

# Educational Case: Acute Cystitis

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*The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289520951923>.<sup>1</sup>*

## Keywords

pathology competencies, organ system pathology, bladder, cystitis, diagnostic medicine, microbiology, antimicrobials, urine

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## Primary Objective

*Objective UTB2.1: Acute Cystitis.* Discuss the typical clinical symptomatology of acute cystitis and the organisms commonly causing this disorder.

Competency 2 Organ System Pathology; Topic UTB: Bladder; Learning Goal 2: Bladder Infection.

## Secondary Objectives

*Objective M2.11: Urine Studies for Cystitis.* Explain the role of urine studies, including culture, in selecting antimicrobial therapy for infectious cystitis.

Competency 3 Diagnostic Medicine and Therapeutic Pathology; Topic M: Microbiology; Learning Goal 2: Antimicrobials.

*Objective M2.12: Diagnosis of UTI.* Describe a testing strategy for a typical uncomplicated community acquired urinary tract infection (UTI) versus a nosocomial UTI in a patient with a Foley catheter and list the key microbiological tests in diagnosis of UTIs.

Competency 3 Diagnostic Medicine and Therapeutic Pathology; Topic M: Microbiology; Learning Goal 2: Antimicrobials.

## Patient Presentation

A 27-year-old woman presents to her primary care physician with a report of urinating more frequently and pain with urination. She denies blood in her urine, fevers, chills, flank pain,

and vaginal discharge. She reports having experienced similar symptoms a few years ago and that they went away after a course of antibiotics. The patient has no other past medical problems. Pertinent history reveals she has been sexually active with her boyfriend for the past 4 months and uses condoms for contraception. She reports 2 lifetime partners and no past pregnancies or sexually transmitted diseases. Her last menstrual period was 1 week ago.

## Diagnostic Findings, Part I

On physical exam, the patient is afebrile, normotensive, and non-tachycardic. She appears well on observation. She has a soft, nondistended abdomen with normoactive bowel sounds. On palpation, she has moderate discomfort in her suprapubic region but no costovertebral angle (CVA) tenderness. A pelvic

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exam is normal with no evidence of abnormal vaginal or cervical discharge or inflammation.

## Questions/Discussion Points, Part I

### *What Is the Differential Diagnosis for This Patient? Which Diagnosis Is Most Likely and Why?*

The top entities in the differential diagnosis include a UTI, vaginitis/cervicitis, and pyelonephritis. The most likely diagnosis in this patient is a UTI, specifically, acute cystitis. Classic UTI symptoms include urinary frequency and urgency and dysuria. Other complaints could include suprapubic pain or discomfort, hesitancy, nocturia, and even gross hematuria. Urinary tract infections are classified by the anatomical location in which the infection and inflammation occur. Risk factors that this patient possesses, which will be discussed later, are female sex, age, recent sexual activity, and a history of prior UTI, which we can infer from her report of previous similar symptoms.<sup>2</sup>

Vaginitis and cervicitis should also be considered in this patient given her history of sexual activity. However, the patient has no reported vaginal discharge or signs of these infections on pelvic examination. Another important diagnosis to consider is pyelonephritis, which involves infection of the upper urinary tract. This is also not likely given her lack of fever, flank pain, and other key symptoms which will be discussed in a later section.

### *Is Laboratory Testing Required To Confirm the Diagnosis in This Patient?*

Laboratory studies are not needed in this patient due to the high likelihood of a UTI, and empirical treatment can be administered. Thus, the importance of a good history and physical exam is highly emphasized when caring for a patient with a possible UTI. Uncomplicated UTIs are commonly observed and treated in the outpatient setting; they are increasingly being diagnosed without an in-person visit via telephone.<sup>2</sup>

### *Which Populations Are at Higher Risk of Contracting a UTI? Why? Discuss the Terms “Uncomplicated UTI” Versus “Complicated UTI”*

Urinary tract infections are due to the colonization of the urinary tract by microbes. Certain populations are at higher risk of infections of the urinary tract. Women are among those most affected by UTIs, with a lifetime incidence rate of almost 50%.<sup>3</sup> The difference between the sexes is attributed to women's shorter urethral length. Women who are sexually active are also at risk of UTI due to the proximity of the urethral meatus to the flora-rich anus. If the patient is a premenopausal, otherwise healthy, and nongravid female, as in this case, she has developed an “uncomplicated” infection.<sup>2,4</sup>

Patients who are predisposed to conditions that make colonization more likely or are exposed to microbes that are more facile in evading the body's natural protective mechanisms are more apt to contract UTIs, and their infections can be more

difficult to treat. These patients have “complicated” infections. Numerous conditions make a patient more susceptible to UTI. These include underlying medical problems or structural abnormalities of the urinary tract such as urinary obstruction, vesicoureteral reflux, underlying urinary tract disease, diabetes, renal papillary necrosis, immunosuppression (medically induced or as a result of HIV infection), treatment with antibiotics, pregnancy, menopause, and spinal cord injuries.<sup>4</sup> The elderly are also at increased risk of UTI, particularly men, many of whom develop obstructive uropathy from benign prostatic hypertrophy.<sup>2,4</sup>

### *When Should a Diagnosis of Pyelonephritis Be Suspected?*

Infection of the kidney is termed pyelonephritis. These patients tend to present acutely with “upper tract signs,” to include fever, chills, flank pain, and CVA tenderness. Symptoms of lower UTI can also be present; however, this is not usually the case. The clinical presentation may vary and can be life-threatening. In the most severely ill, patients may present in septic shock, with hypotension, tachycardia, and tachypnea, especially when infected with a gram-negative organism.<sup>4</sup>

### *Which Laboratory Studies Can Be Performed on Urine To Evaluate a Potential UTI? What Is the Diagnostic Value of Each Test?*

Laboratory tools are commonly utilized in the investigation of UTIs for patients with a complicated UTI, recurrent infections, or an unclear diagnosis based purely on history and physical exam. Again, test results should always be correlated with clinical findings, as false-positive or false-negative results can occur through multiple avenues. Available tests include a urine dipstick, urinalysis with microscopy, and culture and gram stain with sensitivity testing. The first 2 of these have the potential to be performed in physicians' offices. A clean-catch midstream specimen should be submitted to avoid contamination from vaginal or penile microorganisms. Patients should be given a 2% castile soap towelette and instructed in appropriate specimen collection. Men should cleanse the glans, retracting the foreskin first if uncircumcised. Women should cleanse the periurethral area after spreading the labia. Identification of lactobacilli and epithelial cells from the vagina suggest contamination.<sup>4</sup>

General features of the urine can first be examined to include the color, clarity, and odor; but these features are non-specific. For example, cloudy urine can be caused by the presence of white blood cells and/or bacteria in a UTI; but it can also be caused by numerous other pathologic and non-pathologic substances.

Urine dipstick studies, primarily searching for leukocyte esterase and nitrites, are useful when the pretest probability of UTI is high. Leukocyte esterase is an enzyme possessed by white blood cells. Thus, a positive urine dipstick for

leukocyte esterase indicates the presence of inflammatory cells in the patient's urinary tract. Inflammatory cells in the urine are not specific for a UTI, as leukocytes can also be present in other situations such as glomerulonephritis and vaginal contamination. Nitrite is a breakdown product of nitrates, which are normally found in a healthy patient's urine. The dipstick test for nitrite is specific for gram-negative organisms which possess an enzyme enabling them to reduce nitrates. It follows, then, that this test is less useful in the setting of potential gram-positive microbe infection. Also notable is that the nitrite test can be falsely negative in a patient with abundant fluid intake and frequent urination.<sup>2</sup> Multiple other factors including medications, diet, and specimen handling can affect urine dipstick results, as can inappropriate handling or expiration of test strips.

Urinalysis with microscopy provides a window into the kidney and urinary tract. The presence of red blood cells, white blood cells, casts, crystals, and bacteria aid in many diagnoses. Specific to UTI, the presence of white blood cells and red blood cells indicates inflammation and, potentially, infection in the urinary tract.<sup>2</sup> Pyuria, the presence of leukocytes in the urine, is not specific to UTIs as noted above; but the absence of leukocytes should cause one to question a diagnosis of UTI unless the culture is positive. The identification of crystals might suggest the presence of renal calculi, which can serve as a nidus for infection. In fact, some stones (eg, struvite) are the direct result of infection with urea-splitting organisms. Overall, urinalysis is useful; however, the clinical history still plays a key role to avoid under- and overdiagnosis.<sup>4</sup>

Urine culture is the gold standard diagnostic tool for diagnosing UTIs.<sup>2,4</sup> As stated previously, in patients with a convincing clinical history and physical exam consistent with uncomplicated cystitis, no culture is necessary. However, in patients with complicated, severe upper urinary tract, or recurrent UTIs, urine culture should not be foregone, as it is necessary for determining the causative organism and, consequently, for guiding appropriate therapeutic intervention. Furthermore, growth of the organism in culture facilitates sensitivity studies, in which pharmacologic agents are tested on the microbe isolated from the patient. This testing provides medical personnel with information regarding the efficacy of potential therapeutic options in the form of minimal inhibitory concentrations. This information guides narrowing of antibiotic choice from whichever broad-spectrum treatment was initiated when a UTI was first suspected.<sup>2</sup> Some organisms such as *Ureaplasma urealyticum* may not be grown on routine cultures, so a false-negative result is possible. False-positive results are rare, other than due to contamination, which should be suspected in most cases with growth of multiple types of bacteria or vaginal flora.<sup>4</sup>

### What Is Asymptomatic Bacteriuria?

The diagnosis of asymptomatic bacteriuria requires 2 criteria: (1) The urine is culture-positive and (2) the patient does not have symptoms or signs of a UTI. The level of bacteria in culture should reach  $\geq 10^5$  CFU/mL, although it can be lower

in catheterized patients ( $\geq 10^2$  CFU/mL). Asymptomatic bacteriuria is only treated in some groups of patients, including those who are pregnant or undergoing urologic procedures, as it otherwise does not correlate with symptomatic disease or complications.<sup>2</sup>

### Which Microorganisms Most Commonly Cause Acute Cystitis?

In general, gram-negative aerobic rods are the most commonly isolated pathogens implicated in UTIs.<sup>2</sup> *Escherichia coli* is the most common causative organism of UTIs, especially in sexually active young women.<sup>2,4</sup> Microorganisms such as uropathogenic *E coli* (UPEC) with an enhanced ability to bind and to adhere to urinary tract epithelia are more capable of causing infection. Adhesins and pili resistant to the innate immune mechanisms of defense are among the advantageous traits that particularly virulent strains of UPEC possess.<sup>4</sup>

A variety of other Enterobacteriaceae (discussed below) are also found in the setting of catheter-associated UTIs (CAUTIs). However, gram-positive organisms are clinically significant in some settings. *Staphylococcus saprophyticus* is not infrequently implicated in uncomplicated UTIs in young, sexually active women.<sup>2</sup> Group B *Streptococcus* (GBS, *Streptococcus agalactiae*) is of particular concern in pregnant patients. In 1 prospective study, GBS was the second most isolated pathogen behind *E coli* in the urine of asymptomatic bacteriuric pregnant women.<sup>5</sup> Screening pregnant women for asymptomatic bacteriuria plays an important role in decreasing the risk of pyelonephritis during pregnancy.<sup>6,7</sup> Table 1 summarizes the typical microorganisms identified in complicated and uncomplicated UTIs along with the appropriate laboratory testing.

### Discuss CAUTIs and Their Difference From Non-CAUTIs, Including Clinical Features and Causative Microorganisms

Per the Infectious Diseases Society of America,<sup>8</sup> both clinical and laboratory criteria should be met to make the diagnosis of a catheter-associated UTI (CAUTI). The patient should have signs or symptoms of a UTI and no other known source of infection. Culture of the patient's urine sample should yield greater than  $10^3$  colony-forming units (CFU)/mL of at least 1 species of bacteria. The cultured urine should be from a single specimen in those patients who are still catheterized. Catheter-associated UTI can also be diagnosed in those whom have had a catheter removed within the preceding 48 hours, in which case a midstream voided urine is the appropriate specimen.

Catheter-associated UTIs are a type of complicated UTI and are among the most common nosocomial (hospital-acquired) infections in the United States.<sup>4</sup> Urinary catheters facilitate the ascent of microbes into the urinary tract. There are different methods of catheterization, for example, clean intermittent catheterization, indwelling urethral catheters, and suprapubic catheters. Microorganisms can be introduced during the procedure of

**Table 1.** Common Causative Organisms and Indicated Laboratory Tests for Patients With Uncomplicated and Complicated Urinary Tract Infections (UTIs).

Patient characteristics	Most common causative microorganism(s)	Laboratory tests
Uncomplicated UTI		
Premenopausal, healthy female (not pregnant)	<i>Escherichia coli</i> , <i>Staphylococcus saprophyticus</i> , other ( <i>Enterococcus</i> , <i>Proteus</i> , <i>Klebsiella</i> , <i>Citrobacter</i> , etc)	Not necessary unless uncertain by history (use urine dipstick) and/or possible STI (also perform appropriate tests for STIs)
Complicated UTI		
Pregnant female	<i>E coli</i> , Group B <i>Streptococcus</i>	Urinalysis and culture; address other modifiable factors and use prevention strategies if able
Catheter-associated UTI	<i>E coli</i> , other Enterobacteriaceae ( <i>Klebsiella</i> , <i>Serratia</i> , <i>Enterobacter</i> , <i>Pseudomonas</i> , <i>Enterococcus</i> , and <i>Proteus</i> ), <i>Citrobacter</i> , <i>Acinetobacter</i> , <i>Morganella</i> , gram-positive bacteria, yeast	
Structural or functional urinary tract abnormality		
Immunosuppressed		
Male		
Elderly		
Diabetic		
Recent antibiotic use		
Instrumentation of urinary tract		
Prolonged symptoms (>7 days) at presentation		
Pyelonephritis	Organisms similar to uncomplicated UTI	Urine culture, blood cultures

Abbreviation: STI, sexually transmitted infection.

catheterization despite the implementation of sterilization methods. Also, without appropriate catheter care, these indwelling devices can become a nidus for infection, permitting various other flora to travel along the tube and into the urinary tract.<sup>4</sup>

As previously mentioned, *E coli* is the most common causative organism of acute cystitis in uncomplicated UTIs.<sup>4</sup> It is also the most commonly isolated organism in CAUTI.<sup>8,9</sup> However, patients with catheters are at higher risk of infection by organisms less commonly seen in non-catheterized patients. Patients who are catheterized for both short and long periods of time are at increased risk of infection with fungal organisms as well as Enterobacteriaceae such as *Klebsiella*, *Serratia*, *Enterobacter*, *Pseudomonas*, *Enterococcus*, and *Proteus* species.<sup>4,6,9</sup> These organisms are exceptionally well-adapted for invasion given the ability many of them possess to form biofilms. The longer a patient is catheterized, the more likely they are to develop bacteriuria, a symptomatic infection, and potentially colonization of the urinary tract.<sup>4</sup> Thus, timely removal of catheters when no longer necessary is wise.

### How Should Patients With UTIs Be Treated?

The choice of therapy for UTIs depends on the clinical treatment setting, and whether it is a complicated or uncomplicated UTI. An optimal outpatient antibiotic can be taken orally, has a tolerable side effect profile, and is concentrated to a therapeutic level in the patient's urine.<sup>4</sup> Antibiotics that fit this profile are appropriate to give patients who have a low risk for infection with a multidrug resistant strain. Options for therapy include nitrofurantoin monohydrate, trimethoprim-sulfamethoxazole, fosfomycin, and pivmecillinam.<sup>4,10</sup>

Recent infectious disease guidelines reflect growing concern for infection with multidrug resistant organisms.<sup>10</sup>

When therapy needs to be escalated due to infection with a multidrug resistant organism or tissue-invasive disease with bacteremia, options remain for oral therapy. In these situations, it is advantageous to obtain urine culture and microbe antibiotic sensitivities to better eliminate the infection. If hospitalization is indicated and the patient requires parenteral antibiotics, empiric therapy should be initiated. After microorganism sensitivities return, antibiotic therapy can be narrowed to one of the following: a carbapenem, third-generation cephalosporin, fluoroquinolone, ampicillin, and gentamicin.<sup>4</sup>

Pharmacotherapy for complicated UTIs should begin with broad-spectrum therapy and then be narrowed by sensitivities when possible.<sup>4</sup> The grouping which places the patient in the "complicated" category plays a role in treatment selection. For example, UTIs in men typically involve the prostate as well as the bladder, so treatment should target the infection in both organs. Patients who are pregnant require antibiotics that are safe for the fetus.<sup>2</sup> Some complicated UTIs, especially in the case of upper UTIs, are managed inpatient with intravenous antibiotics due to the presence of tissue-invasive disease or bacteremia. In this case, the concentration of antibiotic in the blood and the urine are important. This differs from the treatment of uncomplicated UTIs, which are dependent on the concentration of the pharmacotherapeutic agent in the urine.<sup>4</sup>

Potential correction of modifiable risk factors for UTIs, if present, can also be addressed to prevent recurrent infection. This may include correction of an anatomic or structural abnormality of the urinary tract, consideration of alternative birth control types in a woman who uses a diaphragm with spermicide, removing a urinary catheter, or simply counseling a woman to attempt urination after sexual intercourse.

## Describe Potential Complications of UTIs

Urinary tract infections can be complicated by several conditions depending on the severity and chronicity of the infection and the implicated organism. Severe upper UTIs can lead to acute kidney injury and, if not treated, can lead to permanent kidney damage and fibrosis. Similarly, upper UTIs can be complicated by renal or perinephric abscess(es). Renal abscesses are most found in patients with preexisting kidney disease. Patients infected by a urea-splitting organism are at risk of struvite stones, which are commonly found in the upper urinary tract.<sup>4</sup>

## Teaching Points

- Acute cystitis is a form of UTI and commonly presents with urinary frequency, urgency, and dysuria. Uncomplicated cases of UTIs, those seen in otherwise young, healthy, adult women, can be diagnosed by a thorough history and physical exam.
- Urinary tract infections are most often seen in sexually active, young women and older men with benign prostatic hyperplasia.
- *Escherichia coli* is the most implicated organism in UTIs. Other aerobic gram-negative rods and sometimes gram-positive microorganisms can be implicated, especially in patients with preexisting conditions or indwelling urinary catheters.
- Laboratory investigations, including dipstick tests, urinalysis, and urine culture, can aid physicians in the diagnosis of UTIs when needed and are important to guide effective treatment, especially in complicated UTIs.
- Uncomplicated UTIs can be treated with outpatient oral antibiotics, with choices to include nitrofurantoin monohydrate, trimethoprim-sulfamethoxazole, fosfomycin, and pivmecillinam.
- Complicated UTIs occur in patients at higher risk of infection or in whom the infection may be difficult to treat. Some examples of patients in this category include those with anatomic or other urinary tract obstruction, catheter-associated UTIs, pregnant women, and patients who are immunosuppressed.
- Pyelonephritis is a serious upper UTI which can potentially be life-threatening if not treated promptly.
- Complications of UTIs include renal abscesses, acute kidney injury leading to chronic kidney disease, and struvite calculi.
- Broad-spectrum pharmacotherapy should be initiated for complicated microbial infections of the urinary tract. After sensitivity studies from the patient's urine return, treatment can be narrowed to avoid the development of multi-drug resistant organisms.

## Author's Note

The opinions expressed herein are those of the author and are not necessarily representative of those of the Uniformed Services

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