**College of Pharmacy**

 **Fourth year. Clinical Pharmacy**

 **Infectious Diseases**

 **Urinary Tract Infections**

**Introduction**

1-Infections of the urinary tract represent a wide variety of clinical syndromes including **urethritis**, **cystitis**, **prostatitis**, and **pyelonephritis**.

2-**A urinary tract infection (UTI)** is defined as the **presence of microorganisms** in the urine that **cannot be accounted for by contamination**.

3-**Lower tract infections** include **cystitis** (bladder), **urethritis** (urethra), **prostatitis** (prostate gland), and **epididymitis**.

4-**Upper tract infections** involve the **kidney** and are referred to as **pyelonephritis**.

5-**Uncomplicated UTIs** are **not associated with structural or functional abnormalities** that may interfere with the normal flow of urine or the voiding mechanism.

6-**Complicated UTIs** are the **result of a predisposing lesion of the urinary tract**, such as an abnormality of the urinary tract, stone, indwelling catheter, prostatic hypertrophy, obstruction, or neurologic deficit that interferes with the normal flow of urine and urinary tract defenses.

7-**Recurrent UTIs**, **two or more UTIs occurring within 6 months** or **three or more within 1 year,** are characterized by multiple symptomatic episodes with asymptomatic periods occurring between these episodes.

8-These infections are due to **reinfection** or to **relapse**. **Reinfections** are caused by a **different organism** and account for the majority of recurrent UTIs. **Relapse** represents the development of **repeated infections caused by the same initial organism**.

**Pathophysiology**

1-The bacteria causing UTIs usually originate from bowel flora of the host. Organisms typically gain entry into the urinary tract via **three routes**: the **ascending**, **hematogenous** (**descending**), and **lymphatic pathways**.

2-The most common cause of **uncomplicated UTIs is E. coli**, accounting for more than 80%–90% of community-acquired infections.

3-**Additional causative organisms are** Staphylococcus saprophyticus, Klebsiella pneumoniae, Proteus spp., Pseudomonas aeruginosa, and Enterococcus spp.

4-The urinary pathogens in **complicated or nosocomial infections** may include E**. coli**, which accounts for **less than 50% of these infections**, Proteus spp., K. pneumoniae, Enterobacter spp., P. aeruginosa, staphylococci, and enterococci. **Enterococci represent the second most frequently isolated organisms in hospitalized patients.**

5-**Most UTIs are caused by a single organism**; however, in patients with stones, indwelling urinary catheters, or chronic renal abscesses, **multiple organisms may be isolated.**

**Clinical presentation**

1-The typical signs and symptoms of urinary tract infections are:

* **Lower UTI**: Dysuria, urgency, frequency, nocturia, and suprapubic heaviness, gross hematuria, and costovertebral tenderness.
* **Upper UTI**: Flank pain, fever, nausea, vomiting, and malaise.

2-**Symptoms alone are unreliable for the diagnosis of bacterial UTIs**. The key to the diagnosis of a UTI is the ability to demonstrate significant numbers of microorganisms present in urine specimen.

3-**Older patients frequently do not experience specific urinary symptoms**, but they will present with altered mental status, change in eating habits, or gastrointestinal (GI) symptoms.

4-The presence of **pyuria in a symptomatic patient** correlates with **significant bacteriuria**.

5-The **most reliable** method of diagnosing UTIs is by **quantitative urine culture**.

**Treatment**

**Goals of Treatment**:

1-Eradicate the invading organisms, prevent or treat systemic consequences of infection, prevent recurrence of infection, and decrease the potential for collateral damage with excessively broad antimicrobial therapy.

2-The initial selection of an antimicrobial agent for the treatment of UTI is primarily based on the **severity of the presenting signs and symptoms**, the **site** **of infection**, and whether the infection is determined to be **complicated** or **uncomplicated**.

3-Other considerations include **antibiotic susceptibility**, **side-effect potential**, **cost**, current **antimicrobial exposure**, and the comparative **inconvenience of different therapies**.

**Pharmacologic Therapy**

1-Eradication of bacteria from the urinary tract is directly related to the **sensitivity** of the **organism** and the **achievable concentration** of the antimicrobial agent in the **urine**.

2-Most E. coli remain susceptible to trimethoprim–sulfamethoxazole, although resistance is increasing. In light of rising resistance and in order to decrease the overuse of broad-spectrum antimicrobials, **agents such as nitrofurantoin and fosfomycin are now considered first-line treatments along with trimethoprim–sulfamethoxazole in acute uncomplicated cystitis.**

3-**Table 1** presents an overview of various therapeutic options for outpatient therapy for UTI. **Table 2** describes empiric treatment regimens for specific clinical situations.

**Table 1: Overview of Outpatient Antimicrobial Therapy for Lower Tract Infections in Adults**





**a** Dosing intervals for normal renal function. **DS**, double strength; **SS**, single strength.

**Table 2: Evidence-Based Empirical Treatment of UTIs and Prostatitis**









**Acute Uncomplicated Cystitis**

1-These infections are **predominantly caused by E. coli**, and antimicrobial therapy should be directed against this organism initially.

2-Because the causative organisms and their susceptibilities are **generally known**, a cost-effective approach to management is recommended that includes **a urinalysis and initiation of empiric therapy without a urine culture.**

3-**Short-course** therapy **(3-day therapy)** with trimethoprim–sulfamethoxazole or a fluoroquinolone (eg, ciprofloxacin or levofloxacin, but not moxifloxacin) **is superior to single-dose therapy for uncomplicated infection.**

4-**Fluoroquinolones** should be reserved for patients with suspected or possible **pyelonephritis due to the collateral damage risk**. Instead, a 3-day course of trimethoprim–sulfamethoxazole, a 5-day course of nitrofurantoin, or a **one-time dose of fosfomycin** should be considered as first-line therapy.

5-In areas where there is more than 20% resistance of E. coli to **trimethoprim**–**sulfamethoxazole**, **nitrofurantoin or fosfomycin** **should be utilized**. **Amoxicillin or ampicillin is not recommended** because of the high incidence of resistant E. coli. Follow-up urine cultures are not necessary in patients who respond..

**Complicated Urinary Tract Infections**

**Acute Pyelonephritis**

1-The presentation of **high-grade fever** (>38.3°C) and severe flank pain should be treated as acute pyelonephritis, and aggressive management is warranted.

2-**Severely ill p**atients with **pyelonephritis** should be h**ospitalized and IV drugs administered initially.** **Milder cases may be managed with oral antibiotics in an outpatient setting.**

3-At the **time of presentation**, a **Gram stain** **of the urine** should be performed, along with urinalysis, culture, and sensitivities.

4-In the **mild to moderately symptomatic patient** for whom **oral therapy** is considered, an effective agent should be administered **for 7–14 days**, depending on the agent used.

5-**Fluoroquinolones** (ciprofloxacin or levofloxacin) **orally for 7–10 days** are the **first-line choice in mild-tomoderate pyelonephritis**. Other options include trimethoprim–sulfamethoxazole for 14 days.

6-If a Gram stain reveals **gram-positive cocci**, **Streptococcus faecalis** **should be considered** and treatment directed against this pathogen (**ampicillin**).

7-In **the seriously ill patient**, the traditional initial therapy is **an IV fluoroquinolone**, an aminoglycoside with or without ampicillin, or an extended spectrum cephalosporin with or without an aminoglycoside.

8-If the patient has been **hospitalized in the last 6 months, has a urinary catheter, or is in a nursing home,** **the possibility of P. aeruginosa and enterococci infection, as well as multiple-resistant organisms, should be considered.** In this setting, ceftazidime, ticarcillin–clavulanic acid, piperacillin, aztreonam, meropenem, or imipenem, in combination with an aminoglycoside, is recommended. **If the patient responds to initial combination therapy, the aminoglycoside may be discontinued after 3 days**.

9-**Follow-up urine cultures** should be **obtained 2 weeks after the completion of therapy** to ensure a satisfactory response and to detect possible relapse.

**Urinary Tract Infections in Men**

1-**Therapy in men requires prolonged treatment**. A **urine culture should be obtained before treatment**, because the cause of infection in men is not as predictable as in women.

2-If **gram-negative bacteria are presumed**, **trimethoprim–sulfamethoxazole or a fluoroquinolone is a preferred agent**. Initial therapy is for **10–14 days.**

3-For **recurrent infections in men**, cure rates are much higher with **a 6-week regimen of trimethoprim–sulfamethoxazole.**

**Recurrent Infections**

1-Recurrent episodes of UTI (reinfections and relapses) **account for a significant portion** of all UTIs.

2-These patients are most **commonly women** and can be divided into **two groups**: those **with fewer than two or three episodes per year** and those who develop **more frequent infections.**

3-In patients with **infrequent infections** (ie, fewer than three infections per year), **each episode should be treated as a separately occurring infection.** Short-course therapy should be used in symptomatic female patients with lower tract infection.

4-In patients who have **frequent symptomatic infections**, **long-term prophylactic antimicrobial therapy may be instituted**. Therapy is **generally given for 6 months**, with urine cultures followed **monthly**.

5-In women who experience **symptomatic reinfections in association with sexual activity**, **voiding after intercourse** may help prevent infection. Also, **self-administered, single-dose prophylactic therapy with trimethoprim–sulfamethoxazole** taken after intercourse significantly reduces the incidence of recurrent infection in these patients.

6-Women who **relapse after short-course therapy** **should receive a 2-week course** of therapy.

7-In patients **who relapse after 2 weeks**, therapy should be c**ontinued for another 2–4 weeks.**

8-If **relapse occurs after 6 weeks of treatment**, **urologic examination** should be performed, and **therapy for 6 months or even longer may be considered**.

**Special conditions**

**Urinary Tract Infection in Pregnancy**

1-In patients with **significant bacteriuria**, **symptomatic or asymptomatic** **treatment is recommended** to avoid possible complications during the pregnancy.

2-Therapy should consist of an **agent with a relatively low adverse-effect potential** (cephalexin, amoxicillin, or amoxicillin/clavulanate) administered for **7 days**.

3-**Tetracyclines** should be **avoided** because of teratogenic effects and **sulfonamides** should **not be administered during the third trimester** because of the possible development of kernicterus and hyperbilirubinemia. Also, the **fluoroquinolones should not be given** because of their potential to inhibit cartilage and bone development in the newborn.

**Catheterized Patients**

1-When **bacteriuria occurs in asymptomatic**, short-term catheterized patients **(<30 days**), the use of **systemic antibiotic therapy should be withheld** and the **catheter removed** as soon as possible. If the patient becomes **symptomatic**, the **catheter should again be removed**, and **treatment as described for complicated infections should be started.**

2-The use of **prophylactic systemic antibiotics** in patients with short-term catheterization reduces the incidence of infection over the first 4–7 days.

3-In **long-term catheterized patients**, however, antibiotics only postpone the development of bacteriuria and lead to emergence of resistant organisms.

**Reference**: **Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Edition. 2021.**