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The Laboratorian SM

Urinary Tract Infections in Women and Men

Author: Jack H. Mydlo, MD, FACS.

By definition, urine is normally free of bacteria. Bacteriuria indicates the presence of bacteria in the urine, and this may be asymptomatic or symptomatic. Urinary tract infections (UTIs) can be classified as to their site of origin. They are considered to be the most common bacterial infection. They are usually associated with minimal morbidity.

UTIs are considered the most common bacterial infection, and accounts for nearly 7 million office visits, 1 million emergency room visits, and 100,000 hospital admissions annually. It increases from 1% in school aged girls to 4% in young adulthood. It then increases by 2% for every decade of life.

About 10% of women will have a UTI in any given year. More than half of all women have had at least one UTI in their lifetime. One in three women will have a UTI by the time they reach 24, compared to men, in which UTIs are more common after the age of 50, due to bladder outlet obstruction from an enlarged prostate.

Approximately 5 million physician visits a year are due to urinary tract infections, which can cost around $1.6 billion annually.

Symptomatic UTIs are increased among sexually active women, delayed post-coital voiding, anatomic urinary tract anomalies, reflux, cystocele, stones and bladder diverticula. Other risk factors for UTIs are summarized in **Table 1**.

Table 1: Other Risk Factors for UTIs.

1. Frequency of intercourse
2. Use of a diaphragm
3. Estrogen deficiency
4. Antibiotic usage
5. Infants
6. Pregnant women
7. Elderly
8. Spinal cord injury
9. Indwelling catheters
10. Diabetes
11. Multiple sclerosis
12. HIV-AIDS
13. Urologic pathology

The bacteria that causes most urinary tract infections is from *E. coli*, which is mostly present in the bowel. Other organisms include Proteus, Klebsiella, Enteroccocus and Staphylococcus. The female urethra is short, and bacteria usually enter it via the ascending route.

It is generally believed that some failure of the host defense mechanism allows for colonization of the introitus and vaginal mucosa in women, which is subject to recurrent bacterial infection from outside the urinary tract. While colonized, these women can experience recurrent UTIs every 6-12 months. Although these can be easily treated with antibiotics, they generally recur within weeks to months.

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Urinary Tract Infections (UTIs)

Author: David W. Hilbert, Ph.D.

UTIs are a major source of morbidity and associated healthcare costs in the United States (US). Community-acquired UTIs largely affect women of reproductive age, with 11% of women experiencing one each year, one-third of women having one by the age of 26, and 60% experiencing at least one during their lifetime [1]. In 1997 these infections resulted in 7 million physician office visits and 1 million emergency room visits [2]. Treatment of these infections cost $1.6 billion in 1995 [1], which is the equivalent of $2.2 billion in inflation-adjusted 2009 dollars. UTIs are defined clinically by the presence of a significant level of bacteria in the urine (i.e. bacteriuria). Guidelines vary, but typically a pure culture of between 10^4-10^6 colony forming units (CFUs)/milliliter (mL) of urine is indicative of a UTI. Patient symptoms are painful, urgent and frequent urination, along with malodorous and/or cloudy urine. Signs of infection include the presence in urine of blood (hematuria) or white blood cells (pyuria).

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UPCOMING EVENTS ➤➤

04/1-3	**ACOG-OR:** Oregon Section Sun River, OR
04/13-16	**SCOG:** 52nd Annual Meeting of the South Central Obstetrical & Gynecological Society Charlottesville, VA
04/14-16	**NASPAG:** The North American Society for Pediatric and Adolescent Gynecology (NASPAG) Annual Meeting Chicago, IL
04/27	**NEOG:** New England OBGYN Society, Sturbridge, MA
04/28-29	**MWS:** Matt Weis Symposium 2011 St. Louis, MO
04/30-05/4	**ACOG:** National Meeting Washington, DC
05/22-24	**CLMA:** Clinical Laboratory Management **Association Think Lab,** Baltimore, MD

Urinary Tract Infections (UTIs)

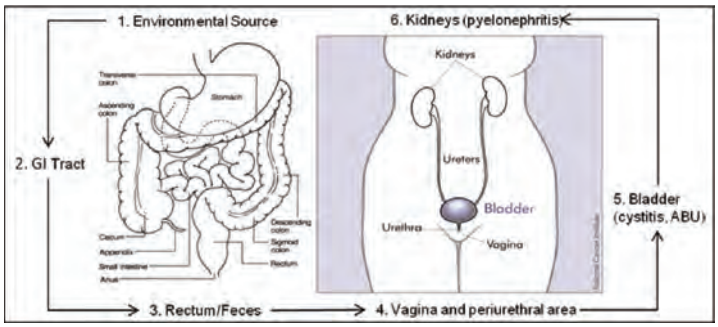

Figure 1. Epidemiology of UTIs. UPEC from an environmental reservoir (1) colonizes the patient GI tract via the oral route (2). UPEC in the GI tract colonizes the rectum and is shed in feces (3), from where it colonizes the vagina and periurethral area (4). UPEC ascends the urethra to the bladder, causing either asymptomatic bacteriuria (ABU) or symptomatic infection (cystitis) (5). In some cases, the infection spreads to the kidneys (pyelonephritis) and possibly to the bloodstream (sepsis) (6). GI tract (author unknown) and female urinary tract (NIH Medical Arts) are public domain images from the National Cancer Institute (NCI).

UTIs comprise a spectrum of diseases of varying severity, with different outcomes and treatment guidelines. Asymptomatic infections are referred to as asymptomatic bacteriuria (ABU), whereas symptomatic infections are classified as either cystitis if they are confined to the bladder or pyelonephritis if the infection has spread to the kidneys (Figure 1). Due the absence of symptoms, ABU is often only discovered through a positive urine culture, and does not require treatment in healthy, non-pregnant women. Cystitis is treated on an out-patient basis with oral antimicrobial therapy. In addition to the symptoms of cystitis, pyelonephritis is characterized by fever, flank pain and vomiting. Pyelonephritis is a serious and potentially life-threatening condition that frequently results in hospitalization—nearly 200,000 such cases were reported in the US in 1997 [3]. Pyelonephritis patients are at very high risk of developing sepsis (i.e. urosepsis), and 25% of all sepsis cases originate from a UTI [4]. The source of UTI pathogens is generally considered to be the patient's own flora. UTIs are preceded by colonization of the vagina and periurethral area by uropathogens from the GI tract (**Figure 1**) [5]. Women are much more susceptible than men to community-acquired UTIs. This susceptibility is due, in part, to the female anatomy in that a much shorter urethra allows pathogens easier access to the bladder. Uropathogenic *Escherichia coli* (UPEC) is responsible for more than 80% of community-acquired UTIs, with most other infections caused by *Staphylococcus saprophyticus*, *Klebsiella* spp., *Proteus mirabilis* and *Enterococcus faecalis* [6].

Recurrence

Although cystitis can be treated on an outpatient basis, recurrence is a major issue. It has been reported that 27% of patients experience another episode within 6 months and 44% experience another episode within 1 year [7, 8]. In addition, one-third of pregnant women who experience a UTI will have an additional episode during the pregnancy [9]. The majority of recurrent infections are due to re-infection by *E. coli* residing in the vaginal and fecal flora, rather than persistence of the primary infecting strain within the bladder [10]. Often the same UPEC clone is responsible for both the index and recurrent episodes [11, 12], and most recurrent UTIs are preceded by vaginal colonization with the infecting UPEC strain [13-15]. A recent study has corroborated these results and extended them by finding that the recurrent infection was often preceded by vaginal intercourse [16]. Treatment recommendations for women susceptible to recurrent UTIs include both continuous and post-coital antibiotic therapy [17]. Structural abnormalities in the urinary tract can lead to vesicoureteral reflux, which strongly pre-disposes individuals to recurrent UTIs. Such abnormalities are normally discovered during childhood, and most adults suffering from recurrent infections have anatomically normal urinary tracts. Ultrasound imaging can be performed if the clinician suspects an anatomical etiology in a patient suffering from recurrent UTIs.

Treatment

Community-acquired symptomatic UTIs are treated with empirical antimicrobial therapy upon diagnosis. The recommended first-line antibiotic therapy for cystitis is either 100 milligrams (mg) of nitrofurantoin per day for 5 days or 160 mg-800 mg of trimethoprim-sulfamethoxazole (SXT) per day for 3 days. Nitrofurantoin should be avoided if pyelonephritis is suspected, as this drug only reaches an effective concentration in the bladder. SXT should be avoided if resistance in the area is >20% or if the patient has been treated with this antibiotic in the last three months. Fosfomycin (3 gram single dose) can also be used, but some studies suggest it is less effective than nitrofurantoin or SXT. Although amoxicillin and ampicillin should be avoided due to endemic resistance, 3-7 day courses of the β-lactam β—lactamase inhibitor combination amoxicillin-clavulanic acid, as well as cephalosporins such as cefaclor, cefdinir and cefpodoxime proxetil, may be used. However, they exhibit less effectiveness and are associated with more adverse effects than the recommended front-line therapies (nitrofurantoin and SXT). Fluoroquinolones (e.g. ciprofloxacin, ofloxacin and levofloxacin) are highly effective in 3-day courses, resistance is minimal and they are well-tolerated, but are only recommended as second-line therapies as they are highly useful for more serious infections and their judicious use will delay the rise of resistance. Pyelonephritis is a much more serious condition, often requiring hospitalization and intravenous administration of antibiotics, such as either ceftriaxone (400 mg) or a consolidated twenty-four hour dose (i.e. 7 mg drug/kg body weight) of an aminoglycoside (gentaminicin or tobramycin), in addition to oral ciprofloxacin.

Pregnancy

Although pregnant women are not at an increased risk for UTIs in general, they are more likely to develop pyelonephritis than non-pregnant women. Approximately 4% to 6% of both pregnant and non-pregnant women exhibit ABU. For otherwise healthy non-pregnant women, there is no need for treatment. However, if ABU is left untreated during pregnancy, 20% to 40% of these women will develop pyelonephritis, often during the third trimester [9]. As a consequence, The American College of Obstetricians and Gynecologists recommends screening for ABU in all pregnant women. Sixteen weeks of gestation was found to be an optimal time for screening [18], and patients with positive cultures should be treated. The most important consideration in treatment is that it must be safe for both mother and fetus. Therefore, fluoroquinolones and trimethoprim should not be used, as they are assigned to FDA pregnancy risk "C" category (gestational risk in animal studies and no adequate human studies). As with non-pregnant patients, nitrofurantoin can be used as a front-line therapy. It is important to note that while nitrofurantoin is effective for treating ABU and cystitis, it is not recommended for pyelonephritis treatment due to poor tissue penetration. In addition, patients with glucose-6-phosphate dehydrogenase deficiency (pregnant or otherwise) should not take nitrofurantoin, as hemolytic anemia is a rare complication for these patients [19]. Patients should have a follow-up urine culture one week later to determine if treatment was successful, as 20% to 30% of patients will require additional treatment. In addition, up to one-third of pregnant women will suffer a recurrent infection during pregnancy. Therefore, after the initial episode, either administration of prophylactic antimicrobial therapy (50-100 mg of nitrofurantoin nightly) or frequent urine cultures should be performed throughout the pregnancy [9]. Any pregnant patient who develops pyelonephritis should be admitted and treated with paranteral antimicrobial therapy (see above). Complications of pyelonephritis during pregnancy include low fetal birth weight and

neonatal death, as well as maternal anemia, hypertension, renal failure and sepsis. Patients who have a UTI caused by Group B Streptococcus at any time during pregnancy should be additionally treated at the onset of labor to prevent vertical transmission to the neonate.

Antimicrobial Resistance

Although current therapies are effective, increasing prevalence of antimicrobial resistance is a major issue. The North American Urinary Tract Infection Collaborative Alliance (NAUTICA) study analyzed resistance among 1,142 UPEC isolates from outpatients at 40 medical centers and found resistance rates of 21% to SXT and 5% to 6% to fluoroquinolones [20]. A similar study in European and South American nations collected 2,315 UPEC isolates and determined that 29% were resistant to SXT and 8% were resistant to ciprofloxacin [21]. The high level of SXT resistance has forced a switch to fluoroquinolones as a front-line therapy in many areas, with predictable consequences. Between 1998 and 2005, a four-fold increase in levofloxacin prescriptions for UTIs at one medical center was correlated with an increase in resistance from 1% to 9% [22]. Another study, analyzing 11,407 UPEC isolates from outpatients, determined that the prevalence of extended-spectrum β-lactamases (ESBLs), capable of hydrolyzing third generation cephalosporins (e.g. ceftriaxone, ceftazidime), increased from 0.21% in 2003 to 3% in 2008 [23]. One possible solution to the problem of ESBL-producing bacteria is fosfomycin. A recent meta-study analyzing 1657 ESBL-producing *E. coli* isolates, most of which were UPEC, found that 97% of them were susceptible to fosfomycin [24].

In addition to general trends of increasing antibiotic resistance, specific multidrug-resistant UPEC clones have emerged. One group of isolates, termed clonal Group A (CGA), accounted for 11% of cystitis isolates, and 50% of SXT-resistant isolates, from three geographically distinct sites in the US [25]. CGA isolates also comprised 34% of SXT-resistant, and 7% of total, SXT-resistant pyelonephritis isolates [26]. Another major antibiotic-resistant UPEC clone is O25:H4-ST131, which expresses the CTX-M-15 ESBL rendering it resistant to third-generation cephalosporins [27]. Another multi-drug resistant UPEc clone is O14:K2:H1, first identified in an outbreak in London in 1997 [28]. These three clonal groups accounted for 37% of total UPEC isolates, 44% of SXT-resistant isolates and 64% of fluoroquinolone-resistant isolates in Canada from 2002-4 [29]. The spread of multidrug-resistant UPEC clones underscores the urgent need for new strategies to prevent and treat UTIs.

New therapies

Newer drugs for UTIs include members of existing classes being tested in the clinic, as well as entirely novel classes of compounds being developed in the laboratory. Doripenem is a broad-spectrum injectable carbapenem β -lactamase, approved by the FDA in 2007 for treatment of complicated UTIs, including pyelonephritis. Analysis of 1,772 clinical *E. coli* isolates (many from complicated UTIs) found that 99.8% of them were susceptible to doripenem, including all 30 ESBL-producers [30]. Analysis of 6 Phase III clinical trials demonstrated that doripenem was as effective as levofloxacin, imipenem, meropenem and piperacillin-tazobactam in treatment of patients with complicated UTIs due to ciprofloxacin-resistant and ESBL-producing *Enterobacteriaceae* (once again, largely UPEC) [31]. Prulifloxacin is a fluoroquinolone approved for treatment of UTIs in Italy and Japan, but not yet approved in the United Sstates. A study of 257 patients with complicated UTIs showed it was as effective as ciprofloxacin for treatment [32]. A number of other compounds are still being developed experimentally, and although far from the clinic, they provide promise as potential future therapies. One new approach to treating UPEC infections is rather than attempting to prevent microbial growth or kill the pathogen, instead is to inhibit its virulence properties so that an infection cannot persist (i.e. antivirulence therapies). This approach has focused on type 1 fimbriae, adhesive structures that are required by UPEC to adhere to the bladder epithelium [5]. Type 1 fimbriae normally bind mannose, and related compounds, such as butyl β -D-mannoside, are bound with much higher affinity and therefore may be useful as decoys to saturate the type 1 fimbriae and prevent bacterial adherence to the bladder epithelium [33].

Prevention

In addition to improving therapy, another major area of research is the prevention of UPEC infections. As is the case for treatment, both traditional and novel strategies are being evaluated. Consumption of cranberry juice is a traditional folk method of UTI prevention and treatment. Roughly a dozen studies have been performed examining the ability of cranberry products to prevent UTIs [34], but only two were randomized placebo-controlled studies with significant patient populations (150 women with a history of UTI). One study found that daily consumption of cranberry juice concentrate reduced the risk of UTI to 16% over a six month period, compared to 36% in the placebo group. A one-year study found that less than 20% of women who consumed cranberry juice or tablets experienced UTIs, compared to 32% in the placebo group [35, 36]. As vaginal and periurethral colonization with UPEC is strongly associated with UTIs [5], another prevention strategy is to use vaginal probiotics to prevent colonization. Small pilot studies have found that vaginal colonization with *Lactobacillus* spp. helps to prevent recurrent UTIs [37-39]. A Phase I trial on the use of vaginal *Lactobacillus* suppositories to prevent recurrent UTIs has recently been completed with minimal patient side effects [40], paving the way for future trials and the possible use of probiotics clinically to prevent UTI.

Development of a vaccine to prevent UTIs is an active research area, but this research has not yet progressed to the clinic [5]. However, mixtures of killed uropathogens, administered either orally or as vaginal suppositories, have been tested for their ability to prevent UTIs. UroVaxom (OM-89) is a lyophilized extract of 18 UPEC strains that is taken orally in Europe to prevent recurrent UTIs. A meta-analysis of five placebo-controlled double-blind studies found that oral consumption of UroVaxom reduced the risk of UTI by 36% over 6 months [41]. These findings were replicated in a large multicenter study (453 patients) that found a 34% reduction in UTIs over one year [42]. A related product is SolcoUrovac, a vaginal suppository containing lyophilized extract from 6 UPEC strains and one strain each of *P. mirabilis*, *Morganella morganii*, *K. pneumoniae* and *E. faecalis*. A Phase II randomized, double-blind placebo-control trial of 75 women with recurrent UTIs over 160 days observed a recurrence rate of 70% for the placebo arm and 27.5% for the vaccination plus booster arm of the study [43].

Summary

UTIs are highly prevalent and a major source of morbidity among women in the US. They are largely caused by uropathogenic *E. coli* (UPEC), and the source of infection is the patient's own fecal flora. The infecting strain can persistently colonize the vagina, leading to frequent recurrent infections. Pregnant patients are a special concern, as they often exhibit ABU which can progress to pyelonephritis. Urine screening and careful selection of antibiotics is necessary for these patients. Although UTIs can be treated with currently available antibiotics, antibiotic resistance to commonly used antibiotics, such as trimethoprim-sulfamethoxazole and fluoroquinolones, is increasing at an alarming rate, in part due to the emergence of multi-drug resistant clonal groups. The use of certain older drugs, such as nitrofurantoin and fosfomycin, may prove to be very useful in dealing with the emergence of antibiotic

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Urinary Tract Infections in Women and Men

Diagnosis

The diagnosis is usually made on history alone. The probability of bacterial cystitis in a woman with dysuria, urinary frequency or gross hematuria is about 50% in the general practice care environment.

Typical symptoms of bacterial cystitis in females include frequency, urgency, dysuria, small-volume voiding, nocturia, and suprapubic pain or pressure. Other symptoms may include fever, flank pain, and/or chills. These symptoms are usually more indicative of pyelonephritis, and may be more serious if not treated. If a female patient has more than 2 UTIs in a 12 month period, one should think of a structural or functional urinary tract abnormality, relapsing infection, or reinfection.

Physical exam

Signs may include bladder distention, suprapubic distention, abdominal tenderness, and/or vaginal discharge.

Diagnostic tests

Urinalysis: On dipstick, leukocyte esterase has a 50% positive predictive value 92% negative predictive value, nitrate has a sensitivity of 35% to 85%. Microscopy: pyuria > 10 WBCs/hpf, bacteruria > 1 organism per oil immersion of uncentrifuged urine correlates with > 10(5) CFU/ml.

The gold standard is urine culture, where > 10(5) colonies indicates a positive culture. However, this definition excludes 30% to 50% of women with classic symptoms of acute bacterial cystitis.

Urologic investigation is usually not warranted in isolated urinary tract infections. However, imaging studies should be performed in the following cases:

1. Women with febrile infections
2. Men
3. Urinary tract obstruction due to prostate, stone, etc.
4. Previous urologic instrumentation or surgery
5. Diabetes
6. Persistent symptoms despite several days of appropriate antibiotic therapy.
7. Rapid recurrence of infection after apparently successful antibiotic therapy.

Renal ultrasound is most appropriate for an initial study to rule out stones, hydronephrosis, abscess, etc. CT w/o contrast for further evaluation when ultrasound is non-diagnostic, should be considered. VCUG is used to detect vesicoureteral reflux in patients with a history of reflux or neurogenic bladder, or urethral diverticulum. Cystoscopy is indicated when unusual organisms are found which may suggest a fistula, or hematuria in the absence of infection.

Evaluation

As is most evaluations of a medical problem, the history can provide us with very valuable information. The clinician should look for hygienic causes, such as UTI's associated with sexual activity. In these cases, peri-coital antibiotics, usually given right before or right after intercourse, as well as bladder emptying, can be a very effective course of treatment.

Hygiene after a female defecates is also a potential etiology. In this author's experience, if you ask the female which way she wipes herself after defecation (front to back, vs. back to front), if she has to think a few seconds about her answer, chances are, she is wiping herself incorrectly. A history of renal or bladder stones, especially without associated hematuria or pain, can certainly be a reason for UTI's and recurrent UTIs' (**Figure 1**).

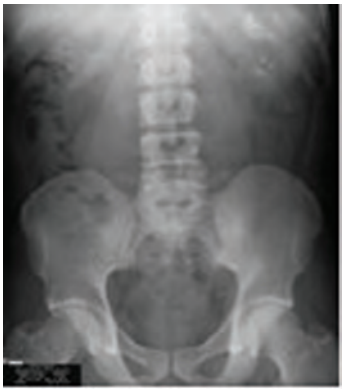

Figure 1: Multiple left renal stones in this otherwise asymptomatic patient caused recurrent UTIs.

Treatment

The treatment of typical bladder urinary tract infections is usually empirical and not based on culture results. The drug should be chosen based on the following:

1. The ability that the drug will be effective against the bacteria that caused the UTI
2. The ability of the drug to have high concentrations in the urine
3. The ability of the drug not to alter the bowel or vaginal flora, or to cause bacterial resistance
4. Lower toxicity
5. Acceptable purchase price to the patient

Urine levels of antibiotics are more important than serum levels for the treatment of UTIs, therefore care must be taken how to interpret susceptibility results. Three days of antibiotic therapy is sufficient to treat most UTI's compared to the typical 5-10 days of treatment that were done in the past. Usually, a 3 day course of TMP-SMX or nitrofurantoin are acceptable to treat the typical UTI.

If the symptoms of UTI persist after adequate treatment, then one should perform urine culture and sensitivity. After a choice of antibiotic is chosen, it should be administered for 7-10 days. Repeat cultures should to done to identify the bacteria to differentiate unresolved UTIs from recurrent infections.

If those infected stones become lodged in the ureter or ureteropelvic junction, it becomes a urological emergency to relieve pressure, otherwise this can result in sepsis and death of the patient (**Figure 2a**). First, decompression should be done by ureteral stent or percutaneous nephrostomy. Once the infection is treated appropriately for several days and urine cultures are sterile, then uretersoscopy, stone basketing, and/or laser lithotripsy can be performed (**Figure 2b**)

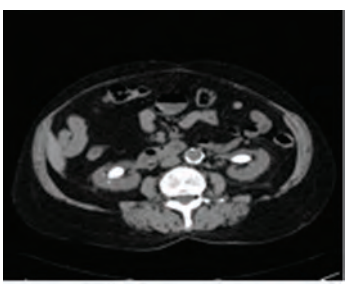

Figure 2a: Bilateral UPJ stones causing obstructed infected urine and sepsis in this patient.

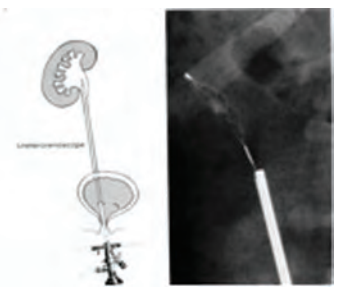

Figure 2b: Once the infection is resolved, treatment by ureteroscopy can be done.

While asymptomatic bacteria is common in older patients, especially those in nursing homes, (20% of women and 10% of men), it is controversial if these need to be treated. The routine treatment of these appears to be unnecessary.

On the other hand, treatment of UTIs in pregnancy warrants treatment, since pregnancy results in physiologic changes that may affect the progression of infection. During pregnancy there is an increase in renal size, increased renal function, and hydronephrosis. There is a 20% to 40% increase in pyelonephritis if asymptomatic bacteruria is untreated in the pregnant female. This can also lead to infant prematurity and mortality. Therefore, it is important to treat ASB in pregnant women and obtain follow-up cultures.

Xanthogranulomatous Pyelonephritis

In patients with a history of stones, recurrent urinary infections, and diabetes, there is an increased chance to develop xanthogranulomatous pyelonephritis, or XGP. This diagnosis can lead to early destruction of the kidney because the stone, sometimes a staghorn calculous, may cause obstruction of the collecting system in the presence of infected urine. It may lead to abscess formation, or just continued flank pain, recurrent UTIs, and possible sepsis if not treated appropriately by nephrectomy (**Figures 3a and 3b**).

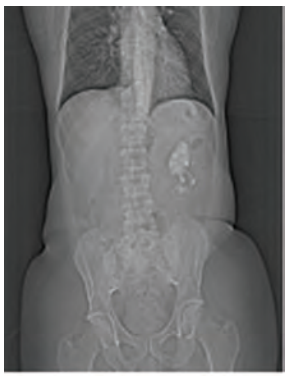

Figure 3a: Plain x-ray of staghorn calculous in patient with XGP

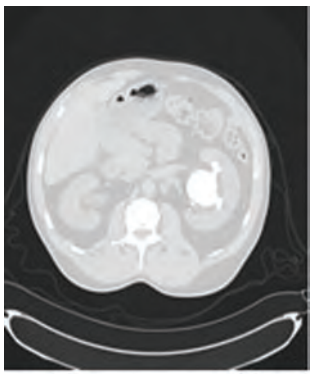

Figure 3b: CT of staghorn calculous in patient with XGP

Pyelonephritis

Infection of the upper urinary tract can result in a significant presentation of fevers, flank pain, and if recurrent, renal scarring and chronic pyelonephritis. There are several routes to ascending upper tract infection:

1. Reflux from the bladder
2. Hematogenous
3. Lymphatic
4. Diabetes
5. Age
6. Female gender
7. Voiding dysfunction

If pyelonephritis progresses, it could lead to abscess formation or more seriously, emphysematous pyelonephritis. Initial treatment could be by percutaneous drainage combined with appropriate antibiotic therapy. Due to the high mortality rate, sometimes total nephrectomy needs to be performed to remove the infectious collection (**Figures 4a and 4b**).

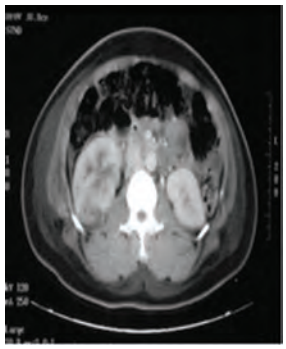

Figure 4a.: Pyelonephritis shows swelling of right kidney and fevers despite being on antibiotic therapy.

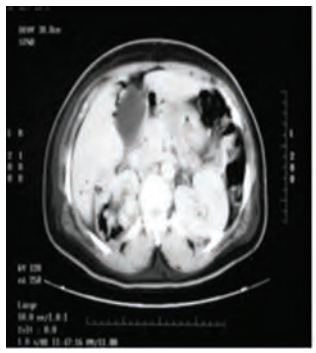

Figure 4b: Persistence of infection led to gas forming Bacteria and abscess collecting in right renal tissue

In men, especially in the older population, recurrent UTIs are seen in those patients with bladder outlet obstruction due to an enlarged prostate, which can be observed on cystoscopy and CT scan (Figs. 5a and 5b). Furthermore, retained urine can cause bladder stones which will further lead to recurrent UTIs (Fig. 5c).

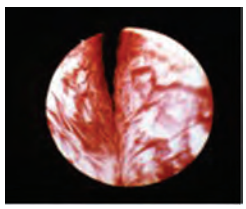

Figure 5a: Cystoscopy reveals enlarged prostate with hypertrophy of lateral lobes impinging on urethra

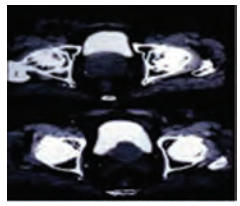

Figure 5b: CT reveals enlarged prostate impinging on bladder, which can cause retained urine

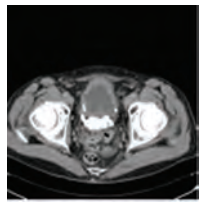

Figure 5c: CT reveals numerous bladder stones which was due to retained urine and caused recurrent UTIs

One of the problems seen in a typical urological practice is when patients are seen by their primary care practitioner for symptoms that may appear like a UTI, such as frequency, urgency, etc and are treated with antibiotics, but their symptoms may not be due to a UTI. Urologic pathology such as transitional cell carcinoma, carcinoma in situ (CIS), stones, etc, can simulate urinary tract infections, and if symptoms do not improve after initial treatment, further evaluation by a urologist should be initiated.

My practice has seen several patients who were treated by the numerous anti-cholinergic medications advertised on television for urgency and frequency, only to have a more serious problem that should have been addressed sooner. Although situations like this are rare and unpredictable, the primary care physician should be alert to the possibility that simple UTI symptoms may be due to something more ominous, especially in the older patient, the smoker, etc.

Prostatitis and chronic pelvic pain syndrome

Prostatitis accounts for approximately one fourth of all male office visits for urologic symptoms. Half of all men will suffer from some symptoms of prostatitis sometime in their lives, and this accounts for 2 million office visits annually in the United States.

Only 10% of prostatitis patients actually have bacterial prostatitis. Acute bacterial prostatitis is classified as class I. Chronic bacterial prostatitis is classified as class II. Nonbacterial prostatitis is classified as class III, and class IV patients have no symptoms, but have evidence of inflammation on expressed fluid, semen, or prostate tissue. They have suprapubic pain, difficulty voiding, low back pain, fevers, and chills.

Urinary Tract Infections in Women and Men

Treatment for acute prostatitis is bed rest, analgesics, hydration, antibiotics, stool softeners, and possible suprapubic cyststomy if in urinary retention. If the patient is acutely ill, then hospitalization with IV ampicillin and gentamycin should be initiated. Once they are an outpatient, they can be managed with TMP-SMX or a fluoroquinolone to prevent re-infections, or the development of chronic prostatitis.

Chronic Pelvic Pain syndrome (CPPS)

Signs and symptoms may be intermittent in nature, and include dysuria, suprapubic pain, frequency, nocturia. Treatment may start with antimicrobials, even in the presence of a negative urine culture, as well as anti-cholinergics, repeated prostate massage, 5 alpha reductase inhibitors, and muscle relaxants such as diazepam.

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***- Jack H. Mydlo, MD, FACS**, a scientific consultant for the Research & Development Department at Medical Diagnostic Laboratories, L.L.C., is also a Professor and Chairperson for the Department of Urology at Temple University School of Medicine.*

resistance. In addition, newer drugs, such as the recently approved doripenem, are highly effective in treating complicated UTIs. Research into novel anti-virulence therapies, such as inhibiting the UPEC fimbriae, is still an early stage but holds promise for future development. Some studies indicate that consumption of cranberry juice or extract may be helpful in preventing recurrent UTIs. In addition, the use of probiotics to prevent vaginal UPEC colonization and the use of an immuno-stimulatory uropathogen extract (SolcoUrovac) are currently in clinical trials to determine their efficacy in preventing recurrent UTIs. In summary, UTIs continue to be a major women's health problem and continued research is necessary to provide effective therapy to these patients.

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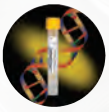
New Tests Announcement



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172 *Klebsiella* species by Real-Time PCR
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129 *Mycoplasma genitalium* by Real-Time PCR
130 *Mycoplasma hominis* by Real-Time PCR
167 *Neisseria gonorrhoeae* by Real-Time PCR
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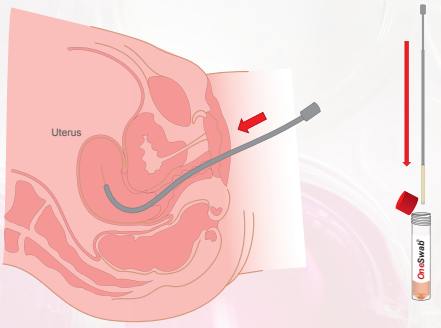
109 *N. gonorrhoeae** & *C. trachomatis* by Real-Time PCR
146 *Proteus mirabilis* by Real-Time PCR
174 *Pseudomonas aeruginosa* by Real-Time PCR
320 *Ureaplasma urealyticum* by Real-Time PCR



e-Quiz

1. Which bacteria causes the most urinary tract infections (UTI)?
2. The "gold standard" urine culture generally dictates that more than 10^5 colonies indicates a positive culture. However, this definition excludes _____ of women with classic symptoms of acute bacterial cystitis.

   a. 5% to 10% c. 15% to 20%
   b. 20% to 30% d. 30% to 50%

3. What percentage of women will experience at least one UTI in their lifetime?

   a. 20% c. 60%
   b. 40% d. 80%

4. **True of False.** The majority of recurrent infections are due to re-infection by E. coli residing in the vaginal and fecal flora, rather than persistence of the primary infecting strain within the bladder
5. **True of False.** The American College of Obstetricians and Gynecologists recommends screening for asymptomatic bacteriuria (ABU) in all pregnant women.

For results to the electronic Epidemiology Quiz, please visit www.mdlab.com and click on the e-Quiz link.

Recent Publications

VENENUM: Peer-Reviewed Papers:

Villasmil M.L., Ansbach A., and Nickels J.T. Jr. 2011. The putative lipid transporter, Arv1, is required for activating pheremone-induced MAP kinase signaling in *Saccharomyces cerevisiae*. *Genetics*. **187**(2): 466-465.

Nolt J., Rice L.M., Gallo-Ebert C., and Nickels, J.T. Jr. 2011. PP2AC5c55 is required for multiple events using meiosis 1. *Cell Cycle*. *Accepted*.

MDL: Research & Development Abstracts:

Huang L, Libby E, Trama J. Identify and Evaluate Novel Biomarker CIP2A for Cervical Cancer Diagnosis. 102nd Annual Meeting of the American Association for Cancer Research (AACR), April 2-6, 2011, Orlando, Florida.

JOURNAL WATCH

Yasufuku T, Shigemura K, Shirakawa T, Matsumoto M, Nakano Y, Tanaka K, Arakawa S, Kinoshita S, Kawabata M, Fujisawa M. 2011. Correlation of overexpression of efflux pump genes with antibiotic resistance in *Escherichia coli* Strains clinically isolated from urinary tract infection patients. *J Clin Microbiol*. **49**:189-94.

Escherichia coli is one of the most common pathogens in urinary tract infections (UTIs), and antibiotic resistance in *E. coli* is becoming a serious problem in treating UTI. Efflux system overexpression is reported to contribute to *E. coli* resistance to several antibiotics. This study investigated the correlation of antibiotic susceptibilities with the over expression of the efflux pump genes such as marA, yhiU, yhiV, and mdfA and with risk factors for antibiotic resistance in *E. coli* isolated from UTI patients. The study examined the expression level of efflux pump genes using quantitative real-time reverse transcription-PCR (qRT-PCR). The authors also tested the in vitro susceptibilities to 12 kinds of antibiotics in 64 clinical strains of *E. coli* isolated from UTI patients. By multivariate analyses they revealed significant relationships between the over expression of (i) marA and MICs of cefepime (FEP) and nalidixic acid (NAL), (ii) yhiV and MICs of minocycline (MIN), and (iii) mdfA and MICs of sitafloxacin (STX). In the investigation of the efflux pump genes, risk factors such as gender and the previous use of fluoroquinolones correlated with the overexpression of marA, and indwelling catheter use correlated with the over expression of mdfA. In conclusion, The authors demonstrated that the increased expression of efflux pump genes such as marA and mdfA can lead to fluoroquinolone resistance in *E. coli*. These results contribute to our knowledge of the efflux system and raise the possibility of developing new agents, such as efflux pump inhibitors (EPIs), to antibiotic-resistant *E. coli*.

J Med Microbiol. 2011 Jan;60(Pt 1):102-9. Epub 2010 Oct 14.
Croxall G, Weston V, Joseph S, Manning G, Cheetham P, McNally A. 2011**.** Increased human pathogenic potential of *Escherichia coli* from polymicrobial urinary tract infections in comparison to isolates from monomicrobial culture samples. *J Med Microbio*l. **60**:102-9.

The current diagnostic standard procedure outlined by the Health Protection Agency for urinary tract infections (UTIs) in clinical laboratories does not report bacteria isolated from samples containing three or more different bacterial species. As a result many UTIs go unreported and untreated, particularly in elderly patients, where polymicrobial UTI samples are especially prevalent. This study reports the presence of the major uropathogenic species in mixed culture urine samples from elderly patients, and of resistance to front-line antibiotics, with potentially increased levels of resistance to ciprofloxacin and trimethoprim. Most importantly, the study highlights that *Escherichia coli* present in polymicrobial UTI samples are statistically more invasive (P<0.001) in in vitro epithelial cell infection assays than those isolated from monomicrobial culture samples. In summary, the results of this study suggest that the current diagnostic standard procedure for polymicrobial UTI samples needs to be reassessed, and that *E. coli* present in polymicrobial UTI samples may pose an increased risk to human health.

Pallett A, Hand K. 2010. Complicated urinary tract infections: practical solutions for the treatment of multiresistant Gram-negative bacteria. *J Antimicrob Chemother*. 2010 **65**:25-33. (Review)

Resistance in Gram-negative bacteria has been increasing, particularly over the last 6 years. This is mainly due to the spread of strains producing extended-spectrum β-lactamases (ESBLs) such as CTX-M enzymes or AmpC β-lactamases. Many of the isolates producing these enzymes are also resistant to trimethoprim, quinolones and aminoglycosides, often due to plasmid co-expression of other resistance mechanisms. CTX-M-producing Escherichia coli often occurs in the community and as *E. coli* is one of the commonest organisms causing urinary tract infections (UTIs) the choice of agents to treat these infections is diminishing. Novel combinations of antibiotics are being used in the community and broad-spectrum agents such as carbapenems are being used increasingly as empirical treatment for severe infections. Of particular concern therefore are reports in the UK of organisms that produce carbapenemases. As resistance is becoming more widespread, prudent use of antimicrobials is imperative and, as asymptomatic bacteriuria is typically benign in the elderly, antibiotics should not be prescribed without clinical signs of UTI. The use of antibiotics as suppressive therapy or long-term prophylaxis may no longer be defensible.

Blango MG, Mulvey MA. 2010. Persistence of uropathogenic Escherichia coli in the face of multiple antibiotics. Antimicrob *Agents Chemother*. **54**:1855-63.

Numerous antibiotics have proven to be effective at ameliorating the clinical symptoms of urinary tract infections (UTIs), but recurrent and chronic infections continue to plague many individuals. Most UTIs are caused by strains of uropathogenic *Escherichia coli* (UPEC), which can form both extra- and intracellular biofilm-like communities within the bladder. UPEC also persist inside host urothelial cells in a more quiescent state, sequestered within late endosomal compartments. The authors tested a panel of 17 different antibiotics, representing seven distinct functional classes, for their effects on the survival of the reference UPEC isolate UTI89 within both biofilms and host bladder urothelial cells. All but one of the tested antibiotics prevented UTI89 growth in broth culture, and most were at least modestly effective against bacteria present within in vitro-grown biofilms. In contrast, only a few of the antibiotics, including nitrofurantoin and the fluoroquinolones ciprofloxacin and sparfloxacin, were able to eliminate intracellular bacteria in bladder cell culture-based assays. However, in a mouse UTI model system in which these antibiotics reached concentrations in the urine specimens that far exceeded minimal inhibitory doses, UPEC reservoirs in bladder tissues were not effectively eradicated. The authors concluded that the persistence of UPEC within the bladder, regardless of antibiotic treatments, is likely facilitated by a combination of biofilm formation, entry of UPEC into a quiescent or semiquiescent state within host cells, and the stalwart permeability barrier function associated with the bladder urothelium.

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