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Urinary Tract Infections

Introduction

Symptomatic and asymptomatic urinary tract infections are a common problem; UTI accounts for >10 million office visits and 1 million hospital admissions per year. UTI's in adults can be grouped by risk factor, etiologic agent, optimal therapy, and expected outcome. A schema taking all these things into account follows:

Table 1. Urinary Tract Infections in Adults

Acute uncomplicated UTI in young women
Acute uncomplicated pyelonephritis
Recurrent UTI's in women
Complicated UTI's in older women
Catheter-associated bacteriuria
Asymptomatic bacteriuria
Candiduria

Definitions:

Lower UTI: cystitis, urethritis, prostatitis

Upper UTI: pyelonephritis, intra-renal abscess, perinephric abscess (usually late complications of pyelonephritis)

Uncomplicated – Simple cystitis of short (1-5 day) duration

Complicated – Long duration or hemorrhagic or
cystitis with anatomical or functional abnormalities

Symptomatic and asymptomatic women

Low colony counts in voided mid-stream urine of **asymptomatic** women are usually indicative of vulvar flora contamination. Some of these asymptomatic women may show quite a few colonies, but if you follow them for a while, they clear up on their own. There is NO need to do anything about this.

In **symptomatic** women (showing symptoms of frequency and dysuria), suprapubic tap (which avoids the vulvar contamination) of the bladder may yield no organisms. In this case, other causes of dysuria such as HSV II, urethritis, or mechanical irritation of the urethra should be considered. In those women who have positive suprapubic tap cultures, they may have fewer than 10^5 CFU/ml (the usual diagnostic cut-off) and still have UTI. In this case, ask the lab to identify the organism. Most of the symptomatic women will have more than 10^5 CFU/ml (v*ide infra*).

Previously, studies of symptomatic women suggested that a threshold of 10^5 CFU/ml on a midstream, clean-voided specimen could reliably differentiate the majority of women with symptomatic UTI's from those with asymptomatic bacteriuria. However, subsequent studies have indicated that as many as 25%-50% of women with frequency and dysuria have $10^2 - 10^4$ CFU/ml *of a urinary pathogen*.

Up to 20% of women with acute uncomplicated pyelonephritis have 10^3 - 10^4 CFU/ml. Nearly all patients with acute, uncomplicated UTI have microscopic pyuria at a level of $\geq$10 leukocytes/μl (measured in a hemocytometer, unspun). Catheterized patients in whom urine specimens are obtained from the catheter should be considered to have UTI's if there are 10^2 - 10^4 CFU/ml.

Epidemiology

A number of different populations are at risk of urinary infection. (Table 2).

Table 2. Populations at Risk for UTI
Newborn
Prepubertal girls
Young boys
Sexually active adult women
Elderly females
Elderly males

Throughout life, urinary tract infections are more common in women than in men. However, in the first 3 months of life, 75% of urinary infections occur in boys. About 1% of preschool girls will have a UTI as compared with 0.4% of boys. In young adults, symptomatic UTI's occur in 20% of women and 0.1% of men. Pregnant women have a 4-10% prevalence of bacteriuria.   Ultimately, one-third of women will have a UTI before they reach age 65. In individuals over age 65 in long-stay hospital wards, the frequency of bacteriuria can reach almost 50% (Table 3). Among patients in acute-care hospitals in the U.S., UTI's develop in 2.4 % (almost 1 million), and UTI's account for 40% of hospital-acquired infections. Urinary infections are a major cause of gram-negative bacteremia and mortality.
(Table 3)

**Table 3: Epidemiology of Urinary-tract Infections by Age Group**

	Females			*Males*	
Age (yr.)	Pre-valence (%)	Risk factors	Pre-valence (%)		Risk factors
<1	1	Anatomic or functional uro-logic abnormalities	1		Anatomic or functional urologic abnormalities
1-5	4.5	Congenital abnormalities, vesicoureteral reflux	0.5		Congenital abnormalities, uncircumcised penis
6-15	4.4	Vesicoureteral reflux	0.5	None	
16-35	20	Sexual intercourse, dia-phragm use, spermicidal jelly	0.5		Homosexuality
36-65	35	Gynecologic surgery, blad-der prolapse	20		Prostate hype-rtrophy, obstr-uction,cathete-rization,surgery
>65	40	All of above, incontinence chronic catherization	35		All of above, incontinence, long-term catherization, condom catheters

Microbiology

The organisms causing uncomplicated UTI in the outpatient differ from those causing infection in catheterized hospitalized patients. *Escherichia coli* causes about 80% of acute infections in patients without urinary tract abnormalities. Other groups include *Staphylococcus saprophyticus* (10%), and occasionally other Gram-negative enterics like *Proteus mirabilis* and *Klebsiella pneumoniae*. Infrequently involved are other Gram-negatives such as *Enterobacter*, *Serratia*, and *Pseudomonas* (especially if the patient's urinary tract has been instrumented).

In contrast, in catheterized patients and individuals with structural abnormalities of the urinary tract, *E. coli* accounts for only 35% of infections and the other Gram-negative species are more important, as are *Enterococcus* spp. and the coagulase-negative staphylococci.

Figure 1

- E. coli 79%
- S. saprophyticus 11%
- Klebsiella 3%
- Mixed 3%
- Proteus 2%
- Enterococcus 2%
- Other 2%
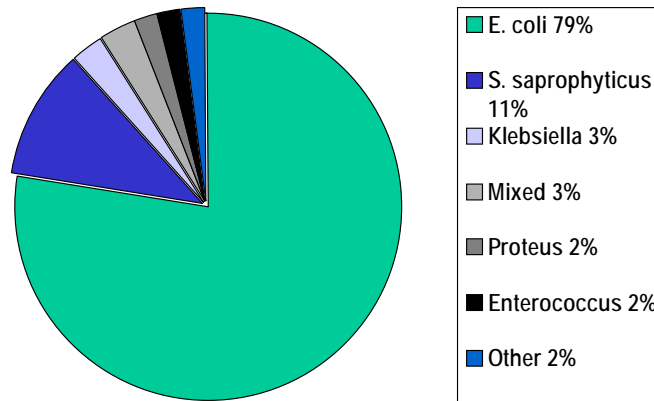
Pathogenesis

Bacteria can enter and spread in the urinary tract by two possible pathways: ascending and hematogenous. Most infections, including all Gram-negatives, enterococci and coagulase-negative staphylococci occur via the ascending route from the urethra $\rightarrow$ bladder $\rightarrow$ kidney. Hematogenous infection to the kidney and the rest of the urinary tract characteristically occurs during *S. aureus* bacteremias; candidal urinary infections can be either ascending or hematogenous. There is little evidence to support a lymphatic spread of infection to the urinary tract with any regularity.

The *E. coli* bacteria which cause UTI's reside in the intestine and thence colonize the perineum and vaginal introitus, displacing the normal flora (diphtheroids, lactobacilli, coagulase-negative staphylococci, and streptococcal species). In women in whom UTI's develop, the urethra is colonized and the uropathogen gains entry to the bladder, presumably by means of the urethral massage that accompanies sexual intercourse. (Figure 2) Whether infection develops depends upon the particular organism, the size of the inoculum, and the adequacy of host defenses.
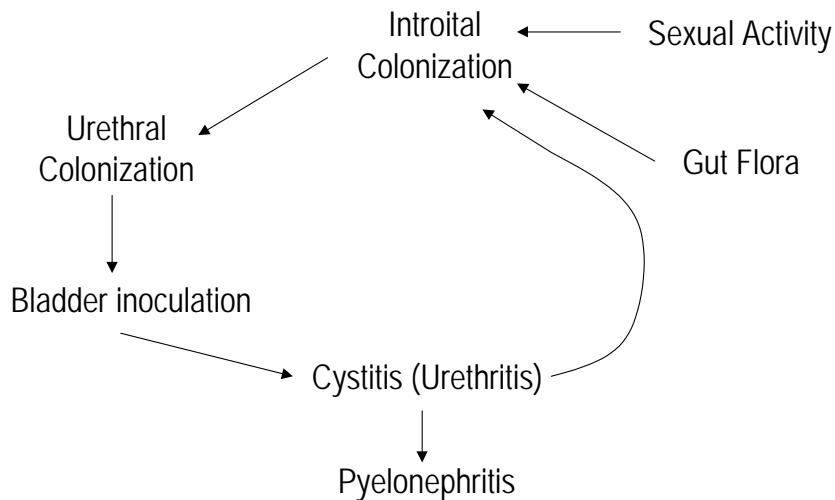

Figure 2

Bacteria which enter the bladder normally are flushed out during micturition. Urine has antibacterial properties (high osmolarity, low pH, high concentration of urea, Tamm-Horsfall protein), although it will support the growth of bacteria. Prostatic secretions are also inhibitory; the bladder mucosa also has some antibacterial properties, and PMN's in the bladder wall will destroy bacteria. (Table 4)

Table 4: Anti-adherence Mechanisms in the Urinary Tract

Normal bacterial flora of vaginal, introital, and
   periurethral regions and urethra
Uromucoid (Tamm-Horsfall protein)
Urinary oligosaccharides
Urinary immunoglobulins (IgG, IgA, S-IgA)
Bladder mucopolysaccharide (glycosaminoglycan)
Mechanical effects of flushing

Factors favoring infection are the short female urethra, sexual intercourse and failing to void soon afterward, diaphragm use, and spermicide use (raises vaginal pH and is toxic to the normal flora, especially the lactobacilli.) Abnormalities of the urinary tract which lead to obstruction of the urinary flow are a major factor in the development of urinary infection.

Extra-renal obstruction due to posterior urethral valves (infant boys) or urethral strictures (adult men) are uncommon but important to consider. More common is incomplete bladder emptying due to prostatic hyperplasia. Dysfunction of the bladder due to mechanical (prostate, pelvic floor relaxation) or neurological causes also contribute to the development of UTI's. Bacteria introduced directly into the bladder by catheterization or instrumentation can proliferate under these conditions.

Vesico-ureteral reflux is a mechanism that allows bacteria to reach the kidney. Such reflux is common in children, particularly when they have urinary infection. At all times a fluid column connects bladder and kidney, and motile bacteria can ascend this fluid. In pregnancy the ureters are compressed and the tone and peristalsis of the ureters are reduced while at the same time reflux of urine is increased. These factors undoubtedly are important in the development of upper tract infection in pregnant women.

Bacterial Factors in Urinary Tract Infection

Only a small number of serogroups of *E. coli* cause most urinary-tract infections. The initial step is adherence of bacteria to uroepithelial cells (Table 5).

Table 5: Urinary Tract Infections

The initial pathogenic event in UTI is an
    encounter between bacteria and host
    mucosa at the tissue surface.
Attachment, binding of bacteria to mucosa,
    is the result of multiple interactions between
    bacterial surface ligands (adhesins) and
    epithelial cells (receptors).

Fimbriae on the surface of *E. coli* and *Proteus* bacteria mediate attachment to receptors on uroepithelial cells. The fimbriae on *E. coli* are of several types. The common ones are called **Type 1 fimbriae**. These attach to mannosides, and their attachment is blocked by mannose. Hence they are called mannose-sensitive (MS-adhesins).

A second type of fimbria is not blocked by mannose (mannose-resistant or MR-adhesins). These attach to epithelial cells with globoseries receptors, and are termed **P-fimbriae**, since the receptor is a constituent of the P-blood group antigen that is expressed on RBC's and urothelial cells. They specifically attach to a digalactoside portion of glycosphingolipids (*gal-gal*-pilus). The P-fimbriae strains are the ones which cause pyelonephritis.

Type 1 fimbriae increase susceptibility to polymorphonuclear phagocytosis, while P-fimbriae block phagocytosis. It is hypothesized that there are dual-phase kinetics of bacterial adherence in the pathogenesis of urinary tract infection. After entry into the bladder, MS-adhesins which are present on the majority of the Enterobacteriaceae, facilitate attachment to the bladder epithelium. However, when the bacteria ascend to the renal parenchyma, they undergo phase variation and do not express type 1 fimbriae which, as noted above, enhance phagocytosis. Rather, in the upper tract, P-fimbriae are expressed, allowing attachment to renal parenchymal cells. Other factors produced by pyelonephritis strains of bacteria include hemolysins, and a siderophore that scavenges iron, called aerobactin. The pyelonephritis strains also are resistant to the bactericidal action of serum.

In an individual with structural abnormalities of the urinary tract or with a catheter, even organisms of low pathogenicity can cause infection of bladder, kidney, or both and the above-described properties of the bacteria are not essential.

Host Factors in Urinary Tract Infection

Important genetic factors predispose to UTI in women. Women who are of P_1 blood group have epithelial cell receptors that mediate attachment of bacteria. 97% of young women with recurrent pyelonephritis are P_1 positive, significantly higher than in uninfected controls. Interestingly, patients who had upper tract disease secondary to ureteral reflux had P_1 phenotype frequency similar to that in the general population. This points up the major importance of structural changes in urinary-tract infection. Urinary obstruction, reflux, or other anatomic changes make it possible for less virulent bacteria to produce a urinary tract infection.

A number of antiadhesive mechanisms of the urinary tract normally protect against urinary-tract infection. These factors operate to minimize attachment and growth of pathogenic bacteria in the urethra, vagina, and vaginal introital area. The normal commensal periurethral flora compete with pathogenic bacteria for attachment sites.

Table 6: UTI in Women - Predisposing factors
Short urethra
Vaginal colonization by pathogens
Diaphragm/Vaginal Spermicide
Sexual intercourse
Lack of post-coital voiding

Vaginal pH is higher in women with recurrent urinary-tract infection; use of a diaphragm may promote colonization because of the manipulation involved in placing it on the cervix. In addition, spermicidal jelly raises the vaginal pH, inhibiting the normal flora and creating an ecological niche that can be filled by enteric bacteria.

Urinary immunoglobulins (IgA, secretory IgA, and IgG) can contribute to protection. The uromucoid material, Tamm-Horsfall protein, can decrease bacterial attachment to the bladder. Bladder mucopolysaccharide, a glycosaminoglycan, alters attachment of bacteria. These materials all function as false receptors for bacteria, preventing their attachment to the bladder mucosa. Also of great importance is the normal mechanical effect of flushing. Urinary stasis is a major risk factor that is seen frequently in patients with neurologic disorders due to diabetes mellitus, multiple sclerosis, and spinal cord injuries. Urinary-tract infections in the latter patients are categorized as complicated.

Catheters

Urinary catheters are extremely likely to lead to colonization of the bladder and subsequent infection. Bacteria adhere to the catheter surface and contribute to the production of a biofilm composed of bacteria, bacterial glycocalyces, host proteins, and urinary salts like apatite and struvite (calcium-magnesium-ammonium sulfate). The bacteria travel beneath this biofilm along the catheter into the bladder. Brief use of indwelling urinary catheters after operations or in critically ill patients to measure urine output will not result in infection for up to 7 days if the catheter connections are left undisturbed and a closed drainage system is scrupulously maintained. Long-term use of urinary catheters will always result in colonization and infection, about 8%-10% per day.

Condom catheters in males are also a potential source of infection, since urine accumulates in the condom part and may reflux into the urethra and upward into the bladder. Chronic condom catheterization carries about the same risk of infection as chronic indwelling (Foley) catheterization. If at all possible, a system of intermittent, straight catheterization should be used, especially in patients who cannot void because of neurologic disease. This relieves stasis of urine in the bladder and prevents damage to bladder mucosa that is in contact with the balloon used to retain the indwelling catheter.

Clinical Presentation

Symptoms of urinary-tract infection vary with the age of the patient and the location of infection. Neonates and children less than 2 years old do not complain
of dysuria: fever, emesis, and failure to gain weight are the usual symptoms. Children
over 3 years will complain of burning on urination and lower abdominal pain; previously toilet-trained children may develop enuresis.

Adult patients with cystitis have dysuria, frequency, urgency, and suprapubic pain. The urine often is cloudy and malodorous and may be bloody. Fever and systemic symptoms usually are absent. Acute dysuria in adult women can also be due to acute urethritis (chlamydial, gonococcal, or herpetic) or to vaginitis/vaginosis.

Acute pyelonephritis is accompanied by fever, usually greater than 101° F., nausea, vomiting, and pain in the costovertebral areas. Rigors (shaking chills) may indicate bacteremia. Patients usually have a marked leukocytosis. Patients with urinary-catheter-associated infection often are asymptomatic, but may have fever, chills, leukocytosis, etc.

Diagnosis

Table 7: Diagnostic Criteria for UTI

Counting WBC/HPF (high power field) is inaccurate and not
reproducible; the preferred method is counting WBC in unspun
urine using a hemocytometer: the result is reported as WBC/μL

The leukocyte esterase test is widely used, but the reliability
varies according to the study. A positive test in someone
with a clinically suspected UTI has a fairly good correlation,
however. False-negatives may be in the 30% range.

The nitrate test is based on the ability of gram-negative bacteria
to convert nitrate $\rightarrow$ nitrite; false-negatives occur if there are
few bacteria or if the infection is gram-positive.

The leukocyte esterase-nitrate test (a combination test) is more
accurate than either, with about a 70% sensitivity in a patient
with clinically suspected UTI.

A Gram's stain of 1 drop (dried) of unspun urine showing
>1 organism/HPF has an 80% correlation with >10^5 CFU/ml
on culture.

A Gram's stain of spun sediment showing no bacteria
strongly argues against a UTI.

Examination of urine is the means by which urinary infection is diagnosed. Proper collection methods are essential. Collection of a clean, mid-stream specimen is the method of choice, since it entails no morbidity, but a straight "in-and-out" catheter specimen should be used if a clean-voided specimen cannot readily be obtained. A specimen taken from a

woman is easily contaminated, but quantitative estimation of the number of bacteria in a voided specimen makes it possible to distinguish contamination from bacteriuria. A count of $>10^5$ bacteria per milliliter indicates infection. However, as noted previously, in symptomatic women, bacterial counts of 10^2-10^4 of *E. coli*, *Proteus*, or *Staphylococcus saprophyticus*, all common urinary pathogens, usually indicate infection, not contamination. The presence of microscopic pyuria (more than 10 leukocytes/μl) in a symptomatic individual is also indicative of infection.

Urine must be processed immediately; if it remains at room (or warmer) temperature, the small numbers of bacteria present as contaminants will grow into "significant" numbers. Hematuria and proteinuria may be present but do not specifically indicate urinary infection, but do suggest that the patient has crossed the line from an uncomplicated cystitis to a complicated cystitis or an upper tract infection. Urine should be cultured in individuals in whom the diagnosis of cystitis is in question or in patients with pyelonephritis. Urine also should be cultured in children, pregnant women, and individuals with underlying structural abnormalities of the urinary tract. In women with simple cystitis, it is more cost-effective to do a leukocyte esterase-nitrate test; if positive, empiric treatment is prescribed; if negative, a culture is done and empiric treatment is prescribed.

It is difficult to determine whether bacteria detected in a specimen come only from the bladder or also from the kidney. Administration of a single, large dose of antibiotic and culture of urine at 48 hours have been used to differentiate upper-tract from lower-tract disease in women. The assumption is that bladder bacteria would be eliminated whereas renal parenchymal bacteria would persist. Unfortunately, this test is not completely reliable. Furthermore, fluoroquinolone antibiotics may remain in the urine at inhibitory levels for up to 5 days.

In males, a technique to localize the site of infection to the urethra, bladder, or prostate has been used. (Figure 3) Four specimens are collected. The first few milliliters of urine (VB1) represent urethral colonization, a mid-stream specimen (VB2) represents the bladder, kidney, or both. After the bladder has been emptied, a prostatic massage is performed and prostate fluid is collected (E.P.S.); a fourth specimen, the first 10 ml of urine after prostate massage (VB3) is also collected. These last two specimens represent prostatic infection.

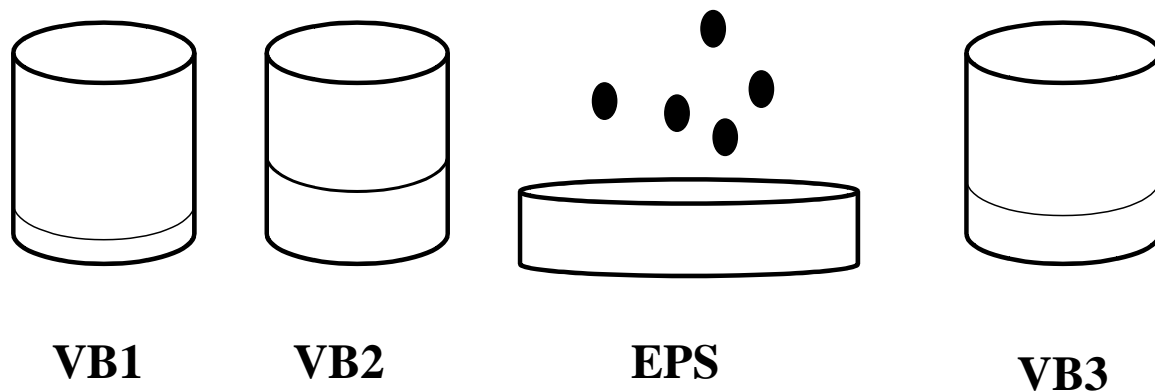**VB1**   **VB2**   **EPS**   **VB3**

Figure 3

Radiographic studies are not indicated in healthy young women with lower-tract disease or with an uncomplicated upper tract infection. In a patient in whom an abnormality of the urinary system is highly likely or if an abscess is suspected, or in a patient with pyelonephritis who does not respond to appropriate therapy within 72 hours, radiographic studies are indicated. (Table 8) In men with urinary tract infections, a careful prostate examination is necessary; if pyelonephritis or a complicated infection is present, radiographic studies are also indicated. Ultrasound can be used for the initial evaluation of the kidneys in both children and adults in whom correctable lesions are suspected to be present.   Cystometric testing, CT scanning, and intravenous pyelography may also be used.

Table 8: Who Should Be Evaluated for
Anatomical Abnormalities because of UTI?

- Children (USG, IVP, VCUG, renal scan)
- Bacteremic Pyelonephritis (USG or IVP)
- History of stones or neurogenic bladders
  (USG or IVP with post-void films)
- Men with first infection (prostate exam)
- Men with second infection
  (USG or IVP with post-void films)

Treatment

Treatment of urinary-tract infection is based on its location (in the upper or the lower tract), and on patient characteristics (Table 9). Lower-urinary-tract infection in the healthy, young female with symptoms of recent onset (< 48 hours) can be treated with a brief course (3 days) of oral antibiotics. All other women with lower tract infections should receive a 5-7 day course. Most antimicrobial agents are excreted by the kidney, providing high concentrations in the urine. This results in rapid reduction and then elimination of bacteria. The antimicrobial agents selected should inhibit *E. coli*, since it accounts for 80% of uncomplicated lower urinary-tract infections. Trimethoprim, co-trimoxazole, and fluoroquinolones are ideal agents, since they are effective orally, they achieve good urine concentrations, and tend not to disturb the anaerobic flora of the gut and the vagina.

In the case of acute pyelonephritis, initial therapy is often given intravenously with completion of therapy orally after the patient is afebrile. Total duration of therapy is 10-14 days. All patients with pyelonephritis should have a repeat urine culture 5-9 days after completing therapy, since a percentage of patients will have symptomatic or asymptomatic relapse; the repeat urine culture will detect this. Such patients should have 2-4 more weeks of therapy

Treatment of patients who are found to have asymptomatic bacteriuria is still controversial. Cultures should first be repeated to establish the diagnosis. A pregnant woman, who has a high risk of pyelonephritis and consequent fetal problems should be cultured and treated during the first trimester. Cultures should be repeated in the third trimester. An individual with known neurological or structural abnormality of the urinary system in whom $\geq 10^5$ CFU/ml of a single species are present should also be treated. Finally, prophylactic pre-operative treatment of asymptomatic bacteriuria is beneficial to those undergoing urologic surgery, as it will reduce the chance of post-operative infections.

Asymptomatic bacteriuria in a patient with an indwelling urethral catheter should not be treated, since the only result will be selection of resistant bacteria (Table 9). In many situations, removal of the catheter will eliminate the bacteria. If organisms are present 48 hours after removal of a catheter, a short course of antibiotic therapy is indicated.

Table 9. General Principles of Treatment

1.	Quantitative cultures may be unnecessary before treatment of typical cases of acute uncomplicated cystitis.
2.	Susceptibility testing is necessary in all recurrent or complicated infections, perhaps not for uncomplicated cystitis.
3.	Identify and correct factors predisposing to infection (obstruction, calculi).
4.	Relief of symptoms may not indicate bacteriologic cure; follow-up cultures are necessary if symptoms recur.
5.	Duration of therapy should probably depend on the site.
6.	Classify recurrences as reinfection or relapse.

Acute cystitis in adult men (which can be caused by the same organisms that possess virulence factors for pyelonephritis) will respond to 7-10 days of treatment, but acute prostatitis from the same organisms will require 6-12 *weeks* to eradicate the offending organism, with a 70% cure rate. Non-bacterial *prostatosis* is probably caused by chlamydiae or ureaplasmata, and will respond to tetracyclines, erythromycins or fluoroquinolones.

Candiduria

This is seen primarily in catheterized patients who are often asymptomatic. However, diabetics may have true candidal UTI's, as may immunocompromised patients.   The persistence of candiduria 48-72 hours after catheter removal, or fever/leukocytosis suggest that the infection is more than asymptomatic and transient colonization. Thought should be given to ruling out possible candidal pyelonephritis in this setting.

It is important to rule out contamination of the urine specimen by vaginal candidosis in the asymptomatic patient. Treatment of infections that do not respond to catheter removal is indicated; oral fluconazole or bladder irrigation with amphotericin B have been used successfully.