Diagnosis and Management of Urinary Tract Infections and Pyelonephritis

10

Laura J. Hintz

Contents

L.J. Hintz, FNP-BC, CUNP
Midwest Prostate and Urological Institute, Saginaw Center for Female Urology, Saginaw, MI, USA
e-mail: laurahintz@mpui.org

M. Lajiness, S. Quallich (eds.), *The Nurse Practitioner in Urology*,
DOI 10.1007/978-3-319-28743-0_10

Objectives

1. Define urinary tract infection, and differentiate its presentation in men and women.
2. Identify causes and the presentation of pyelonephritis.

Diagnosis and Management of Urinary Tract Infections

The purpose of this chapter is to assist nurse practitioners, particularly those specializing in urology, on how to recognize and manage urinary tract infections. Unfortunately, the lack of knowledge in assessing both a urine specimen correctly and the inability to correlate this information with a patient's presenting signs and symptoms is cause for frequent misdiagnosis of urinary tract infections. In addition, the misuse and overuse of antibiotics in today's society has made treating urinary tract infections more complicated. This chapter will review the different types of infections, the diagnostic testing required, as well as population-specific guidelines for proper management.

Definitions

Urinary tract infection (*UTI*) is an inflammatory response of the urothelium to bacterial invasion that is typically associated with bacteriuria and pyuria. The term acute cystitis is often used interchangeably.

Bacteriuria is the presence of bacteria in the urine and it may be symptomatic or asymptomatic.

Asymptomatic bacteriuria (*ASB*) is the isolation of bacteria from the urine in significant quantities that would be consistent with infection but in the absence of local or systemic urinary tract symptoms.

Pyuria is the presence of white blood cells in the urine. This typically indicates an inflammatory response secondary to an infectious process caused from bacteria. Pyuria without bacteriuria warrants evaluation for tuberculosis, stones, or cancer. Pyuria in the presence of bacteriuria is indicative of "true" infection.

Acute pyelonephritis is the presence of bacteriuria and pyuria, in addition to the presence of specific symptoms (i.e., fever, chills, and flank pain), indicating an interstitial inflammation of the renal parenchyma.

Incidence and Epidemiology

Urinary tract infections (UTIs), also referred to as acute cystitis, are the most common bacterial infection and are responsible for between four and eight million clinic visits (Hanno 2014). Therefore, this ranks UTIs as the most common cause for

ambulatory care visits in the United States. The direct costs are more than $1.6 billion per year (Hanno 2014).

Urinary tract infections affect men, women, and children. In women, the incidence is higher in the younger population, typically at the onset of sexual activity. The risk factors relevant to the premenopausal woman are the use of spermicides and sexual frequency. The incidence will increase slowly again after menopause due to the changes in the vaginal tissues and the increased pH of the vagina as a result of estrogen deficiency.

Of the millions of UTIs reported, women account for approximately 85 % of them. Eleven percent of women will report having had a UTI during any given year (Hanno 2014). Fifty percent of all women will report having had at least one infection in their lifetime. By the age of 24, one in three women will have had a urinary tract infection. UTIs in men are less common until after the age of 50 when the incidence of enlarged prostate increases, contributing to bladder outlet obstruction and urinary retention.

Nearly 25 % of women with a first UTI will have a second episode within 6 months. Nearly 50 % of women will report a second UTI within a year of experiencing their first UTI (Hanno 2014). Whether the infection is left untreated, or treated with short-term, long-term, or prophylactic antibiotic therapy, the risk of reoccurrence remains unchanged. Therefore, the symptomatic episodes are more of a nuisance than a health threat in the healthy population.

Asymptomatic bacteriuria (ASB) occurs in 3 % of women in their early twenties (Hanno 2014). It increases 1 % at the onset of intercourse, which typically occurs during the late teenage years. It will also increase 1 % per decade of life. In the pregnant population, the implications are more concerning, even though the incidence is similar to that of the nonpregnant population. This is due to the increased risk for pyelonephritis, in those harboring bacteria in the urinary tract. During pregnancy, it is of increased concern during the second and third trimester. Based on some studies, it is suggested that there is a 20–40 % incidence of pyelonephritis, if ASB is left untreated, in the pregnant population (Hanno 2014).

Other populations at risk are those suffering from diabetes and multiple sclerosis. Female diabetic patients have a higher incidence of UTI than do male diabetics. UTIs are also considered complicated in the ambulatory diabetic patient, and there is an increased risk for pyelonephritis, as well as other complications, if left untreated. When UTIs occur in multiple sclerosis patients, increased exacerbations and progression of the disease may be observed. As for the elderly, non-catheterized patient population, 11–25 % percent can develop transient ASB (Hanno 2014). In turn, it is difficult to eradicate the persistent colonization that can occur in up to 50 % of the elderly population. In the 65 years and older population, as many as 20 % of women and 10 % of men will have bacteriuria, and routine treatment is considered unjustified, unless special circumstances exist.

Catheter-associated urinary tract infection (CAUTI) has also become of great concern over the past several years. They are the most common cause of nosocomial infection (Stamm and Norrby 2001). The end result is an increased risk for falls, delirium, and immobility in the older population and an increased financial burden on the health care system. Most of the uropathogens responsible for CAUTIs gain access by

extraluminal (direct inoculation when inserted) or intraluminal (reflux of uropathogens from failure to maintain a closed system). As soon as the catheter is inserted, bacteria will start to develop colonies known as biofilms (living layers). These biofilms are collections of microorganisms with altered phenotypes that adhere to a medical device, such as the catheter and/or collection bag. The biofilm is protective against antimicrobials and the host immune response. The risk of colonization increases in relation to the duration of catheterization and reaches nearly 100 % at 30 days (Hanno 2014).

Risk factors for UTIs
Sexual intercourse
A new sex partner within the past year
Use of spermicides
Use of diaphragm/cervical cap
Estrogen deficiency
Previous UTI
History of UTI in first degree female relative
Urinary retention
Benign prostatic hyperplasia
Steroid use

Subpopulations at increased risk
Infants
Pregnant women
Elderly
Spinal cord injury
Indwelling catheters
Diabetes
Muscular sclerosis
Acquired immunodeficiency disease
Underlying urological abnormalities

Pathophysiology

The model for uncomplicated UTIS is that bacterial virulence is crucial for overcoming normal host defenses (Hanno 2014). However, in complicated UTIs the paradigm is reversed; the bacterial virulence is not as critical as the host factors. UTIs are typically initiated by a potential urinary pathogen migrating from the bowel. In some cases the pathogens arise from the vaginal flora, as a direct result of inoculation during sexual activity. These pathogens then begin to colonize the vagina and perineum with enteric organisms. As the organisms move to the periurethral mucosa, they ascend through the urethra into the bladder (urethritis and/or cystitis) and in some cases through the ureter to the kidney (pyelonephritis).

Most infections in women represent an ascending infection, and this process of infection is related to the relatively short length of the female urethra. UTIs are less common in the younger male, with the incidence increasing in the aging male. The male urethra is considerably longer than the female, which makes ascending infections less common. Most UTIs in older men are typically related to a voiding dysfunction that puts them at risk for acquiring an infection (i.e., urinary retention secondary to an enlarged prostate), or they may acquire it after some form of instrumentation.

In relation to the pediatric population, UTIs may be responsible for a significant source of morbidity; this is particularly true when there are associated anatomic abnormalities. The most common abnormality in children is vesicoureteral reflux. The risk associated with reflux is renal scarring, as a result of ascending UTIs, causing pyelonephritis. In this population, when any UTI is suspected, it is recommended that a complete workup be performed. The diagnosis and treatment of UTIs in the pediatric population is a topic that needs to be reviewed in depth, in a separate discussion. For the purpose of this book, we will only focus on the adolescent and adult population.

Classification

Urinary tract infections may be classified by several different categories: complicated or uncomplicated, upper tract or lower tract, and first infection, unresolved bacteriuria, or recurrent infection. Recurrent infections can be separated into two separate classifications of "reinfection" or "bacterial persistence." On occasion, UTIs may be classified by the type of organism.

Uncomplicated UTIs may be defined as a UTI in the setting of a functionally and structurally normal urinary tract, in a patient that is typically afebrile. This type of infection typically occurs in women, and the uropathogen is one that is susceptible to and eradicated by a short course of an inexpensive oral antimicrobial therapy. Complicated UTIs are typically defined as pyelonephritis and/or a structural or functional abnormality that decreases the efficacy of antimicrobial therapy. In most cases, complicated UTIs are caused by bacteria that are resistant to many antimicrobials. CAUTIs are classified as complicated and the rate of infection averages about 5 % per day (Bernard et al. 2012).

The diagnosis of upper UTI refers to an infection of the kidney (pyelonephritis). The lower urinary tract (LUT) refers to infections of the bladder (cystitis) or urethra (urethritis). As for the organism responsible for the infection, it may be caused by bacterial, fungal, viral, or parasitic organisms.

E. coli, a gram-negative bacillus, accounts for 75–90 % of community-acquired cases of acute uncomplicated cystitis. It accounts for 50 % of the nosocomial infections (Hanno 2014). In women, another 5–15 % are caused by *Staphylococcus saprophyticus*, a gram-positive coccus (Ellsworth and Onion 2012). The remaining UTIs are typically caused by *Enterobacteriaceae*, such as *Klebsiella pneumoniae*, and gram-positive bacteria such as *Enterococcus faecalis* and *Streptococcus*

agalactiae (group B streptococcus). However, the two latter gram-positive organisms often represent contamination of the voided specimen, when isolated from a voided urine.

UTIs categorized as first infections are typically new or an isolated infection that is separated by a previous infection of at least 6 months, such as the "honeymooners' UTI." Unresolved bacteriuria occurs during therapy and implies that the urinary tract is not sterilized during the treatment period. Recurrent UTIs are subdivided into *reinfection* and *bacterial persistence*. Reinfection accounts for up to 80 % of the cases and is typically a direct result of recurrence caused from a new organism outside of the urinary tract. In the majority of these cases, there is no underlying anatomic issue. Bacterial persistence typically refers to a recurrent infection caused by the same uropathogen, despite the sterilization of urine with therapy. This category of recurrence is less common and is most likely a result of something specific within the urinary tract (i.e., calculus or obstructive prostate). The long-term goal for treating recurrent UTIs should be to improve quality of life, while minimizing antibiotic exposure.

Among the younger and healthier female population, the reinfection rate is 25 % within 6 months after the first urinary tract infection (Hooten 2012). In this healthier population and in the majority of patients, about two-thirds of the cases are "recurrent" involving the same bacteria that is believed to have caused the first infection. The term reinfection is said to occur when a patient presents with new signs and symptoms of a UTI after a previous infection has been eradicated and in the presence of a "new" organism.

Presentation

In most patients, the presenting signs and symptoms may include dysuria (pain with urination), frequency, urgency, nocturia (nighttime voiding), suprapubic pain, gross hematuria, malodorous urine, and low back pain. Fever with an uncomplicated UTI is unusual. Therefore, acute pyelonephritis should be considered when fever, tachycardia, and/or costovertebral angle pain are present. In addition, patients with suspected pyelonephritis may present as ill appearing and seem uncomfortable.

Uncomplicated UTI	Pyelonephritis
Dysuria	Fever (temp > 38 °C)
Urgency	Chills
Frequency (voiding smaller amounts)	Nausea
Gross hematuria	Vomiting
Cloudy urine	Flank pain
Malodorous urine	Any combination of uncomplicated UTI signs and symptoms
Low back pain	Costovertebral angle tenderness with palpation
Suprapubic pain and tenderness with palpation	

History and Physical Examination

The patient's history is the most important tool for diagnosing an uncomplicated UTI. Always include an evaluation of the patient's current urinary tract symptoms, past history of urinary tract infections, and any other urinary tract problems or conditions. Follow that with a routine family history, social history (specifically looking at smoking history), and any antibiotic use in the previous 6 months. In addition, one should also inquire into the patient's sexual history, with a special focus on any known history of sexually transmitted infections (STIs). Finally, one should support the detailed history with a focused physical exam and urinalysis.

Female Examination
- Temperature
- Check post void residual
- Evaluate the possibility of pregnancy and history of reproductive issues
- Include pelvic exam, assessing for cystocele, and if symptoms indicate a possible pelvic infection or urethritis
- Examine low back, abdomen, and suprapubic area for tenderness, pain, or abnormalities

Male Examination
- Temperature
- Check post void residual
- Evaluate any history of prostate problems
- Examine genitals, low back, and abdomen for tenderness, pain, or abnormalities
- Examine rectum and prostate for prostate enlargement, growths, inflammation, or pain

Abnormal Findings
- Pain or discomfort in response to pressure on the lower back, abdomen, or the area above the pelvic bone (10–20 % of patients have suprapubic tenderness in uncomplicated UTIs)
- Costovertebral angle tenderness is typically indicative of pyelonephritis
- Growths or abnormalities detected during the pelvic or rectal exam
- Enlarged or tender prostate gland (men only)
- Discharge from the urethra

Differential Diagnosis

Among the female population, interstitial cystitis (IC) and sexually transmitted infections (STIs) are the most common diagnoses that present with similar symptoms. Dysuria is common with cystitis, urethritis, and vaginitis. However, cystitis is more likely when the signs and symptoms also include frequency, urgency, and/or

hematuria. If the symptoms are of severe or sudden onset and in the absence of vaginal irritation and/or discharge, then cystitis is also more likely. The probability of acute UTI is greater than 50 %, in women with any one of the signs or symptoms. It increases to more than 90 % when there is a combination of symptoms, such as dysuria and frequency, without vaginal irritation or discharge. A urine culture is typically positive with bacterial cystitis.

Urethritis is typically caused by *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or the herpes simplex virus. Vaginitis is caused by *Candida* species or *Trichomonas vaginalis*. Pyuria is commonly seen in cystitis and urethritis but is less likely in vaginitis. The symptoms of urethritis also tend to be mild, gradual in onset, and include vaginal discharge. Vaginal irritation or discharge, if present, is a symptom suggestive of vaginitis and reduce the likelihood of the diagnosis of bacterial cystitis by 20 %. In a patient that has a documented history of bacterial cystitis, as evidenced by a positive urine culture, and they present again, with similar symptoms, the likelihood of true infection approaches 90 % (Hanno 2014).

In the male population, prostatitis, epididymitis, and STIs are the most common diagnoses that present with similar symptoms when compared to acute cystitis. However, with acute bacterial prostatitis, in addition to the typical dysuria, frequency, urgency, and nocturia, additional constitutional symptoms, such as fever, chills, and malaise, may also occur. Patients may also report complaints of perineal and/or low back pain. On exam, the prostate may feel enlarged and boggy, with acute tenderness. Epididymitis occurs more commonly in the adolescent and elderly male population but can affect men of all ages. In the population of men under the age of 35, the form of transmission is sexual and is typically caused by *C. trachomatis* and *N. gonorrhoeae* pathogens. In the elderly population, *E. coli* and *Pseudomonas* are the most common offending pathogens. Indwelling catheters, in the elderly population, are also responsible for the development of epididymitis, through a retrograde mechanism. In patients, with epididymitis, the presenting symptoms may include a tender hemiscrotum, in addition to a swollen epididymis. The scrotum may be warm, erythematous, and swollen. Fever, chills, voiding symptoms, and pain that radiates to the ipsilateral flank may also occur.

Diagnostic Testing

Commercially available dipsticks that test for leukocyte esterase (an enzyme released by leukocytes), and for nitrites (which is reduced from nitrates by some bacteria), are an appropriate alternative to urinalysis and urine microscopy, to diagnose cases of acute uncomplicated cystitis. When obtaining a urine specimen for evaluation, it is recommended that in order to avoid contamination, the patient should obtain a midstream, clean-catch urine specimen. Since nitrites and leukocyte esterase are the most accurate indicators of uncomplicated cystitis in symptomatic patients, the urine dipsticks are convenient and cost effective. However, critical evaluation of each individual patient's case needs to be evaluated cautiously since even negative results for both tests do not reliably rule out the presence of infection.

Urine sediment after centrifuge will show microscopic bacteriuria in 90 % of infections with 10^5 colony-forming units (CFU/mL). Microhematuria is evident in 50 % of infections and pyuria in about 80–90 %. However, pyuria can also be the result of several other inflammatory conditions of the urinary tract. The normal vaginal flora can appear to be gram-negative bacteria on urinalysis which can lead to a false-positive result. Alternatively, if the urine is diluted from a high fluid intake, in a symptomatic patient who is voiding frequently, which prevents the bacteria from multiplying to the high counts associated with UTI, then the urine result may be a false negative. Based on a recent meta-analysis, a urine dipstick that is positive for nitrituria will increase the odds of a positive culture by a factor of 11 (Hanna 2014). The same analysis demonstrates that the finding of leukocyte esterase increases the likelihood of a positive culture by a factor of 3 (Hanna 2014). Colony counts of midstream urine specimens ranging from 10^2–10^4 CFU/mL that are caused by *E. coli*, *S. saprophyticus*, or *Proteus* sp. occur in one-third of patients who present with acute symptomatic cystitis. Therefore, a pure culture must be considered significant, regardless of the colony count in the presence of symptoms.

Urine cultures are recommended for those patients with suspected acute pyelonephritis; patients with unresolved symptoms or those with symptoms that recur within 2–4 weeks after the completion of treatment. In addition, a urine culture should be performed on patients who present with atypical symptoms. The benefit of a urine culture is to confirm the presence of bacteriuria and the antimicrobial susceptibility of the infecting uropathogen.

There are studies that have compared voided urine specimens and bladder-aspirate specimens in women with cystitis. The studies indicate that the traditional criterion for a positive culture of voided urine (10^5 colony-forming units per milliliter) is less sensitive for bladder infection. In addition, 30–50 % of women with cystitis have colony counts of 10^2–10^4 colony-forming units per milliliter in voided urine (Hooten 2012). Therefore, according to one source, in the presence of typical signs and symptoms, a colony count greater than or equal to 10^3 colony-forming units per mL, of a uropathogen, is diagnostic of acute uncomplicated cystitis and does represent a positive culture (Colgan and Williams 2011) . Most laboratories do not quantify bacteria below a threshold of 10^4 colony-forming units per milliliter from voided urine specimens. Therefore, with a culture report of "no growth," caution should be used when interpreting the results, in a patient who presents with signs and symptoms of cystitis. Routine posttreatment urinalysis or urine cultures are not necessary in asymptomatic patients, except in those where hematuria was initially present. If hematuria persists, then cystoscopy and additional testing should be performed to rule out other urological pathology.

Imaging

Typically, no further studies beyond urinalysis and urine cultures are needed to diagnose acute uncomplicated cystitis. In those patients that present with atypical

symptoms of acute uncomplicated cystitis, those who do not respond to initial antimicrobial therapy, those with a history of recurrent UTIs, or those with suspected pyelonephritis may need imaging studies to rule out complications and other disorders. A brief description of the recommended testing follows, along with a generic cost analysis of each test.

Ultrasound (U/S) Ultrasonography is the recommended initial screening tool if testing is indicated. It is noninvasive, is cost effective, has no risk of contrast reaction, and has no risk of radiation exposure. Ultrasonography is able to identify calculi, obstruction of the upper urinary tracts, abscess, and other congenital abnormalities. Renal ultrasounds are the most cost-effective treatment option.

Intravenous Pyelogram (IVP) IVP is essential for visualizing the ureters, the details of calyceal anatomic structures and the presence of calyceal dilatation, and the presence of stricture, stones, or obstruction. The calyceal details are necessary for diagnosis of reflux nephropathy as well as papillary necrosis.

Imaging studies should be considered in the following
Women with febrile infections
Men
If urinary tract obstruction is suspected and with history of
Calculi
Ureteral tumor
Ureteral stricture
Congenital ureteropelvic junction obstruction
Previous urologic surgery or instrumentation
Diabetes
Persistent symptoms despite several days of appropriate antibiotic therapy
Rapid recurrence of infection after apparently successful treatment

Computed Tomography (CT Scan) CT scan offers the best anatomic detail but its cost prevents it from being used for screening. It is more sensitive than ultrasound in the diagnosis of acute focal bacterial nephritis and renal and perirenal abscess (it may demonstrate stones or obstruction).

Patients with known pyelonephritis should have a CT scan with contrast or a U/S to assess the presence of foci of pyelonephritis in the renal cortex or cortical or perinephric abscesses. Immediately after a CT scan with contrast, it is possible to obtain the equivalent of an IVP by taking a KUB (X-ray of kidney, ureter, and bladder) film of the patient in the prone position and observe the anatomic structures of the collecting system and ureters, as the contrast is cleared into the bladder.

Magnetic Resonance Imaging (MRI) MRI provides much greater contrast between different soft tissues than a CT scan. It relies on obtaining a radiofrequency

(RF) signal from alignment and subsequent relaxation of protons in hydrogen atoms in water in the body. It should never be utilized in routine practice or as a first-line diagnostic test. It is typically used in follow-up when the ultrasound has already been performed and has been unable to fully answer the diagnostic question. The CT and magnetic resonance imaging (MRI) provide the best anatomic data as well as the cause and extent of the infection.

Comparison of the Cost of Radiologic Testing

Test	Cost $
Renal ultrasound (US)	$
Intravenous pyelogram (IVP)	$$
Computed tomography (CT) scan (with and without contrast)	$$$
Magnetic resonance imaging (MRI)	$$$$
*Medicare allowable charges	

Risk Factors

Some of the risk factors for UTIs, along with the causes of bacterial persistence, and the factors that increase the risk of complications from UTIs are shown in tables below.

Causes of bacterial persistence
Infected stones
Chronic bacterial prostatitis
Unilateral infected atrophic kidney
Vesicovaginal fistula
Intestinal fistula
Ureteral anomalies
Infected diverticula
Foreign bodies (stent or catheters)
Infected urachal cyst
Infected medullary sponge kidney
Infected papillary necrosis
Ureteral stump after nephrectomy

Factors that increase the risk of complications from UTIs
Urinary tract obstruction
Infection from urea-splitting bacteria
Diabetes
Renal papillary necrosis
Neurogenic bladders

Factors that increase the risk of complications from UTIs
Pregnancy
Congenital urinary tract anomalies
Elderly patient with acute bacterial prostatitis
End-stage renal disease on hemodialysis
Immunosuppression after a renal transplant

Management of Urinary Tract Infections

Behavioral Modifications

The majority of behavioral interventions are aimed at prevention. There are many different sources, including research done by Dr. Thomas Hooton, that report avoiding the use of spermicide or diaphragm/spermicide use is beneficial. In addition, decreasing the frequency of coitus and the practice of urination after may reduce the risk of infection. Finally, one should encourage women to utilize proper cleansing technique following voiding, using a front to back motion when wiping. The use of bubble baths has also been questioned. The practice of pushing fluids and maintaining a high intake of water is also recommended. Patients should also be encouraged to void every 2–3 h and to take their time to empty completely.

Oral Supplements

There have been several studies looking at the use of cranberry juice to prevent urinary tract infections. Cranberry juice does inhibit bacterial attachment to epithelial cells. Based on a meta-analysis done in 2012, it was concluded that adults that consumed cranberry juice on a regular basis were 38 % less likely to develop symptoms of UTI. In addition, the cranberry may reduce the symptoms of UTI by suppressing the inflammatory response. It remains unclear which ingredients in cranberry products may be responsible for the overall benefit. Cranberry is essentially safe and inexpensive and is recommended for the prevention of UTI. However, it is not currently recommended as a treatment for acute cystitis.

Treatment

The management of UTIs has become quite complicated due to the increasing prevalence of antibiotic-resistant uropathogens. Complicated nosocomial UTIs were primarily responsible for antibiotic resistance in the past. However, as things change the resistance has spread to uncomplicated community-acquired UTIs. It is important to try and understand the antibiotic resistance rates within the area that one is practicing. Urine levels are more important than serum levels in relation to the efficacy of antibiotics treating UTIs. When an antibiotic appears to be a poor choice based on sensitivity data-related serum levels, they may actually be a good choice if they have a high urinary excretion rate.

Ampicillin has the highest rate of resistance and should not be used for empiric treatment (Hanno 2014). It is followed by fluoroquinolones (broad spectrum) which have around a 30 % resistance rate, and trimethoprim has only about a 20 % resistance rate (Hanno 2014). Once the culture and sensitivity results are available, the least expensive and the most limited spectrum antibiotic is preferred. However, it is important to interpret antibiotic susceptibility carefully because the tests are typically based on serum levels of a drug. It is also of benefit if one keeps in mind the local antibiotic resistance rates. This information is more likely to be available in hospital settings, which reflects cultures of inpatients, or those with complicated and/or recurrent infections and may overestimate the rates of resistance in relation to patients diagnosed with uncomplicated UTI.

The recommended treatment option for the majority of uncomplicated UTIs is a single dose to a 5-day course of antibiotics, depending on the antibiotic preference. Sulfas have become the most widely prescribed antibiotic for uncomplicated outpatient UTIs, along with nitrofurantoin, and have an estimated overall clinical cure rate of 85 % (Bastani 2001). Unfortunately, in the ambulatory care setting, US surveys demonstrate that fluoroquinolones are the most commonly used antimicrobials for UTIs (Hooten 2012).

Sulfas are broad spectrum and they effectively reduce the fecal, vaginal, and periurethral colonization. The side effects of this drug class are typically skin rash and gastrointestinal (GI) upset. They are also considered potentially lifesaving antibiotics. The overuse of this class raises the risk for resistance in the future.

First-generation cephalosporins are appropriate in treating uncomplicated UTI. However, the second- and third-generation cephalosporins should be reserved for infections requiring a broader coverage. In general, cephalosporins have poor activity against *Enterococcus*.

There is one natural occurring antibiotic, fosfomycin, that can be administered as a single dose therapy. It gives a very high urinary concentration that kills bacteria rapidly, reducing the opportunity for mutant selection. It may be less efficacious in some situations; however, even when the urine is sterile, the patient may report persistent symptoms for an average of 48 h after. In turn, the patient may be concerned as to whether the infection is really eradicated and may cause them to ask for additional antibiotic therapy. In this situation, the use of urinary analgesics may be beneficial.

Choose antibiotics based on the following:
1. Likelihood that it will be active against enteric bacteria that commonly produce UTIs
2. High concentration level of the antibiotic in the urine
3. Tendency not to alter the bowel or vaginal flora
4. Selection for resistant bacteria
5. Limited toxicity
6. Available at a reasonable cost/covered by patient insurance

If treating with nitrofurantoin, one should consider that it is *not* recommended in the elderly population or those with renal impairment. Routine monitoring of patient's renal function is recommended in all patients over 65 years of

age. In those patients with moderate to severe renal impairment, the therapeutic urinary concentration of nitrofurantoin may not be achieved. These patients are also at risk for peripheral neuropathy. Nitrofurantoin is well tolerated, has good efficacy, and does tend to be effective against *Pseudomonas* and *Proteus* species. If symptoms persist after 2–3 days of therapy, one can always consider changing the antibiotic to a more expensive, broad-spectrum antibiotic. However, the recurrence of symptoms after the initial short-course therapy would indicate the need for culture and sensitivity testing, and retreatment should be for a 7–10-day period.

Fluoroquinolones have a very broad spectrum of activity against the majority of uropathogens, including *Pseudomonas*. However, it is not recommended to use this drug class in treating uncomplicated UTIs. This class has limited gram-positive activity and is not effective in treating *Enterococcus*. Fluoroquinolones are very expensive agents and should be reserved for the treatment of complicated UTI, pseudomonal infections, or treatment of resistant organisms.

Antimicrobial Agents for the Management of Uncomplicated UTI

Tier	Drug	Dosage	Pregnancy category
First	Fosfomycin (Monurol)	3-g single dose	B
	Nitrofurantoin (macrocrystals)	100 mg BID for 5 days	B
	Trimethoprim-sulfamethoxazole (Bactrim/Sulfa)	160/800 BID for 3 days	C
Second	Ciprofloxacin (Cipro)	250 mg BID for 3 days	C
	Ciprofloxacin, extended release (Cipro XR)	500 mg QD for 3 days	C
	Levofloxacin (Levaquin)	250 mg QD for 3 days	C
Third§	Ofloxacin	200 mg QD for 3 days Or 400 mg single dose	C
	Amoxicillin/clavulanate (Augmentin)	500/125 mg BID for 7 days	B
	Cefdinir (Omnicef)	300 mg BID for 10 days	B
	Cefpodoxime	100 mg BID for 7 days	B

Adapted from Colgan and Williams (2011)

Recurrent Bacterial Cystitis

It is critical to obtain a detailed culture history when attempting to differentiate whether a recurrent bacterial infection is caused from a site of bacterial persistence inside or outside of the urinary tract. Ninety-five percent of recurrent infections are caused from a source outside the urinary tract (Hanno 2014). However, when the

cause is considered to be from outside the urinary tract, then a full urological workup is necessary. Therefore, it is crucial to identify the bacteria responsible for the infection. In a case, where one has treated the UTI successfully, identified by antimicrobial eradication (negative culture) and reinfection occurs by a varying strain of *Enterobacteriaceae*, this is specific in indicating reinfection. The only other factor that may cause a similar scenario is reinfection from an enterovesical fistula. In the case of a fistula, the urine is never sterilized, and the infection may be with multiple organisms, which should raise the suspicion for a fistula.

If urinary symptoms persist or recur within 1–2 weeks after completing treatment, then this suggests infection with an antimicrobial-resistant strain. A culture *should* then be performed and therapy should be initiated utilizing a broad-spectrum antibiotic (fluoroquinolones). As urological specialists, it is acceptable to start with a broad-spectrum antibiotic, with the expectation that treatment may need to be altered based on the final culture and sensitivity results. In individuals that experience episodes of cystitis that recur at least 1 month after successful treatment, then treatment should be initiated utilizing a first-line course regime. If recurrence is within 6 months, then consideration should be given to a first-line antimicrobial other than the one that was initially used. Due to high resistance rates, this is especially true when considering the use of trimethoprim-sulfamethoxazole.

If it is determined that a recurrent infection is caused by gram-negative introital colonization, prophylaxis should be considered. In relation to postcoital cystitis, also called "honeymoon cystitis," it is recommended to have the patient void after intercourse and to use a single low-dose antibiotic. The typical recommended antibiotic dose for these patients, which has remained effective over the years, would be TMP-SMZ (one dose of double strength), cephalexin (250 mg), or nitrofurantoin 50–100 mg) after intercourse (Bastani 2001). This regimen tends to work well in patients who are having less frequent intercourse. If the patient is having intercourse more than four times per week, then it is better to only treat symptomatic infections with a short course of antibiotics to reduce the overall antibiotic use.

Over the years, patients have also been treated with long-term prophylactic use of antibiotics. This therapy may have been utilizing nitrofurantoin (50–100 mg every night) or TMP-SMZ (1/2 tab every other night). Typically after 6–12 months, the therapy could be stopped in the hopes that the colonization with uropathogenic gram-negative organisms has resolved. Over the next 6 months, if a patient develops 2–3 episodes of UTI, then another course of prophylaxis would be initiated (Hanno 2014).

The current goal in treating UTIs is to decrease the overall use of antibiotics while maintaining a quality of life. Several studies have looked at different strategies that can be used to achieve this goal. One of these strategies is the "self-start" strategy. This relies on the patient to make the clinical diagnosis of UTI, which is typically not difficult for these patients, when the previous infections have been confirmed by a positive culture. These patients are given a prescription for an antibiotic (i.e., TMP-SMZ, cephalexin, or nitrofurantoin), to be taken for 2–3 days at the onset of symptoms. If symptoms persist or reoccur beyond this initial therapy, then an office visit is recommended for culture and sensitivity testing. Self-start therapy works very well in the patient who has been well educated.

Special Situations

There are certain populations in which an otherwise uncomplicated UTI requires more attention. There are physiologic changes that take place during pregnancy that have important implications in regard to ASB and the progression of infection. During pregnancy there is an increased renal size, altered renal function, hydroureteronephrosis, and anterosuperior displacement of the bladder. The rate of pyelonephritis in pregnant females is much higher than that of the nonpregnant female and a 20–40 % increase in acute pyelonephritis if ASB is left untreated in the pregnant population (Hanno 2014). In turn, it is associated with higher rates of prematurity and perinatal mortality. In a pregnant woman with acute uncomplicated UTI, one could consider treating with amoxicillin (250 mg every 8 h), ampicillin (250 mg every 6 h), nitrofurantoin (100 mg every 6 h), or even an oral cephalosporin. As previously noted, amoxicillin and ampicillin are no longer first-line recommendations due to their ability to interfere with the fecal flora.

Young healthy men with no complicating risk factors may be treated with a 7–10-day course of antibiotics. The recommended course of treatment is TMP-SMZ (double strength every 12 h), trimethoprim (100–200 mg every 12 h), or a fluoroquinolone, and a pretreatment culture and sensitivity is recommended in this population. In the middle-aged and elderly population, who are sexually active, no further workup is needed if the infection is eradicated with antibiotic therapy. However, in the younger, nonsexually active, population or when there is a high clinical suspicion, then further workup can be done to look for an abnormality of the urinary tract. One might obtain imaging studies to assess the kidneys, ureters, and bladder, a cystoscopy, and a post void residual.

Patients with indwelling catheters, whether short term or long term, pose a risk for infection. It should be noted that for every day that a catheter is left indwelling, the risk of infection raises 3–10 % per day (Bernard et al. 2012). The Center for Disease Control (CDC) has completed studies evaluating the majority of circumstances where an indwelling catheter may be utilized. The recommendations can be reviewed at http://www.cdc.gov/hicpac/pdf/CAUTI/CAUTIguideline2009final.pdf and a brief summary of the recommendations are as follows:

- Limit long-term use, especially for the treatment of incontinence, unless the patient has a stage 3 decubitus
- Limit use in nursing home patients and consider intermittent or external catheters if possible
- Only use for specific surgical procedures when necessary, not as a routine surgical intervention and remove the catheter within 24 h or as soon as possible

In addition, the CDC guidelines support the use of indwelling catheters when attempting to promote comfort and quality of life for the terminal patient and those patients whom will be experiencing prolonged immobilization (i.e., spinal surgery or traumatic injuries, such as pelvic fractures).

Pyelonephritis

Incidence

Acute uncomplicated pyelonephritis is much less common than cystitis. There is an estimated ratio of 1:28 cases of pyelonephritis to that of cystitis, with an annual incidence of 25 cases per 10,000 women between the ages of 15–34 years (Hooten 2012).

Presentation

As previously shown in table (__), the classic symptoms of pyelonephritis are any combination of cystitis symptoms, accompanied by bacteriuria, pyuria, fever, chills, flank pain, and/or nausea and vomiting. One should remember that patients with flank pain and UTI do not necessarily have pyelonephritis, and the reverse is true in that patients may actually have a case of pyelonephritis in the absence of local and systemic symptoms. The majority of patients with acute pyelonephritis will be ill appearing and may have additional symptoms such as malaise or hypotension. It should create a high level of suspicion if a patient has any of the known risks factors, listed in the table below.

Risk factors for pyelonephritis
Vesicoureteral reflux
Obstruction of the urinary tract (congenital ureteropelvic junction obstruction, stone disease, pregnancy)
Genitourinary tract instrumentation
Diabetes mellitus
Voiding dysfunction
Age (renal scarring rarely begins in adulthood; this is typically related to reflux in children)
Female gender

Classification

Pyelonephritis may be caused by several different routes:

1. Ascending: Bacteria reach the renal pelvis through the collecting ducts at the papillary tips and then ascend through the collecting tubules. The presence of urinary reflux from the bladder or increased intrapelvic pressures caused by lower urinary tract obstruction can also cause upper urinary tract infection.
2. Hematogenous: This tends to be the result of *Staphylococcus aureus* septicemia or *Candida* in the blood stream. Hematogenous causes are uncommon.
3. Lymphatic: This is an intraperitoneal infection (i.e., abscess) caused by an unusual form of extension to the renal parenchyma.

The majority of acute uncomplicated pyelonephritis cases can be managed in the outpatient setting. However, if one has diabetes, a renal stone, hemodynamic instability, or is pregnant, then they should be hospitalized for the initial 2–3 days of parenteral therapy. Pyelonephritis can lead to sepsis, hypotension, and even death, especially if the infection is caused by an unrecognized upper tract obstruction.

Flank tenderness is a prominent finding on physical exam. In addition, an infected urine with large amounts of granular or leukocyte casts in the sediment is also indicative for the diagnosis. Eighty percent of the cases of pyelonephritis are caused by *E. coli*. In patients who have undergone a form of urinary tract instrumentation, who have had a previous indwelling catheter, or those that have developed a nosocomial infection, the microorganism responsible for the infection in these situations is typically *Pseudomonas*, *Serratia*, *Enterobacter*, *and Citrobacter*. In patients with stone disease, one should suspect *Proteus* or *Klebsiella*. Both of these microorganisms contain the enzyme urease, which has the ability to split urea with the production of ammonia and an alkaline environment. This leads to the precipitation of the salt struvite (magnesium ammonium phosphate), which form branched calculi. These calculi harbor bacteria in the interstices of the renal calculi. These types of stones are referred to as staghorn calculi, which can lead to chronic renal infection.

Diagnostic Testing

Laboratory testing and radiology studies can assist in differentiating the cause. One should order both urine and blood cultures to rule out sepsis. An intravenous urogram may demonstrate normal results or it may show renal enlargement secondary to edema. It is necessary to distinguish whether focal enlargement is a result of a renal mass or abscess. A delayed appearance of the pyelogram or a diminished nephrogram may be caused by inflammation. When assessing an imaging study, the most important thing to rule out is the presence of obstruction and/or urolithiasis. Both of which could lead to a life-threatening situation if left undiagnosed and untreated. Ultrasound is useful in some cases; however, CT may demonstrate the patchy decreased enhancements that suggest focal renal involvement.

Complications

Abnormal findings and complications associated with pyelonephritis are:

(a) Xanthogranulomatous pyelonephritis (XGP) – severe and chronic renal infection that destroys the kidneys.
(b) Chronic pyelonephritis – rare in the absence of an underlying functional or structural abnormality of the urinary tract.
(c) Renal insufficiency – rare complication.

(d) Hypertension – is noted in over 50 % of patients.
(e) Renal abscess – collection of purulent material confined to the renal parenchyma.
(f) Infected hydronephrosis – bacterial infection of a hydronephrotic kidney and can often be associated with destruction of the renal parenchyma.
(g) Perinephric abscess – typically results from a rupture of a cortical abscess or hematogenous seeding from another infection site.
(h) Emphysematous pyelonephritis – acute necrotizing parenchyma and perirenal infection caused by gas-forming uropathogens.

Management

In the majority of cases, acute uncomplicated pyelonephritis can be treated on an outpatient basis. However, the patient should be hospitalized in the following situations:

- Nausea or vomiting
- Dehydrated
- Pregnant
- History of non-adherence to medical therapies
- Evidence of septicemia

Urine cultures should be obtained on all suspected cases of pyelonephritis. On all hospitalized patients, one should obtain blood cultures and baseline labs to check renal functioning. The results of the blood cultures tend to be positive in approximately 15–20 % of patients (Bastani 2001).

Initial treatment for uncomplicated pyelonephritis should be started using a fluoroquinolone pending cultures results. It is becoming a more common practice to administer a single parenteral dose of ceftriaxone (1 g), a consolidated 24 h dose of an aminoglycoside (i.e., gentamicin), or a fluoroquinolone before initiating oral antibiotics (Hanno 2014).

Clinical Pearls

- In uncomplicated UTIs, there is no association between recurrent infections and renal scarring, hypertension, or renal failure.
- Methenamine or hexamine hippurate are used as urinary antiseptics for chronic therapy, which reduces the risk of antibiotic resistance and efficacy may be increased if used as adjuvant therapy to cranberry supplements.
- Asymptomatic bacteriuria, in the elderly population, may be unjustified and is typically ineffective.

- It is a challenge clinically to differentiate between upper and lower UTI; however, it is most often not necessary because management and treatment are similar.
- Recurrent UTI tends to be biological in nature and not necessarily related to personal hygiene.
- When investigating UTIs, the best overall screening tool remains the retroperitoneal ultrasonography.
- Due to the risk of pulmonary fibrosis with nitrofurantoin use, it is not recommended as a long-term prophylactic antibiotic of choice. However, it remains an excellent option for short-course treatment of recurrent UTI.
- If a male patient has no culture documented history of a UTI, then it is unlikely that he will have a diagnosis of chronic bacterial prostatitis.

In the outpatient setting, it is recommended to treat with a 10-day course of antibiotics using a fluoroquinolone or trimethoprim-sulfamethoxazole. In the presence of sepsis, it is recommended to treat for 14 days. According to the Infectious Disease Society of America (IDSA), the recommendation is to treat with ciprofloxacin 500 mg BID for 7 days or levofloxacin 750 mg QD × 5 days (2011). If the patient demonstrates improvement within 72 h, then continue the oral antibiotic therapy and obtain a repeat urine culture at 4 days on and 10 days off of the medication. If no improvement is noted, then the patient should be hospitalized and one should review the culture and sensitivity results. In the presence of an obstruction or abscess, treatment and/or drainage of the causative factor would be recommended. Complicated cases of pyelonephritis requiring hospitalization or a procedure may also require up to 3 weeks of antibiotic therapy.

Bibliography

Bass-Ware A, Weed D, Johnson T, Spurlock A (2014) Evaluation of the effect of cranberry juice on symptoms associated with a urinary tract infection. Urol Nurs 34(3):121–127

Bastani B (2001) Urinary tract infections. In: Noble J, Greene HL II, Levinson W, Modest GA, Mulrow CD, Scherger JE, Young MJ (eds) Textbook of primary care medicine, 3rd edn. Mosby, Inc., Missouri, pp 1364–1371

Bernard MS, Hunter KF, Moore KN (2012) A review of strategies to decrease the duration of indwelling urethral catheters and potentially reduce the incidence of catheter-associated urinary tract infections. Urol Nurs 32(1):29–37

Center for Disease Control and Prevention (2005) Urinary tract infections [Disease Listing]. Retrieved from http://www.cdc.gov/ncidod/dbmd/diseaseinfo/urinarytractinfections_t.htm

Center for Disease Control and Prevention (2009) Guideline for prevention of catheter associated urinary tract infections 2009. Retrieved from http://www.cdc.gov/hicpac/pdf/CAUTI/CAUTIguideline2009final.pdf

Colgan R, Williams M (2011) Diagnosis and treatment of acute uncomplicated cystitis. Am Family Phys 84(7):771–776, Retrieved from http://www.aafp.org/afp/2011/1001/p771.html

Ellsworth P, Onion DK (2012) The little black book of urology, 3rd edn. Jones & Bartlett Learning, Sudbury, pp 68–71

Goldman HB (2001) Evaluation and management of recurrent urinary-tract infections. In: Kursch ED, Ulchaker JC (eds) Office urology: the clinician's guide. Humana Press Inc., Totowa, pp 105–111

Gould CV, Umscheid CA, Agarwal RK, Kuntz G, Pegues DA, Healthcare Infection Control Practices Advisory Committee (HICPAC) (2009) Guideline for catheter associated urinary tract infections 2009. Center for Disease Control and Prevention. Retrieved from http://www.cdc.gov/hicpac/pdf/cauti/cautiguideline2009final.pdf

Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE (2011) International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

Hanno PM (2014) Lower urinary tract infections in women and pyelonephritis. In: Hanno PM, Guzzo TJ, Malkowicz SB, Wein AJ (eds) Penn clinical manual of urology, 2nd edn. Elsevier Saunders, Philadelphia, pp 110–132

Harlow HF (1983) Fundamentals for preparing psychology journal articles. J Compar Physiol Psychol 55:893–896

Hooten TM (2012) Uncomplicated urinary tract infection. N Engl J Med 366:1028–1037, Retrieved from http://www.nejm.org/doi/full/10.1056/NEJMcp1104429

Macfarlane MT (2013) Urology, 5th edn. Lippincott Williams & Wilkins, Philadelphia, pp 86–110

Sandock DS, Kursh ED (1995) Urinary tract infections in adult females. In: Resnick MI, Novick AC (eds) Urology secrets. Hanley & Belfus, Inc., Philadelphia, pp 205–207

Society of Urological Nurses Association (2010) Prevention & Control of Catheter-Associated Urinary Tract Infection (CAUTI) [Clinical Practice Guidelines]. Retrieved from https://www.suna.org/sites/default/files/download/cautiGuideline.pdf

Stamm WE, Norrby SR (2001) Urinary tract infections: disease panorama and challenges. J Infect Dis 183(Suppl 1):S1–S4. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11171002

Uphold CR, Graham MV (1998) Clinical guidelines in family practice, 3rd edn. Barmarrae Books, Gainesville, pp 601–607