually active women ranges between 0.5 to 0.7 UTIs per person year and by the age of 24 one third of women will have been diagnosed with a UTI.[10,11]

DIAGNOSIS

UTIs are often labeled as either uncomplicated or complicated. Uncomplicated UTIs are defined as a symptomatic bladder infection with laboratory tests consistent with a UTI; while a complicated UTI is defined as a symptomatic UTI caused by functional or structural abnormality, having had urinary instrumentation, having systemic diseases such as renal insufficiency, diabetes, or immunodeficiency, or having undergone organ transplantation.[12] UTIs can also be broken down into three separate categories: cystitis, asymptomatic bacteriuria and acute pyelonephritis.

CYSTITIS

Cystitis is commonly seen in the primary care office and is characterized by dysuria, frequency and urgency of urination with or without associated suprapubic pain in premenopausal women but malaise, nocturia, incontinence and foul smelling urine in post-menopausal women.[13,14] Although cystitis produces significant short-term morbidity, there are little to no long-term consequences.[13] In non-pregnant women, these infections have no long-term adverse effects on renal function, no increased mortality, and if left untreated rarely

progress to upper urinary tract infections.[15] This holds true even for individuals with recurrent cystitis.[15] When treating uncomplicated cystitis with antibiotics, women are more likely to have complete clinical symptom resolution and microbiological eradication.[16] However, they also have higher rate of adverse events secondary to the usage of antibiotics.[16]

The diagnosis of a UTI should first be based on the patient's symptoms but should also be used in conjunction with a urinalysis. Urinalysis with presence of red blood cells, high nitrite levels, and leukocyte esterase are concerning for a potential underlying UTI.[2] A positive urinalysis should be followed by urine culture with anti-microbial susceptibility testing, which is the gold standard for a definitive diagnosis.[2] Urine culture allows for identification of the causative agent and for antimicrobial susceptibility testing to be performed. Antibiotics should then be tailored accordingly to the results. Previously $\geq 10^5$ colony-forming units (CFU)/mL of midstream urine was considered a positive culture, however, recent literature has changed the diagnostic criteria to include 10^3 CFU/mL urine, in the presence of overt UTI symptoms.[2,17] Following treatment, repeat urinalysis for cure is currently not recommended unless symptoms recur.[18]

ASYMPTOMATIC BACTERIURIA (ASB)

Asymptomatic bacteriuria (ASB) is defined as bacteria in the urine without clinical signs or symptoms of a UTI.[9] The overall prevalence of ASB in women is 3.5% and increases following sexual intercourse.[19] In women aged 5-14, 1% will have ASB with the rate of this condition increasing with age.[20] When over age 80, 20% of women will have a diagnosis of ASB.[20] The prevalence of ASB in pregnancy ranges from 2 to 20% with one fifth of these patients developing acute pyelonephritis if left untreated.[21]

ASB is a microbiologic diagnosis that occurs when the detected organism outcompetes a uropathogenic organism.[9] This in turn prevents a clinical manifestation of infection. Therefore, routine screening and treatment for ASB is not recommended in the general population except during pregnancy.[6,9] Screening and treatment of ASB during pregnancy could decrease maternal and fetal mortality by 77%.[22] In the general population, however, treatment of ASB can lead to development of a UTI and antimicrobial resistant bacteria.[23]

ACUTE PYELONEPHRITIS

Acute pyelonephritis is defined by an infection of the renal pelvis and kidney that usually results from ascent of a bacterial pathogen up the ureters from the bladder to the kidneys.[24] The incidence of acute pyelonephritis is 59.0/10,000 for females and 12.6/10,000 for males in the general population with a hospitalization rate of 11.7/10,000 for women and 2.4/10,000 for men.[25,26] A good history and physical examination is the key to aid the physician in the diagnosis. Patients may present with or without urinary symptoms. Associated symptoms for acute pyelonephritis include fever, chills, back/flank pain, nausea or vomiting.[6,24] On physical examination, costovertebral angle tenderness is almost universal to pyelonephritis and its absence should raise the question of an alternate diagnosis.[24]

Diagnostic testing should include urinalysis and urine culture with susceptibility. The presence of white blood cell casts indicates a renal origin of pyuria and is highly indicative of pyelonephritis.[24] Post-treatment urinalysis and culture are not warranted in asymptomatic patients but may be of value in those whose symptoms do not improve in three days.[24] Imaging is not warranted in those who remain asymptomatic but those who have recurrence of symptoms or do not respond to therapy in 72 hours should undergo imaging to assess for a structural abnormality.[27] According to the American College of Radiology CT of the abdomen and pelvis is the diagnostic imaging modality of choice.[27]

PATHOGENESIS

The most common pathogen associated with UTIs is Escherichia coli (*E. coli*), an opportunistic pathogen.[2,6,9] When examining community-acquired UTIs, *E. coli* is the source in 80-90% of all cases and constitutes 74.4% of cases in the outpatient setting, 65% of hospital-acquired infections and 47% of health care associated infections.[9,28] Various *E. coli* strains have been shown to be commonly shared among pets, humans (non-sex and sex partners), and between humans and pets.[29,30] It is therefore not uncommon for multiple individuals within the same household to be infected with the same strain of *E. coli*.

UTIs are felt to develop via the fecal-perineal-urethral route of infection since most uropathogens, including *E. coli*, originate in the rectal flora.[9] The uropathogens then have an interim phase of vaginal and periurethral colonization and subsequently enter the bladder via the urethra.[31] It is unclear the exact means of ascension through the urinary tact but it is widely felt that motility mediated by flagella may play an important role in *E. coli* infections.[32]

The first line of defense for UTI prevention is the hosts response to inhibit attachment of *E. coli* to the urothelim. This is completed via the flow, acidity, and the high osmolarity of urine.[33] *E. coli* that avoid the first line of defense are able to invade the urothelium and then activate a release of immune mediators including cathelicidin or defensins and interleukin 6 and 8.33. Following the release of immune mediators, type 1 fimbrial adhesion FimH binds to the integrin of the bladder urothelium.[34] A signal cascade is activated that allows the

E. coli to be surrounded and enveloped by the host plasma membrane.[34] Once the *E. coli* are brought into the membrane, they rapidly multiply and form intracellular bacterial communities that exhibit biofilm like properties.[35] The intracellular bacterial communities are then able to dissociate and migrate out of the urothelium and then reinvade the urothelium, which reinitiates the entire process.[36]

Although *E. coli* is the most common pathogen to cause UTIs, several other pathogens do cause UTIs in varying degrees. The gram negative organisms *Klebsiella* spp, *Pseudomonas aeruginsoa* and *Proteus spp* and the gram positive organisms *Streptococcus agalactiae* and *Staphylococcus saprophyticus* all can cause UTIs in the general population.

RECURRENCE

Recurrent UTIs are defined as two uncomplicated infections within six months or three infections within one year with at least one confirmed with a urine culture.[1] The probability for recurrence following an initial UTI is 25% at six months and 46% at one year for young women.[2, 37] Also a patient's likelihood of recurrence increases if they have had more than one prior UTI.[37] If close temporal proximity between infections is encountered, the etiology of the infections are more likely to be caused by the same strain of bacteria.[37] Persistence and relapse of UTIs are most common with phylogenetic group B2 *E. coli* while cure and reinfection UTIs are common with the phylogenetic group D E. coli. [9]

Recurrent UTIs have multiple possible etiologies. The same uropathogenic strain can persist in the gastrointestinal tract and can repeatedly colonize the bladder.[37] When relapse with the preceding infecting *E. coli* occurs, the strains are felt to have a greater biofilm formation capacity which allows better adherence to the bladder. Alternatively, a different uropathaogenic strain can be introduced into the gastrointestinal tract or a new strain can be directly introduced from the environment into the perineal area and invade the bladder.[37]

A final etiology for recurrent UTIs is quiescent intracellular reservoirs. Quiescent intracellular reservoirs remain in the bladder urothelium following clearance of the initial UTI.[9] These remain undetected by the immune system and are less susceptible to antimicrobials. *E. coli* is therefore able to persist inactive for prolonged periods of time within the bladder urothelium.[9, 37] Stimulation of facet cell exfoliation leads to activation of the quiescent intracellular reservoirs.[9] This then causes cell differentiation and proliferation cascades which results in recurrence of infection.[9] Low levels of estrogen have been shown to increase the levels of quiescent intracellular reservoirs.[9] This serves as an explanation for recurrent UTIs in postemenopausal women.

TREATMENT

Following diagnosis of a UTI, spontaneous resolution of symptoms and sterilization of the urine occurs in approximately 25% of patients after 5-7 weeks with no antibiotic treatment and this number rises to 80% at 5 months.[38] However, it has been shown that antimicrobials are superior to placebo in clinical and microbiological success due to the timeliness of eradication.[39] After anti-microbial initiation, patients should begin to note symptom relief by 36 hours.[40]

Currently no single agent is considered the best agent for uncomplicated cystitis according to the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases latest recommendations.[41] Empiric treatment of uncomplicated cystitis should be based upon on the susceptibility patterns in the physician's area, risk of adverse effects, resistance rates and the risk of collateral damage.[41] Nitrofurantoin or fosfomycin trometamol were both given the highest recommendation for treatment of uncomplicated UTIs and if *E. coli* resistance rates are known to be less than 20%, trimothroprim-sulfamethoxazole is also an acceptable first line agent.[41] The fluoroquinolones also carry a high recommendation for treatment of uncomplicated UTIs in short duration but should be considered an alternative secondary to their propensity for collateral damage.[41]

Beta lactam agents including amoxicillin-clavulanate, cefdinir, cefaclor, cephalexin and cefpodoxime-proxetil are considered appropriate choices for therapy if other agents cannot be used.[41] However, the beta lactam agents have a propensity for decreased efficacy and increased adverse effects as compared to other anti-microbials.[41] Additionally, ampicillin and amoxicillin/clavulanic acid are not recommended due to high resistance patterns worldwide.[41]

For acute uncomplicated pyelonephritis both ciprofloxacin and trimothroprim-sulfamethoxazole should be considered first line agents if the relative resistance rate of the uropathogens is low *(Table 1, page 30)*.[41] However, if the resistance rate is unknown for trimothroprim-sulfamethoxazole or greater than 10% for the fluoroquinolone then a single intravenous does of a long acting anti-microbial is recommended prior to starting either of these.[41] Oral beta lactam agents are currently less effective than other anti-microbials for acute pyelonephritis and if used should be prescribed for between ten and fourteen days.[41]

REDUCTION OF UTIs

Prophylaxis with antimicrobial agents can be an effective strategy to reduce the incidence of UTIs but does come with possible adverse effects. Low-dose daily antibiotic prophylaxis in the means of nitrofurantoin , cephalexin, or trimethoprim-sulfamethoxazole has been shown to reduce the incidence of

TABLE 1:

Treatment of uncomplicated UTIs in the non-pregnant population

	Dose	Dose	Duration
Asymptomatic Bacteriuria	No treatment recommended		
Cystitis	First Line		
	Fosfomycin	3 grams	Single Dose
	Nitrofurantoin	100 mg BID	Five Days
	Trimethoprim/sulfamethoxazole	160/800 mg BID	Three Days
	Second Line		
	Ciprofloxacin	250 mg BID	Three Days
	Ciprofloxacin, extended release	500 mg QD	Three Days
	Levofloxacin	250 mg QD	Three Days
	Ofloxacin	200 mg QD	Three Days
	Third Line		
	Amoxicillin/clavulanate	500/125 mg BID	Seven Days
	Cefdinir	300 mg BID	Ten Days
	Cefpodoxime	100 mg BID	Seven Days
Pyelonephritis	Ciprofloxacin	500 mg BID	Seven Days
	Ciprofloxacin, extended release	1000 mg QD	Seven Days
	Levofloxacin	750 mg QD	Five Days

UTIs.[42] If a patient's UTIs are known to coincide with sexual activity, a single dose of antibiotic administered postcoitally is recommended.[43]

Caution must be used with routine use of antibiotic prophylaxis. Daily administration of antibiotics increases the antimicrobial resistance in both the gastrointestinal and urinary tracts. After one month of daily prophylaxis with trimethoprim-sulfamethoxazole, 86% of fecal *E. coli* and 91% of bacteriuria *E. coli* display resistance.[44] While nitrofurantoin has a significantly lower risk of resistance, it is also less effective against uropathogens aside from *E. coli* and is not recommended for long-term use in elderly patients or those with decreased renal function.[45-47] Furthermore, the presence of quiescent intracellular reservoirs may enable bacteria to be entirely intractable to any antimicrobial treatment and prophylaxis.[48]

Many alternative strategies to reduce the risk of recurrent UTIs are known and even more are being developed. These include modification of external risk factors including diaphragm or spermicide use, patient-initiated antibiotic treatment at an early stage, immunoactive prophylaxis, prophylaxis with food additives, and local hormone treatment in postmenopausal women.[16] Cranberry products have extensively been studied regarding the efficacy in UTI prevention. These products have been shown to decrease the ability of *E. coli* to adhere to the urothelium and also within human vaginal epithelial cells.[49,50] However, two recent meta-analyses showed that cranberry only carries a slight protective effect against UTI in the general population.[51, 52] Further investigation and research is necessary to determine if these products are able to effectively treat or prevent UTIs.

Methenamine salts have also been used in the prophylaxis of UTIs.[53] A recent Cochrane Review reported that methenamine may be effective for preventing UTIs in those without renal tract abnormalities or a neurogenic bladder in the short term.[55] However, it is recommended that further randomized controlled trials need to be conducted in order to assess the efficacy of methenamine's long term potential.[55]

A pilot study comparing the efficacy of ciprofloxacin versus ibuprofen for the treatment of uncomplicated UTIs was

recently completed. It was shown that ibuprofen has potential utility for this indication. Both treatments showed equal efficacy for symptom resolution and bacterial clearance with ibuprofen being non-inferior to ciprofloxacin. Though this study was underpowered, it suggests that the anti-inflammatory effect may help to eradicate uropathogens but further validation is needed.[54]

A vaccine to protect against urinary tract infections is also being developed. It consists of a vaginal suppository containing ten heat-killed strains of uropathogenic bacteria.[55] A total of six strains of *E. coli* and one strain each of P. mirabilis, M. morganii, K. pneumonia, and E. faecalis are included.[55] During phase 2 testing the vaccine has been shown to reduce the incidence of *E. coli* UTI in sexually active women aged 20-50 with a history of recurrent UTIs.[55] However, no statistically significant difference was seen in development of anti–*E. coli* antibody levels between the experimental and placebo group.[55] Further investigation through a phase 3 trial is required prior to routine utilization.

CONCLUSION

In conclusion, UTIs remain a large burden on society despite the ease in which they can be treated. Recurrence rates are typically high as compared to other disease processes despite adequate anti-microbial treatment. The primary care physician should be aware of current recommendations for both treatment and prophylaxis of UTIs in the general population. Further research is needed to determine strategies to better treat not only the disease but also to halt its recurrence.

DISCLOSURES:

Dr. Ashurst – Author for Emergency Medicine Practice with the company EB Practice, LLC.

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