12.2.2

Urinary Tract Infection (UTI)

Watch the video on Urinary Tract Infections.

Urinary Tract Infections (UTIs) are bacterial or viral infections of any portion of the urinary tract. Before further discussion, let's review the normal physiologic mechanisms that safeguard against an infection in the urinary tract.

Host Defenses

Within the bladder, there are several mechanisms that collectively work to fend off microbes that may cause UTIs:

- **Washout phenomenon:** The act of micturition "washes out," or removes pathogens from the kidneys and bladder. In doing so, urine is kept sterile.
- **Local Immunity:** Along the urinary tract, secretory IgA and neutrophils help neutralize and remove bacteria known to cause UTIs.
- **Mucin layer:** Epithelial cells lining the bladder secrete a substance known as mucin which is a heavily glycosylated protein that forms a protective layer between the epithelial cells and the urine. This protective coating prevents the colonization of bacteria within the bladder. In women, estrogen plays a key role in stimulating bladder epithelium to maintain the protective mucin layer.
- **Vaginal flora:** The female genitourinary tract houses eubacteria that help defend against harmful bacteria. Most notably, *Lactobacillus* species utilize the sugars found in the mucin layer to generate lactic acid, which lowers the pH of urine. While the *Lactobacilli* remain unaffected, the acidic environment is toxic to many other pathogens.
- **Prostate secretions:** Fluid secreted from the prostate has antimicrobial activity due to the presence of zinc. Although its mechanism remains unexplained, zinc ions prevent bacterial attachment to the bladder wall.

Impairment in any number of the above mechanisms predisposes individuals to developing UTIs; pathogens face less resistance to colonization and trigger an inflammatory response that is responsible for the pathogenesis of UTIs.

Risk Factors

Understanding the following risk factors for developing UTIs will help identify at–risk populations and support clinical UTI diagnosis:

Female gender: In the adult population, UTIs are far more common in women. Females have shorter urethras which facilitate bacterial infection, especially since the vaginal vestibule is easily contaminated with fecal bacteria. In sexually active women, the use of spermicidal contraceptives kills the good bacteria found within the vagina and enhances the likelihood of bacterial colonization in the bladder. Finally, the loss of estrogen in postmenopausal women results in decreased mucin production that normally protects the bladder wall from bacterial attachment.

Elderly: Dehydration and decreased immune activity are two common findings among the elderly. Dehydration reduces urinary output in which bacterial "washout" is minimized. Declining immune function results in decreased IgA antibodies and innate immune cells along the urinary tract epithelium. For these reasons geriatric populations are more prone to developing UTIs.

Urinary catheterization: Often called a Foley or indwelling catheter, urinary catheterization is a medical implant commonly used in the hospital setting to assist patients unable to void their bladder. Prolonged catheterization (> 2 weeks) may result in **biofilm** formation within the indwelling catheter, a slimy and antibiotic–resistant substance that becomes a safe haven for bacterial colonization. In fact, catheter–induced bacteriuria remains the most frequent cause of gram–negative septicemia in hospitalized patients.

Diabetes: In the setting of diabetes, the elevated glucose levels in the blood may contribute to bacteriuria. In such hyperglycemic condition (> 300 mg/dL), the kidneys are unable to reabsorb all the filtered glucose. As a result, glucose is lost in the urine (glycosuria) which provides nutrients for potential infectious microbes.

Urinary tract abnormalities: Individuals may have structural and/or functional abnormalities in their urinary tract which may enhance the risk of infection. Examples include:

- **Neurogenic bladder:** Characterized by problems with bladder control in individuals with a history of underlying neurologic disorders, which may be central or peripheral. Common examples include spinal cord injury and stroke. These conditions may result in a spastic or flaccid activity of the detrusor (smooth) muscle in the bladder wall, which may manifest as urge incontinence or urinary retention, respectively. In cases of urinary retention, the lack of wash out increases risk of UTI.
- **Obstructions and Reflux:** Reflux, or the backflow of urine, is an abnormality commonly seen in individuals with a bladder outlet obstruction (e.g., pregnancy in women, BPH in men, as well as obesity). Normally, the ureters insert into the bladder at a steep angle, and parallel the bladder wall in the most distal ends of the ureter. In doing so, the bladder wall contains a mucosal flap, or a valve that maintains the one–way flow of urine. In an abnormality called **vesicoureteral reflux**, there is a backflow of urine from the bladder into the ureter. If the urine is contaminated with bacteria (bacteriuria), the reflux could propel bacteria up the ureters. Vesicoureteral reflux commonly occurs in children with congenital defects of the ureters and in adults with the aforementioned causes of bladder outlet obstruction.

Urethrovesical reflux, or the backflow of urine from the urethra into the bladder, might occur in conditions that raise the intra–abdominal pressure. Physiologic functions, such as squatting or coughing, commonly cause this type of reflux in women.

Classification

Clinically, urinary tract infections are diagnosed as lower and upper, or cystitis and pyelonephritis, respectively. Although urethritis and prostatitis are infections that involve the urinary tract, differentiating between these sites becomes difficult or impossible—particularly in children. The fact that infection often spreads from one area to the other also makes distinguishing the exact tissue infected challenging. For these reasons, the term UTI usually refers to pyelonephritis and cystitis in clinical practice.

UTIs are further classified as complicated and uncomplicated. For example, an uncomplicated cystitis might describe a lower UTI that occurs in a non–pregnant, premenopausal and otherwise healthy female. By contrast, complicated UTIs are those that occur in the presence of certain risk factors, such as pregnant or postmenopausal women and men with a known diagnosis of BPH.

Etiology

E. coli is the most common cause of UTIs. Other uropathogens include:

- **Other gram–negative bacteria**, including *Enterobacter* species (such as *Klebsiella* and *Proteus),* as well as *Pseudomonas aeruginosa*
- **Gram–positive bacteria**, such as *Staphylococcus. aureus* (i.e. MRSA), *Enterococcus faecalis*, and *Staphylococcus saprophyticus* (second most common bacterial cause of UTIs, particularly in young, otherwise healthy women)

- ***Candida* species**, fungal urinary tract infections most commonly develop in hospitalized patients with indwelling catheters, and often occur simultaneously with an active bacterial infection.

Pathogenesis

Cystitis: We will limit our discussion of the pathogenesis of cystitis to that caused by *Escherichia coli*, the most common UTI pathogen.

In catheterized patients, *E. coli* may adhere to the surface of an indwelling catheter using their many fimbriae. The catheter then serves as the point of entry enabling access to the bladder.

Having entered the bladder, *E. coli* adheres to the surfaces of epithelial cells lining the bladder wall and initiates the formation of **biofilms**, which are slimy layers composed of microbial products. Biofilm formation protects bacteria from host defenses and antibiotic treatments thus enabling growth and survival in an otherwise hostile environment.

Pyelonephritis: By definition, pyelonephritis is an upper urinary tract infection, which includes the renal tubules, interstitium and pelvis. Acute pyelonephritis commonly develops secondary to active cystitis via the ascending route, in which the same pathogen that caused cystitis flows up the ureter and colonizes in kidney tissue.

In other cases, pyelonephritis develops secondary to an acute infection outside of the genitourinary system, such as septicemia or infective endocarditis. These cases highlight examples of the hematogenous route, wherein the bacteria gains renal entry via the systemic circulation. Hematogenous route of pyelonephritis is more likely to develop in debilitated, chronically ill individuals, and those on long–term immunosuppressive therapy.

Clinical Manifestations

Listed below is the clinical spectrum of signs and symptoms that a typical acute UTI might induce:

- **Cystitis:** Dysuria, urinary frequency and urgency, suprapubic pain, and hematuria. Fever and other symptoms of systemic illness (e.g. increased CRP and ESR) suggest acute, complicated UTI in which the infection has spread beyond the bladder.
- **Pyelonephritis:** Fever, chills, flank pain, costovertebral angle tenderness, nausea and vomiting. Symptoms of cystitis are often observed but not universally present.

Note that the constellation of signs and symptoms tend to vary for each patient population. For older men, their spectrum of UTI presentation includes pelvic or perineal pain, suggesting cystitis that is likely attributed to prostatitis and/or BPH. By contrast, individuals with neurogenic bladder might present with urinary incontinence. The elderly or debilitated often present with generalized, non–specific symptoms that might suggest an infection (*e.g.*, fever and chills), but without clear manifestations that raise the suspicion of an infection localized to the urinary tract.

Diagnosis

While UTIs remain a *clinical* diagnosis (does not require laboratory workup), additional urine studies could improve the sensitivity and specificity of the diagnosis as well as help facilitate more effective treatment.

Urinalysis

- Microscopic evaluation of the urine sample might reveal **pyuria**, a marker of infection that is defined as the presence of more than five WBCs per high–power field (hpf). In addition, hematuria may be found, which is present in nearly half of cystitis cases. Finally, it is equally important to establish the (squamous) epithelial cell count as a form of quality control of the urine sample. In most practices, the presence of more than five epithelial cells per hpf is considered a contaminated specimen and that other findings in the urine sample are unreliable.
- Dipstick tests are quick, inexpensive screening tools for markers of infection. They can detect the presence of nitrites and leukocyte esterase. A positive nitrite test indicates the presence of gram–negative bacteria, which is capable of converting the endogenous nitrates into nitrites in the urine. Leukocyte esterase (LE) is an enzyme found in neutrophils and other WBCs. A positive LE test, defined as more than 10 WBCs per hpf, establishes pyuria as well.

Urine culture: The standard threshold to establish bacterial colonization that is reflective of bacteriuria is ≥ 10^5 colony forming units (CFU)/mL of urine. A Gram stain may be performed on the acquired culture in order to determine the causative bacteria in the patient with suspected UTI.

Keep in mind that these laboratory findings, in isolation, have a poor predictive value, and should not be solely relied on for the diagnosis of UTI. Each of the urine studies listed above may provide a false–positive or false–negative finding. Urine WBCs may be falsely low in patients with neutropenia or leukopenia. Likewise, the positive pyuria from either microscopy or dipstick test may be secondary to occult dehydration, acute kidney injury (AKI), sexually–transmitted infections (STI), appendicitis, or diverticulitis. Also, the negative nitrite test should not rule out nitrite–negative uropathogens, such as *P. aeruginosa*, or gram–negative species like S. saprophyticus or *enterococci.* Finally, the urine culture may also be false–negative due to recent antibiotic use.

As such, keep these laboratory findings in the context of the clinical picture—the presenting signs and symptoms, as well as the contributing risk factors unique to the patient.

Treatment

The treatment approach to individuals with UTIs include determining the need for hospitalization and/or antimicrobial therapy. In deciding an appropriate treatment plan, consider the causative pathogen for the infection, the acuity/chronicity of the infection, and aforementioned complicating factors of the patient.

Antibiotic therapy: For individuals requiring an empiric antibiotic therapy, always refer to the antibiogram specific to the facility. Due to the widespread and increasing pattern of antibiotic resistance, it is paramount to first understand local resistance patterns to various antibiotic agents. Below are two antibiotic drugs commonly used in the management of UTIs.

Trimethoprim/sulfamethoxazole (Bactrim, Septra) is a combination of two antibiotic drugs: trimethoprim and sulfamethoxazole, both of which interfere with the bacteria's ability to produce folate. Folate is essential for the production of nucleic acids needed to generate new cells. While we can obtain enough folate from our diet, bacteria must produce their own folate. These antibiotics concentrate in the urine and inhibit enzymes that are necessary for the bacteria to convert PABA into folate.

Ciprofloxacin (Cipro) is an antibiotic that belongs to the fluoroquinolone ("quinolone") class. Ciprofloxacin has good gram–negative coverage, which makes it useful in the treatment of UTIs. Its mechanism involves the inhibition of the bacterial DNA gyrase (topoisomerase), an enzyme necessary for bacterial replication.

Other medications/remedies

Phenazopyridine (Pyridium OTC) is an expensive, over–the–counter medication that may help alleviate the dysuria, irritation, and urinary urgency associated with UTIs. Phenazopyridine often causes a discoloration of urine, which may appear dark orange or reddish.

Cranberry / blueberry juice has been suggested to help prevent/treat UTIs, however evidence is conflicting as to whether it is beneficial to treat cystitis. There is some evidence that these products may help resist bacterial attachment to the bladder wall, but there is no evidence that this can cure a raging UTI or prevent one if a person is high risk.