Urinary Tract Infections (UTI)

5th year medical students' curriculum
Section of urology
Department of Special Surgery
Faculty of Medicine
Mut'ah University

Dr. Fadi Sawaqed
Associate Professor of Urology
Functional & Neuro-Urology

Urinary tract infection (UTI) is a term that is applied to a variety of clinical conditions ranging from localized infection of the bladder with lower urinary tract symptoms to pyelonephritis with severe infection of the kidney and the potential for resultant urosepsis.

Accurate diagnosis and treatment of a UTI is essential to limit its associated morbidity and mortality and avoid prolonged or unnecessary use of antibiotics.

Unfortunately, because of the increasing rates of bacterial resistance to various antibiotics, medical therapies are becoming less efficacious

EPIDEMIOLOGY

Epidemiology of UTI by age, group, and sex.

Incidence (%)			
Age (y)	Female	Male	Main risk factors
<1	0.7	2.7	Foreskin, anatomic GU abnormalities
1–5	4.5	0.5	Anatomic GU abnormalities, functional GU abnormalities
6–15	4.5	0.5	Functional GU abnormalities
16–35	20	0.5	Sexual intercourse, diaphragm use
36–65	35	20	Surgery, prostate obstruction, catheterization
>65	40	35	Incontinence, catheterization, prostate obstruction

GU = genitourinary; UTI = urinary tract infection.

In the neonatal period males are twice as likely as females to experience a UTI. From ages 1 to 6 months the rate of UTI is equal between genders, but from 6 to 12 months of age the rate of UTI in male and female children is 1 to 4.

Overall, UTIs are more common in females

The incidence of UTI in uncircumcised males is 85% higher than circumcised males

Risk factors for pediatric UTI include circumcision status, history of prior UTI, and sexual activity among older populations.

In addition, anatomical abnormalities like vesicoureteral reflux, ureterocele, ureteropelvic junction obstruction, posterior urethral valves, neurogenic bladder, and bladder and bowel dysfunction portend a higher rate of UTI.

At least 12–30% of patients with a history of symptomatic UTI will experience a recurrence

Upward of 60% of adult women will report having a UTI during their lifetime, and 11% will report having at least one infection per year

The major risk factors for women 16–35 years of age are related to sexual intercourse, spermicide use, and diaphragm use.

Certain medical conditions like diabetes, obesity, sickle cell trait, and anatomic congenital abnormalities can increase the risk of UTI.

Later in life, the incidence of UTI increases significantly for both males and females. For women between 36 and 65 years of age, gynecologic surgery and bladder prolapse appear to be important risk factors.

In men of the same age group, prostatic hypertrophy/obstruction, catheterization, and surgery are relevant risk factors.

For patients older than 65 years, the incidence of UTI continues to increase in both sexes. Incontinence and chronic use of urinary catheters are important risk factors in these patients.

In those younger than 1 year and those older than 65 years, the morbidity and mortality of UTI are the greatest

PATHOGENESIS

Understanding of the mode of bacterial entry, host susceptibility factors, and bacterial pathogenic factors is essential to tailoring appropriate treatment for the diverse clinical manifestations of UTI.

Bacterial Entry

It is generally accepted that periurethral bacteria with a uropathogen from the gut ascending into the urinary tract causes most UTI. The colonization of the urethra and migration to the bladder leads to invasion of the bladder mediated by pili and adhesions factors.

Most cases of pyelonephritis are caused by the ascent of bacteria from the bladder, through the ureter, and into the renal parenchyma. Consequently, the short nature of the female urethra combined with its close proximity to the vaginal vestibule and rectum likely predisposes women to more frequent UTIs than men

Other modes of bacterial entry are uncommon causes of UTI. Hematogenous spread can occur in immunocompromised patients and in neonates. Staphylococcus aureus, Candida species, and

Mycobacterium tuberculosis are common pathogens that travel through the blood to infect the urinary tract.

Lymphatogenous spread through the rectal, colonic, and periuterine lymphatics has been postulated as a cause for UTI;

Direct extension of bacteria from adjacent organs into the urinary tract can occur in patients with intraperitoneal abscesses or vesicointestinal or vesicovaginal fistulas.

Host Defenses

In females, normal vaginal and periurethral flora contain microorganisms like lactobacillus that help prevent uropathogenic colonization

Unobstructed urinary flow with the subsequent washout of ascending bacteria is essential in preventing UTI.

In addition, the urine itself has specific characteristics (its osmolality, urea concentration, organic acid concentration, and pH) that inhibit bacterial growth and colonization.

It also contains factors that inhibit bacterial adherence, such as Tamm–Horsfall glycoprotein (THG)

The epithelium lining the urinary tract not only provides a physical barrier to infection but also has the capacity to recognize bacteria in order to activate innate host defenses.

Specific serum and urinary antibodies are produced by the kidney to enhance bacterial opsonization and phagocytosis and inhibit bacterial adherence

Other important host factors include the normal flora of the periurethral area or the prostate

Bacterial Pathogenic Factors

The ability of E. coli to adhere to epithelial cells is mediated by ligands located on the tips of the bacterial fimbriae (pili).

Most uropathogenic *E. coli* strains produce hemolysin, which initiates tissue invasion and makes iron available for the infecting pathogens

The presence of K antigen on the invading bacteria protects them from phagocytosis by neutrophils

CAUSATIVE PATHOGENS

Most UTIs are caused by a single bacterial species. At least 80% of the uncomplicated cystitis and pyelonephritis in premenopausal women are due to *E. coli*, with most of

Other less common uropathogens include *Staphylococcus saprophyticus, Klebsiella, Proteus*, and *Enterobacter* spp. and enterococci.

In hospital-acquired UTIs, a wider variety of causative organisms is found, including *Pseudomonas* and *Staphylococcus* spp.

In children, the causative bacterial spectrum is slightly different but there is still a predominance of *E. coli* among inpatient and outpatient populations. *Enterobacter*, *Enterococcus*, and *Klebsiella* species make up the remainder of common culprits of pediatric UTI.

Anaerobic bacteria, lactobacilli, corynebacteria, streptococci (not including enterococci), and *Staphylococcus epidermidis* are found in normal periurethral flora. They do not commonly cause UTIs in healthy individuals and are considered common urinary contaminants.

DIAGNOSIS

An uncomplicated UTI consists of an infection in an otherwise healthy patient with normal urinary tract atomy. On the other hand, a complicated UTI can occur when anatomic abnormalities, immunocompromised state, or multi-drug-resistant bacteria allow for increased bacterial colonization or decreased therapeutic efficacy

Diagnosis of UTI in an adult is sometimes difficult to establish and relies on urinalysis and urine culture. Occasionally, localization studies may be required to identify the source of the infection. Most often, the urine is obtained from a voided specimen. Standard diagnosis of UTI is completed by urinalysis and urine culture of 100 CFU/mL (where CFU = colony-forming units) of bacteria.

American Academy of Pediatrics (AAP) guidelines suggest that if a urinalysis demonstrates positive leukocyte esterase or nitrite on testing, urine should be obtained via catheterization or suprapubic aspiration for culture prior to start antimicrobial therapy

In children who are not toilet-trained, a urine collection device, such as a bag, is placed over the genitalia, and the urine is cultured from the bagged specimen. These two methods of urine collection are easy to obtain, but potential contamination from the vagina and perirectal area may occur.

A negative urine culture via a bagged specimen in children ensures that there is a low likelihood

If a patient has an indwelling catheter, a urine specimen should be obtained from the collection port on the catheter.

Urinalysis

The urine can be immediately evaluated for leukocyte esterase, a compound produced by the breakdown of white blood cells (WBCs) in the urine and is 95% sensitive for UTI in children with symptoms. Positive leukocyte esterase indicates the presence of 5–15 WBC per high-power field (hpf). Urinary nitrite is produced by reduction of dietary nitrates by many Gram-negative bacteria. Esterase and nitrite can be detected by a urine dipstick and are more reliable when the bacterial count is >100,000 colony-forming units (CFUs) per milliliter. Combined positive nitrite and leukocyte esterase on urine dipstick analysis is 80–90% sensitive and 60–98% specific for UTI

Microscopic examination of the urine for WBCs and bacteria is performed after centrifugation. For children, urine concentration should be taken into consideration when diagnosing infants with UTI. A pyuria threshold of 3 WBC/ hpf in dilute urine and 6 WBC/hpf in concentrated urine is noted for a diagnosis of UTI

Urine Culture

The gold standard for identification of UTI is the quantitative culture of urine for specific bacteria.

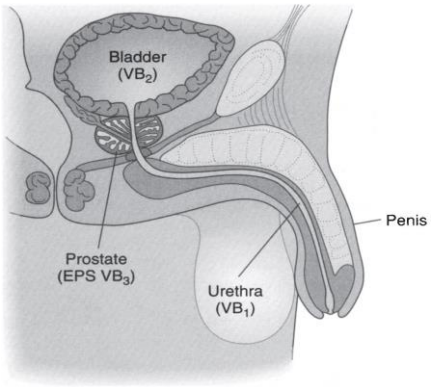
Defining the CFU/mL that represents clinically significant infection can be difficult. It is dependent on the method of collection, the sex of the patient, and the type of bacteria isolated.

Traditionally, cultures demonstrating 100,000 CFU/mL are considered diagnostic of a UTI, but now AAP guidelines suggest pyuria and 50,000 CFU/mL of a single organism are diagnostic of UTI

Localization Studies

Occasionally, it is necessary to localize the site of infection. For upper urinary tract localization, the bladder is irrigated with sterile water and a ureteral catheter is placed into each ureter. A specimen is collected from the renal pelvis. Culture of this specimen will indicate whether infection in the upper urinary tract is present.

In men, infection in the lower urinary tract can be differentiated (Figure). A specimen is collected at the beginning of the void and represents possible infection in the urethra (VB1). Next, a midstream specimen (VB2) is collected and represents possible infection in the bladder. The prostate is then massaged and the patient is asked to void again (VB3), this specimen represents possible infection of the prostate.



ANTIBIOTICS

The goal in treatment is to eradicate the infection by selecting the appropriate antibiotics that would target specific bacterial susceptibility.

The general principles for selecting the appropriate antibiotics include:

- Consideration of the infecting pathogen (antibiotic susceptibility, single-organism vs polyorganism infection, pathogen vs normal flora, community vs hospital-acquired infection);
- The patient (allergies, underlying diseases, age, previous antibiotic therapy, other medications currently taken, outpatient vs inpatient status, pregnancy);
- The site of infection (kidney vs bladder vs prostate

- Because most antibiotics are cleared from the body by the liver or the kidney, certain antimicrobial agents need to be adjusted in the presence of liver or renal disease:

Renal diseases (Cr clearance <30 mL/min)
Aminoglycosides
β-Lactams
Cefoxitin, ceftizoxime
Cefonicid, ceftazidime
Cefuroxime, cefepime
Cefpirome, moxalactam
Carbenicillin, ticarcillin, ticarcillin–clavulanate
Vancomycin
Tetracyclines (except doxycycline)
Sulfonamides
Hepatic diseases (with elevated bilirubin)
Chloramphenicol
Tetracyclines
Clindamycin, rifampin, pefloxacin
Renal–hepatic diseases
Ceftriaxone
Cefoperazone
Carbenicillin
Ticarcillin
Azlocillin
Mezlocillin
Piperacillin

Recommended antimicrobial agents and duration of therapy based upon the type of UTI for adults.

Diagnosis	Choice of antibiotics	Duration of therapy
Cystitis	1st: TMP-SMX 2nd: Fluoroquinolone	1–3 days
Pyelonephritis	1st: Gluoroquinolone 2nd: 2nd-generation cephalosporin 3rd: Aminopenicillin/BLI	7–10 days
Complicated UTI[a]	1st: Fluoroquinolone 2nd: Aminopenicillin/BLI 3rd: 3rd-generation cephalosporin Aminoglycosides	Afebrile: 2 weeks Febrile: continue for additional 3–5 days after last fever (minimum 2 weeks)
Prostatitis	1st: Fluoroquinolone 2nd: 2nd-generation cephalosporin 3rd: 3rd-generation cephalosporin	Acute: 2 weeks Chronic: 4–6 weeks
Epididymitis	1st: Fluoroquinolone 2nd: 2nd-generation cephalosporin *or* 1st: Doxycycline 2nd: Macrolide	14 days
Urethritis[b]	1st: IM ceftriaxone + azithromycin 2nd: Doxycycline	Single dose 7 days

[a]Complicated UTI: infection in the setting of metabolic, immunocompromised, functional, or anatomic abnormality

[b]If suspicion of sexual transmitted disease as source.

Trimethoprim–Sulfamethoxazole
Trimethoprim–sulfamethoxazole (TMP-SMX) is commonly used to treat many UTIs, except those caused by Enterococcus and Pseudomonas spp. It interferes with the bacterial metabolism of folate.

Adverse reactions occur in 6–8% of patients using this medication; they include hypersensitivity reactions, rashes, gastrointestinal upset, leukopenia, thrombocytopenia, and photosensitivity. TMP-SMX should not be used in patients who have a folic acid deficiency state, glucose- 6-phosphate dehydrogenase deficiency, or acquired immunodeficiency syndrome (AIDS), or in pregnant patients.

Fluoroquinolones
Fluoroquinolones have a broad spectrum of activity, especially against Gram-negative bacteria. Although they have adequate activity against *Staphylococci* species, fluoroquinolones do not have good activity against *Streptococci* species and anaerobic bacteria. They interfere with the bacterial DNA gyrase, preventing bacterial replication.

Adverse reactions are infrequent and include mild gastrointestinal effects, dizziness, and lightheadedness. Fluoroquinolones should not be used in patients who are pregnant and should be used judiciously in children because of potential damage to developing cartilage.

Nitrofurantoin
Nitrofurantoin has good activity against most Gram-negative bacteria (except for *Pseudomonas* and *Proteus* spp.), *Staphylococci*, and *Enterococci* species. It inhibits bacterial enzymes and DNA activity.

It should not be used in patients with renal impairment as the drug may not reach adequate concentrations in the urine and, thus, it is not recommended in patients with a creatinine clearance below 30 mL/min. Adverse reactions are relatively common and include gastrointestinal upset, peripheral polyneuropathy, and hepatotoxicity. Long-term use may result in pulmonary hypersensitivity reaction and interstitial changes. In addition, it should be used with caution in elderly patients. Nitrofurantoin becomes highly concentrated in the urine but demonstrates poor tissue penetration. For this reason, it should not be used for complicated UTI, pyelonephritis, or prostatitis.

Aminoglycosides
Aminoglycosides are commonly used in the treatment of complicated UTI. They are highly effective against most Gram-negative bacteria. When combined with ampicillin, they are effective against enterococci. They inhibit bacterial DNA and RNA synthesis. The principal adverse effects of aminoglycosides are nephrotoxicity and ototoxicity

Cephalosporins

Cephalosporins have good activity against most uropathogens. First-generation cephalosporins have good activity against Gram-positive bacteria, *E. coli*, and *Proteus* and

Klebsiella spp. Second-generation cephalosporins have increased activity against anaerobes and *Haemophilus influenzae.* Third-and fourth-generation cephalosporins have broader coverage against Gram-negative bacteria but less against Gram-positive bacteria. The cephalosporins inhibit bacterial cell wall synthesis. Adverse reactions include hypersensitivity and gastrointestinal upset.

Kidney infections

Acute Pyelonephritis

Acute pyelonephritis is defined as inflammation of the kidney and renal pelvis, and its diagnosis is usually made clinically.

Presentation and Findings

Patients with acute pyelonephritis present with chills, fever, and costovertebral angle tenderness. They often have accompanying lower tract symptoms such as dysuria, frequency, and urgency. Sepsis may occur, with 20–30% of all systemic sepsis resulting from a urine infection. Urinalysis commonly demonstrates the presence of WBCs and red blood cells in the urine. Leukocytosis, increased erythrocyte sedimentation, and elevated levels of C-reactive protein are commonly seen on blood analysis. Bacteria are cultured from the urine
when the culture is obtained before antibiotic treatment is instituted. *E. coli* is the most common causative organism, accounting for 70–80% of the cases. *Klebsiella*, *Proteus*, *Enterobacter*, *Pseudomonas*, *Serratia*, and *Citrobacter* spp. account for the remaining cases. Of the Gram-positive bacteria, *Streptococcus faecalis* and *S. aureus* can be important causes of pyelonephritis. In reproductive-age women, sexual activity and patient and family history of UTI are associated with an increased risk of developing pyelonephritis. Diabetes and urinary incontinence also independently increase this risk

Management

The management of acute pyelonephritis depends on the severity of the infection. In patients who have toxicity due to associated septicemia, hospitalization is warranted. Approximately 10–30% of all adult patients with acute pyelonephritis require hospitalization

The usual pathogen is *E. coli* or other *Enterobacter* sp. for which empiric therapy with intravenous ampicillin and aminoglycosides is effective against a broad range of uropathogens, including enterococci and *Pseudomonas* species. Alternatively, amoxicillin with clavulanic acid or a third-generation cephalosporin can be used.

For adults, treatment with fluoroquinolones or TMP-SMX is well tolerated and effective. Outpatient treatment with an initial parental antibiotic (ceftriaxone or gentamicin) followed by oral therapy for 7–14 days has been shown to have a 12% admission rate

If bacteremia is present, parenteral therapy should be administered for 7–10 days and then the patient should be switched to oral treatment for an additional10–14 days.

Pregnant patient with concerns for pyelonephritis requires admission with parental antibiotics secondary to the risk of preterm labor

Emphysematous Pyelonephritis

Emphysematous pyelonephritis is a necrotizing infection characterized by the presence of gas within the renal parenchyma or perinephric tissue. About 95% of patients with emphysematous pyelonephritis have diabetes; women experience this condition 6 times more commonly than men. Other contributing factors include renal failure, immunosuppression, obstructed upper tracts, and polycystic kidneys

Patients with emphysematous pyelonephritis present with fever, flank pain, and vomiting that fails initial management with parenteral antibiotics. Pneumaturia may be present. Bacteria most frequently cultured from the urine include *E. coli* (66%)*; Klebsiella pneumonia* (26%)*;* and *Proteus, Pseudomonas, and Streptococcus* spp.

The diagnosis of emphysematous pyelonephritis is made after radiographic examination. Gas overlying the affected kidney may be seen on a plain abdominal radiograph (kidneys, ureters, bladder [KUB]). CT scan is much more sensitive in detecting the presence of gas in the renal parenchyma than renal ultrasonography.

In the management of emphysematous pyelonephritis, prompt control of blood glucose and relief of urinary obstruction are essential, in addition to fluid resuscitation and parenteral antibiotics

Renal Abscesses

Renal abscesses result from a severe infection that leads to liquefaction of renal tissue; this area is subsequently sequestered, forming an abscess. They can rupture out into the perinephric space, forming **perinephric abscesses**. When the abscesses extend beyond the Gerota's fascia, **paranephric abscesses** develop.

Hematogenous spread of staphylococci, particularly from infected skin lesions. Patients with diabetes, those undergoing hemodialysis, or intravenous drug abusers have been at high risk for developing renal abscesses.

predominance of abscesses caused by *E. coli* (75%), with the remaining 25% caused by *Klebsiella, Proteus, Enterobacter, Streptococcus,* and *S. aureus.* Abscesses that form in the renal cortex are likely to arise from hematogenous spread, whereas those in the corticomedullary junction are caused by Gram-negative bacteria in conjunction with some other underlying urinary tract abnormalities, such as stones or obstruction

The most common presenting symptoms in patients with renal/perinephric abscesses include fever, flank or abdominal pain, chills, and dysuria. Many of the symptoms have lasted for more than 2 weeks

Renal abscesses can be accurately detected using ultrasonography or CT scans.

US: anechoic mass within or displacing the kidney, posterior acoustic enhancement, or lack of vascularity on Doppler imaging

CT scans can demonstrate an enlarged kidney with focal areas of hypoattenuation early during the infection.

The appropriate management of renal abscess must first include appropriate antibiotic therapy

If the patient does not respond within 48 hours of treatment, percutaneous drainage under CT scan or ultrasound guidance is indicated, particularly for abscesses >3 cm

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis (XGP) is a form of chronic bacterial infection of the kidney. The affected kidney is almost always hydronephrotic and obstructed. In most cases, XGP occurs unilaterally. Severe inflammation and necrosis obliterate the kidney parenchyma. Characteristically, foamy lipid-laden histiocytes (xanthoma cells) are present and may be mistaken for renal clear cell carcinoma

Patients with XGP commonly present with flank pain, fever, chills, and persistent bacteriuria. A history of urolithiasis is present in about 35% of patients

On physical examination, a flank mass can often be palpated. Urinalysis commonly demonstrates leukocytes, bacteria, and proteinuria. Serum blood analysis reveals anemia and may show hepatic dysfunction in approximately 50% of the patients

E. coli or *Proteus* species are commonly cultured from the urine.

Computed tomography scan is the most reliable method in imaging patients suspected of having XGP. It usually demonstrates a large, heterogeneous, nonenhancing reniform mass.

On contrast-enhanced images, these lesions will have a prominent blush peripherally, while the central areas, which are filled with pus and debris, do not enhance.

The management of XGP is dependent on accurate diagnosis. In some cases, XGP is misdiagnosed as a renal tumor and a nephrectomy is performed and a diagnosis is made pathologically. In those in whom a diagnosis of XGP is suspected, kidney-sparing surgery such as a partial nephrectomy is indicated in focal disease. However, when the infection is diffuse, a nephrectomy with excision of all involved tissue is warranted.

Acute Cystitis

Acute cystitis refers to urinary infection of the lower urinary tract, principally the bladder. Acute cystitis more commonly affects women than men. The primary mode of infection is ascending from the periurethral/vaginal and fecal flora. The diagnosis is made clinical.

In children, the distinction between upper and lower UTI is important. In general, those in whom acute cystitis developed seldom require any extensive radiologic investigation, but those who have

febrile UTI require further radiologic studies. Recommendations for children include a screening renal bladder ultrasound and, if abnormal, proceed with voiding cystourethrogram

Patients with acute cystitis present with irritative voiding symptoms such as dysuria, frequency, and urgency. Low back and suprapubic pain, hematuria, and cloudy/foul-smelling urine are also common symptoms. Fever and systemic symptoms are rare. Typically, urinalysis demonstrates WBCs in the urine, and hematuria may be present. Urine culture is required to confirm the diagnosis and identify the causative organism.

E. coli causes most of the acute cystitis with *Proteus, Klebsiella*, and *Enterobacter* spp. following in frequency

Management of acute cystitis consists of a short course of oral antibiotics TMP-SMX, nitrofurantoin, and fluoroquinolones have excellent activity against most pathogens that cause cystitis

In adults and children, the duration of treatment is usually limited to 3–7 days

Recurrent cystitis/UTI is caused by either bacterial persistence or reinfection with another organism

Management of recurrent cystitis, again, depends on its cause. Surgical removal of the infected source (such as urinary calculi) is needed to treat bacterial persistence. Similarly, fistulas need to be repaired surgically to prevent bacterial reinfection. In most cases of bacterial reinfection, medical management with prophylactic antibiotics is indicated. Low-dose continuous prophylactic antibiotic has been shown to reduce the relative risk for clinical recurrence per patient year to 0.15

Acute Bacterial Prostatitis

Acute bacterial prostatitis refers to inflammation of the prostate associated with a UTI. It is believed that infection results from ascending urethral infection or reflux of infected urine from the bladder into the prostatic ducts.

Acute bacterial prostatitis is uncommon in prepubertal boys but frequently affects adult men. It is the most common urologic diagnosis in men younger than 50 years and third most common in men older than 50 years

Patients with acute bacterial prostatitis usually present with an abrupt onset of constitutional (fever, chills, malaise, arthralgia, myalgia, lower back/rectal/perineal pain) and urinary symptoms

(frequency, urgency, dysuria). They may also present with urinary retention due to swelling of the prostate.
Digital rectal examination reveals a tender, enlarged gland that is irregular and warm. Urinalysis usually demonstrates WBCs and occasionally hematuria.
Serum blood analysis typically demonstrates leukocytosis.
Prostate-specific antigen levels are often elevated.
The diagnosis of prostatitis is made with microscopic examination and culture of the prostatic expressate and culture of urine obtained before and after prostate massage.

Treatment with antibiotics is essential in the management of acute prostatitis. Empiric therapy directed against Gram-negative bacteria and enterococci should be instituted immediately while awaiting the culture results. Trimethoprim and fluoroquinolones have high drug penetration into prostatic tissue and are recommended for 4–6 weeks

Patients who have sepsis, are immunocompromised or in acute urinary retention, or have significant medical comorbidities would benefit from hospitalization and treatment with parenteral antibiotics. Ampicillin and an aminoglycoside provide effective therapy against both Gram-negative bacteria and enterococci.

Patients with urinary retention secondary to acute prostatitis should be managed with a suprapubic catheter because transurethral catheterization or instrumentation is contraindicated

****** The End ******