

URINARY TRACT INFECTION

Abstract

Urinary tract infection (UTIs) is one of the commonest infection affecting humans especially females. The most causative agent of both complicated and uncomplicated UTIs are *E.coli Klebsiella spp*, *Proteus spp*, *Staphylococcus aureus*, *Enterococcus spp*, *Candida spp*. The predisposing factors plays an important role in developing infections. Frequency, dysuria and urgency are the symptoms of lower UTI but fever, systemic manifestation are also seen in upper UTI. Correct identification of etiological agent is important for treatment and preventing the drug resistance.

Keywords: Urinary tract infection, Significant bacteriuria, complicated and uncomplicated UTI

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I. INTRODUCTION

A microbial invasion of the urinary system, which runs from the renal cortex of the kidney to the urethral meatus, results in urinary tract infections (UTIs), the most prevalent disease affecting humans, primarily women. UTIs include pyelonephritis (infection of kidney/upper urinary tract), cystitis (infection of bladder/lower urinary tract), proctitis.

Complicated UTIs are symptomatic disease in a man or woman with an anatomical abnormalities or instrumentation of urinary tract or with any predisposing factors. Uncomplicated UTIs refers to acute disease in non pregnant outpatient women without any underlying abnormalities or instruments of urinary tract.

II. CLASSIFICATION

UTIs are classified into two types depending upon the anatomical sites involved, upper UTI and lower UTI.

Table 1: Upper and lower UTI

| | Upper UTI | Lower UTI |
|-----------------|--------------------------------|-----------------------------|
| Anatomical site | Kidney, ureter | Bladder, urethra |
| Symptoms | Local, systemic manifestations | Urgency, frequency, dysuria |
| Route | Both descending and ascending | Ascending |
| Frequency | Less common | Common |

1. **Health Care Associated Urinary Tract Infection:** Infection developing in a patient after two days of placing indwelling urinary catheter
2. **Catheter associated bacteriuria (CA-bacteriuria)-** presence of significant bacteriuria in a catheterized patient. It is classified into catheter associated UTI (CAUTI)- CA bacteriuria with symptoms and catheter associated asymptomatic bacteriuria (CA-ASB)- CA bacteriuria without symptoms or signs.

III. EPIDEMIOLOGY

Urinary tract infection is most frequent bacterial infection and fifth most common type in health care associated infection. It is predominantly seen in female. About 12-16% of hospitalized patients will have an indwelling urinary catheter and the 3-7% of risk is increased in acquiring CAUTI. Complications associated with CAUTI increase the hospital stay, cost and mortality.

IV. ETIOLOGY

Uropathogenic *Escherichia coli* is the most common organism responsible for causing 70-80% of UTI. Other gram negative organisms such as *Klebsiella*, *Proteus* and gram positive organisms including *Staphylococcus* and *Enterococcus* are also important agent. Parasites and viruses are not associated with UTI. Among fungi, *Candida albicans* is frequent cause of UTI.

Table 2: Common Organisms Associated with UTIs

| Bacterial Agents | Other agents |
|--|---|
| Gram negative bacilli <i>E.coli</i> <i>Klebsiella spp</i> <i>Citrobacter, Enterobacter</i> <i>Proteus spp</i> <i>Pseudomonas spp</i> <i>Acinetobacter spp</i> | Fungus <i>Candida albicans</i> Parasites <i>Schistosoma hematobium</i> <i>Trichomonas vaginalis</i> |
| Gram positive cocci <i>Staphylococcus aureus</i> <i>S.saprophyticus</i> <i>Enterococcus spp</i> | Viruses Adenovirus JC and BK virus Herpes simplex virus |

Bacteria responsible for causing CAUTI are of mostly multi drug resistant. **In short term catheterized patients**, it is of monomicrobial pathogens and in long term catheterized patients, it is of polymicrobial pathogens including gram positive and gram negative organisms. *Candida spp* is also commonly associated with CAUTI.

V. PRE DISPOSING FACTOR

UTI is prevalent affecting 10% of people at some point in their life.

- **Gender:** UTI affects women more often than men. The short urethra and close proximity of the urethral meatus to the anus, which are features of the female urogenital system contribute to the problem. Sexual intercourse facilitates the entry of bacteria into female urethra. Almost 50% of women acquire UTI at least once at some point in their lifetime.
- **Age:** The prevalence is common in both the genders during the first year of their life. After that the incidence decreases for males and again during their old age, the prevalence increases due to the prostate enlargement, which prevents the bladder from emptying completely. In contrast, the incidence increases for female and reinfection is also commonly seen, sometimes even within one year.
- **Pregnancy:** Changes in anatomy and hormonal balance during pregnancy favour the growth of UTIs. During pregnancy, many of women experience asymptomatic bacteriuria, which can occasionally cause life threatening illness.
- **Anomalies of the Urinary's Tract Structure and Function** can cause urine stasis, which

increases the risk of infection by obstructing urine flow. When the normal valve like mechanism at the vesiculoureteric junction is weakened, urine can flow back in to the ureters and occasionally even upto renal pelvis (**Vesicoureteral reflux**).

- **Bacterial Virulence** pili present in few bacteria helps in adhesion to uroepithelium
- **Genetic Factors** Receptors present in many individuals present on uroepithelial cells favors the attachment of bacteria. The gram negative bacteria is the most commonest organisms causing UTI which leads to urosepsis especially in hospitalized patients. Nosocomial UTIs occurs mainly because of the presence of urinary catheters.

VI. PATHOGENESIS

The Urinary tract can be infected by either ascending or descending route. The most frequent route is **ascending route** where endogenous bacteria enters the urinary tract by sexual intercourse or instrumentation. Bacteria has virulence factors mainly fimbriae (p and mannose resistant fimbriae) in *Escherichia coli* helps in adhesion to urethral epithelium which leads to colonization. Bacterial toxins facilitates the ascension by inhibiting peristalsis causing cystitis. Further ascension occurs when there is vesico ureteric reflux which results in pyelonephritis. Tubular obstruction and damage occurs due to the inflammatory cascade leading to interstitial nephritis.

Hematogenous seedling of pathogens leads to bacteremia results in invasion of renal parenchyma called as **descending route**. Certain organisms (*S.aureus*, *Salmonella*, *M.tuberculosis*, *Leptospira* and *Candida*) are invasive and are frequently associated with pyelonephritis indicates the origin of descending route. However the most of the infections affecting kidney are by ascending route.

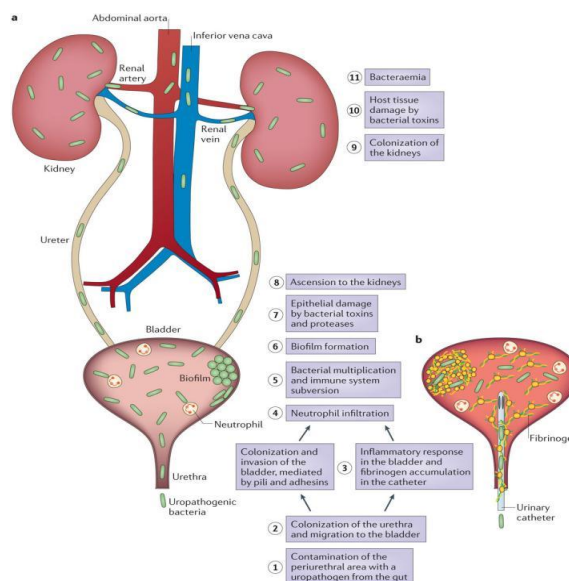


Figure 1: Pathogenesis of Urinary Tract Infections

Source: Nature Reviews Microbiology

- 1. Uncomplicated Urinary Tract Infection (UTI):** When uropathogens from the gut infect the periurethral region (step 1) and are able to colonise the urethra. Subsequent migration to the bladder (step 2) The invasion and colonisation of the superficial umbrella cells occur by the expression of pili and adhesins (step 3). Clearance of extracellular microorganisms is started by host inflammatory responses, including neutrophil infiltration (step 4). Some bacteria multiply (step 5) and build biofilms (step 6) in order to elude the immune system, either by host cell invasion or through morphological changes that make them resistant to neutrophils. The host cells are damaged by the toxins and proteases (step 7), which then releases vital nutrients that encourage bacterial survival and ascent to the kidneys (step 8). Kidney colonization (step 9) results in bacterial toxin production and host tissue damage (step 10). If left untreated, UTIs can ultimately progress to bacteraemia if the pathogen crosses the tubular epithelial barrier in the kidneys.
- 2. Complicated Urinary Tract Infection (UTI):** The same steps similar to uncomplicated infections are followed by uropathogens including periurethral colonisation (step 1), advancement to the urethra, and migration to the bladder (step 2). The bladder must be weakened for the pathogen for invasion. Catheterization is important factor for compromised bladder. Because catheterization triggers a strong immune response (step 3), fibrinogen builds up on the catheter, creating the perfect habitat for uropathogens that express fibrinogen-binding proteins to attach and neutrophil infiltration (step 4). The bacteria grow (step 5), build biofilms (step 6), cause epithelial damage (step 7), and can cause infection of the kidneys (steps 8 and 9). Toxin production induces tissue damage (step 10). If left untreated, uropathogens that cause complicated UTIs can also progress to bacteraemia by crossing the tubular epithelial cell barrier (step 11).
- 3. Host Factors:** An key factor in preventing UTIs is host defence mechanisms and classified into urinary factors and mucosal immunity. Urinary factors includes acidic urine and high urine osmolality which inhibits pathogens, urine flow of mechanism flushing. Mucosal immunity offers the secretaion of cytokines by uroepithelial cells, presence of mucosal IgA prevents the attachment of pathigens to uroepithelium. Tamm-Horsfall protein secreted by epithelial cells of kidney binds to type I fimbriae of *E.coli* acts a an anti-adherence factor. The presence of long urethra in men and zinc in prostatic secretion acts as bactericidal thereby it prevents the development of UTI.

In catheterized patients, microorganisms enter the urinary tract either by extraluminal or intraluminal surface of the catheter through four main entry points. Extraluminal spread is through patients endogenous flora, hands of health care personnel or inanimate objects. If asepsis is not maintained at the time of insertion or maintenance of catheter, risk of migration of bacteria is highly possible. Presence of urinary catheter itself is a risk because flushing of urethral flora is disturbed which leads to migration of flora into the bladder results in colonization and subsequent infection. Intraluminal spread happens when the drainage bag is through open type or when closed system is breached leads to reflux of contaminated urine from urinary bag.

VII. CLINICAL MANIFESTATIONS

The clinical manifestations of UTI can exist in various forms.

1. **Asymptomatic UTI** refers to isolation of significant bacteriuria but the patient has no local or systemic symptoms related to urinary tract. This is significant in a group of people including pregnant women, those undergoing prostatic surgery or people undergoing any urological procedure. Hence the treatment for asymptomatic UTI in these patients are highly recommended. Asymptomatic UTI, on the other hand is not clinically relevant in non pregnant women, elderly or premenopausal women
2. **Lower UTI:**
 - **Cystitis** presents with frequency, dysuria, urgency, and suprapubic tenderness. It is not associated with systemic manifestations. In some rare cases, hematuria is seen.
 - **Acute urethral syndrome:** Symptoms are similar to lower UTI and it is commonly occurs in young sexually active women. Pyuria is present with bacterial count is often low. It is majorly caused by the common etiological agent of UTI and rarely by gonococcus, *Chlamydia*, herpes simplex virus.
 - **Upper UTI/Pyelonephritis:**
 - Fever, chills, lower back discomfort or pain in the costovertebral angle, nausea and vomiting are the common symptoms.
 - Patients with obstruction, diabetes, sickle cell disease, or analgesic nephropathy frequently exhibit papillary necrosis.
 - Emphysematous pyelonephritis is a serious condition that most usually affects diabetic patients and produce gas in the perinephric and renal tissues.
 - When there is a persistent urinary obstruction, which results in the suppurative destruction of renal tissue, xanthogranulomatous pyelonephritis also develops.
 - **Prostatitis** present as urgency, dysuria, frequency, fever, bladder obstruction, pain in the prostate, pelvic or perineal area. Vaginitis in women and prostatitis in men can cause similar symptoms but can be differentiated clinically.
 - **Recurrent UTI infection** refers to acute cystitis with 2 episodes in 6 months or 3 episodes in 12 months. It is more common in female.

VIII. LABORATORY DIAGNOSIS

The normal urinary tract is devoid of any bacteria except urethral mucosa. Thus the urine can easily become contaminated with bacteria from vaginal canal, perineum or urethra. The normal flora and possible pathogens are given in the table 2.

| Commensal | Possible pathogens |
|----------------------------------|---|
| Diphtheroids | <i>Enterobacteriaceae</i> |
| <i>Lactobacillus spp</i> | <i>Staphylococcus aureus</i> |
| Coagulase negative staphylococci | <i>Staphylococcus epidermidis</i> (elderly men) |
| α -hemolytic streptococci | <i>Staphylococcus saprophyticus</i> (young women) |
| <i>Bacillus spp</i> | <i>Enterococcus spp</i> |
| | <i>Pseudomonas spp</i> |
| | <i>Acinetobacter spp</i> |
| | <i>Corynebacterium urealyticum</i> |

1. Specimen Collection: Urine samples are collected by mid stream flow by clean catch technique. The following instructions should be given to women about the sample collection. First two or three gauze pads soaked with soapy water are used in a forward to back motion to clean the periurethral region and the perineum before being rinsed with sterile saline or water. To remove bacteria from urethra, the labia should be held apart while voiding and the few millilitres of urine should be passed into a bedpan or toilet bowl. After that the midstream urine is collected in a clean, wide mouth container. Men only need to clean their urethral meatus before midstream collection; no soapy water preparation is essential.

Suprapubic aspirations are done for neonates and children. The procedure is performed when bladder is full, suprapubic skin covers the bladder is disinfected and sterile drapes are then put on. In the immediate area where aspiration is to be performed, a subcutaneous injection of an anaesthetic solution (1% lidocaine HCl) is administered. A 10mL of urine is aspirated into the syringe using a short bevel spinal needle that has been extended into the bladder. This technique is invasive and is rarely done.

The catheter tube should be used to collect urine; the uro bag should not be used. To wash off any microorganisms that might have trapped in the catheter tip during transit through the urethra, the first few millilitres of urine from the catheter tip should be discarded. Urine samples from indwelling catheters are not recommended since it is not possible to differentiate the bacteria that have colonized the catheter from potential pathogens.

- 2. Transport and Storage:** Urine sample can refrigerate at 4-6°C and when delay in transportation of urine is anticipated for more than 2 hours boric acid can be added.
- 3. Screening tests for Bacteriuria**
- **Direct examination Wet mount examination** is done to demonstrate pus cells in urine. Significant pyuria is defined as having >8pus cells/mm³.
 - **Leukocyte esterase test** leukocyte esterase is an enzyme produced by pus cells in urine and a strip method is used to detect the enzyme, which is a rapid and cheaper method

- **Nitrate Reduction Test (Griess test)** Reagent impregnated dipstick designed to detect the urine nitrite
- **Gram Staining** presence of one organism/oil immersion field is considered as significant. It is useful in pyelonephritis and invasive cases of UTI. Use of Gram staining is limited when bacterial count is low and teh pus cells are deteriorated.
- **Culture** The gold standard for diagnosing UTIs is the detection of significant bacteria in the urine culture.
- **Quantitative Culture** Calibrated loop method (semi-quantitative method) and pour plate method (quantitative method) is used to count the number of colonies. Urine sample is inoculated into MacConkey agar and blood agar or single medium such as CLED agar (cysteine lactose electrolyte deficient agar) can be used.
- **Kass Concept of Significant Bacteriuria** Significant bacteriuria is defined as colony count of $>10^5$ colony forming units/mL (CFU/mL). Count between 10^4 - 10^5 CFU/mL is considered as probable significant and should be clinically correlated. Less than $<10^4$ CFU/mL is considered as no significant bacteriuria.

Low count is sometimes considered as significant among the patient on antibiotic or diuretic therapy, pyelonephritis, acute urethral syndrome, suprapubic aspiration sample.conditions.

Table 3: Identification

| Organisms | Gram staining-culture smear | Culture | Biochemical reaction |
|-----------------------------|-----------------------------|---|---|
| <i>Escherichia coli</i> | Gram negative bacilli | BA: gray moist colonies CLED or Mac: flat lactose fermenting colonies | Catalase positive, ICUT test: I ⁺ C ⁻ U ⁻ TSI A/A gas+ H ₂ S ⁻ , Motile |
| <i>Klebsiella species</i> | Gram negative bacilli | BA: gray mucoid colonies CLED or Mac: mucoid lactose fermenting colonies | Catalase positive, ICUT test: I ^{-/+} C ⁺ U ⁺ TSI A/A gas+ H ₂ S ⁻ , Non Motile |
| <i>Citrobacter species</i> | Gram negative bacilli | BA: gray mucoid colonies CLED or Mac: mucoid lactose fermenting colonies | Catalase positive, ICUT test: I ^{+/-} C ⁺ U ⁻ TSI A/A or K/A gas+ H ₂ S ^{-/+} , Motile |
| <i>Enterobacter species</i> | Gram negative bacilli | BA: gray mucoid colonies CLED or Mac: mucoid lactose fermenting colonies | Catalase positive, ICUT test: I ⁻ C ⁺ U ⁻ TSI A/A gas+ H ₂ S ⁻ , Motile |

| | | | |
|-------------------------------------|--|--|--|
| <i>Proteus species</i> | Gram negative bacilli | BA: swarming growth CLED or Mac: Non lactose fermenting colonies | Catalase positive, oxidase negative, ICUT test: I ^{+/-} C ^{+/-} U ⁺ TSI K/A gas ^{+/-} H ₂ S ⁺ , PPA positive, Motile |
| <i>Acinetobacter species</i> | Gram negative bacilli | BA: gray colonies CLED or Mac: Non lactose fermenting colonies | Catalase positive, oxidase negative, ICUT test: I ⁻ C ^{+/-} U ⁻ TSI K/K gas ⁻ H ₂ S ⁻ , Non Motile |
| <i>Pseudomonas species</i> | Gram negative bacilli | BA: gray colonies CLED or Mac: Non lactose fermenting colonies | Catalase positive, oxidase positive, ICUT test: I ⁻ C ⁺ U ⁻ TSI K/K gas ⁻ H ₂ S ⁻ , Motile |
| <i>Staphylococcus aureus</i> | Gram positive cocci in clusters | BA: Golden yellow colonies | Catalase positive, coagulase positive |
| <i>Staphylococcus saprophyticus</i> | Gram positive cocci in clusters | BA: White non hemolytic colonies | Catalase positive, coagulase negative, resistant to novobiocin |
| <i>Enterococcus</i> | Gram positive cocci in pairs or short chains | BA: Translucent non hemolytic colonies Mac: Magenta pink colonies | Bile aesculin test positive |

Abbreviations: CLED- cysteine lactose electrolyte deficient agar, Mac- MacConkey agar, BA- Blood agar, I- indole test, C- Citrate test, U- urease test, T- triple sugar iron agar test, A/A Acid/Acid; K/A alkaline/Acid; K/K Alkaline/Alkaline, H₂S hydrogen sulphide, PPA- phenylalanine deaminase

- 4. Antimicrobial Susceptibility Testing:** It is done by conventional method (disk diffusion) or MIC method by VITEK identification.

IX. TREATMENT

Treatment depends on the antimicrobial susceptibility testing. Nitrofurantoin, cotrimoxazole, fosfomycin and quinolones are the preferred drugs. Beta lactum agents with inhibitors or carbapenems are used for resistant organisms which is frequently associated with health care associated infections.

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