A REVIEW ON URINARY TRACT INFECTION

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ABSTRACT

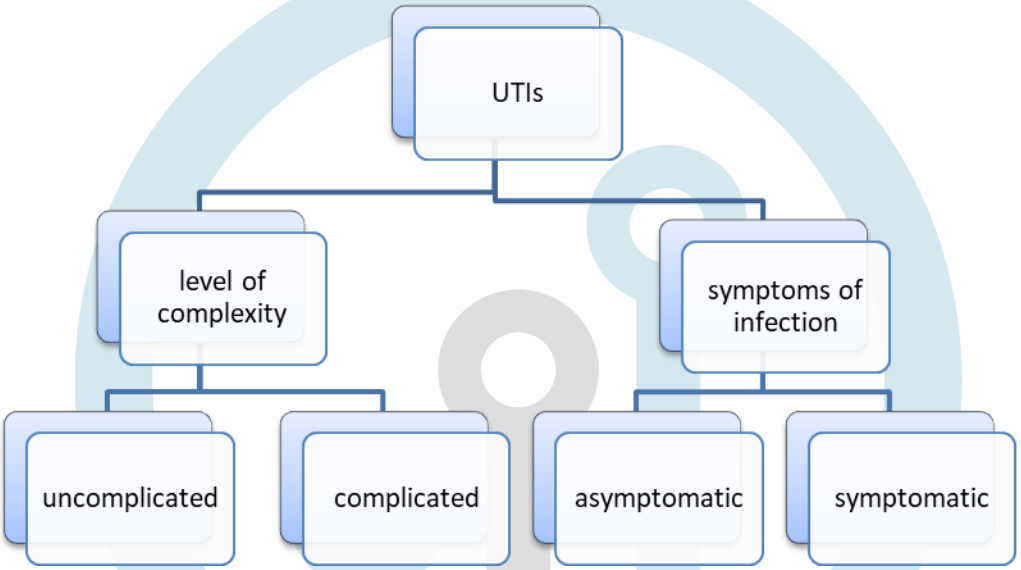
Urinary tract infections (UTIs) are highly prevalent microbial diseases that can affect individuals across all ages and sexes, typically involving inflammation of the urinary tract. Their severity ranges from mild forms such as cystitis, or bladder infection, to critical and potentially fatal conditions like uroseptic shock. UTIs are the most frequent cause for which antibiotics are prescribed after medical consultations. While they may cause discomfort, they can also escalate into serious health concerns. Research indicates that around 12% of males and up to 40% of females will experience at least one symptomatic UTI during their lifetime. A significant difficulty in managing UTIs lies in diagnostic errors, which contribute to misuse of antibiotics, delayed treatment, and poorer outcomes in septic situations. Consequently, early and accurate diagnosis, along with appropriate antibiotic therapy, is essential to avoid complications such as urosepsis. This review outlines the common symptoms and risk factors of UTIs, examines conventional and modern diagnostic approaches, and evaluates available treatment strategies with or without antibiotic use.

❖ Introduction-

Urinary tract infections are difficult Health issues around the world. Anatomical or functional defects are the most frequent causes of infections. All people, male or female, young or old, are susceptible to these illnesses. This occurs as a result of the urethra acting as both an entrance for bacteria into the urinary tract and a channel for urine to exit. In both men and women, the bacteria typically form colonies near the urinary tract opening. Usually, when you urinate, they are rinsed out. When these colonies enter the bladder prior to urination and are not removed by pee, infections result. Women are more likely than men to get UTIs, and 81% of all UTIs are documented in women. [1]

Depending on the infection site and the host's health, UTIs are frequently divided into lower or upper, difficult and simple subtypes. Higher UTIs impact the kidneys and ureters, as in pyelonephritis, whereas lesser UTIs impact the bladder and urethra. Moreover, straightforward UTIs are urinary tract infections that are anatomically or functionally normal. All cases that are not uncomplicated UTIs, However, are considered difficult UTIs.[2]

❖ Classification-



1. Level of complexity-

i. Complicated UTIs

An infection that has a higher chance of not responding to therapy is known as a complicated UTI. To ensure appropriate therapy, these infections frequently need longer treatment durations, different medicines, and occasionally extra diagnostic investigations, thus proper identification is essential. A complicated urinary tract infection (UTI) refers to any UTI that is not classified as simple, as previously described. As such, any UTIs occurring in immune compromised individuals, males, pregnant women, or those accompanied by fever, kidney stones, sepsis, urinary blockages, catheters, or affecting the kidneys are classified as complicated infections.[3,4,5]

Examples of a complicated UTI include:

- Atypical organisms causing UTI.
- Recurrent infections despite adequate treatment (multidrug-resistant organisms).
- Infections occurring in pregnancy (including asymptomatic bacteriuria).
- Infections in renal transplant and spinal cord injury patients.
- Infections in patients with impaired renal function, dialysis, or anuria.
- Infections following surgical prostatectomies or radiotherapy.

ii. Uncomplicated UTIs

The bladder and associated structures may become infected with bacteria during an uncomplicated urinary tract infection (UTI). This condition typically impacts individuals without urinary tract abnormalities or additional factors such as diabetes, weakened immune systems, recent urological procedures, or pregnancy. An uncomplicated UTI is also referred to as a lower tract UTI or cystitis.

Although patients frequently seek therapy for symptom relief, many simple UTIs cure on their own without medication. The goal of treatment is to stop the infection from becoming more widespread or developing into an upper tract condition like pyelonephritis, which can harm sensitive nephron tissues and ultimately result in consequences like hypertension.[6,7,8]

2. Symptoms of infection

i. Asymptomatic UTIs

Asymptomatic bacteriuria, defined as the presence of bacteria in the urine in the absence of urinary symptoms, is a common clinical finding that often warrants a decision about whether to initiate antimicrobial therapy. The term "asymptomatic urinary tract infection" (UTI) is frequently used to describe bacteriuria . There has been a great deal of debate on how best to treat bacteriuria. But the data from clinical studies conducted over the last three decades is enough to back up management recommendations for the majority of populations. The best strategy differs for every patient group.

ii. symptomatic UTIs

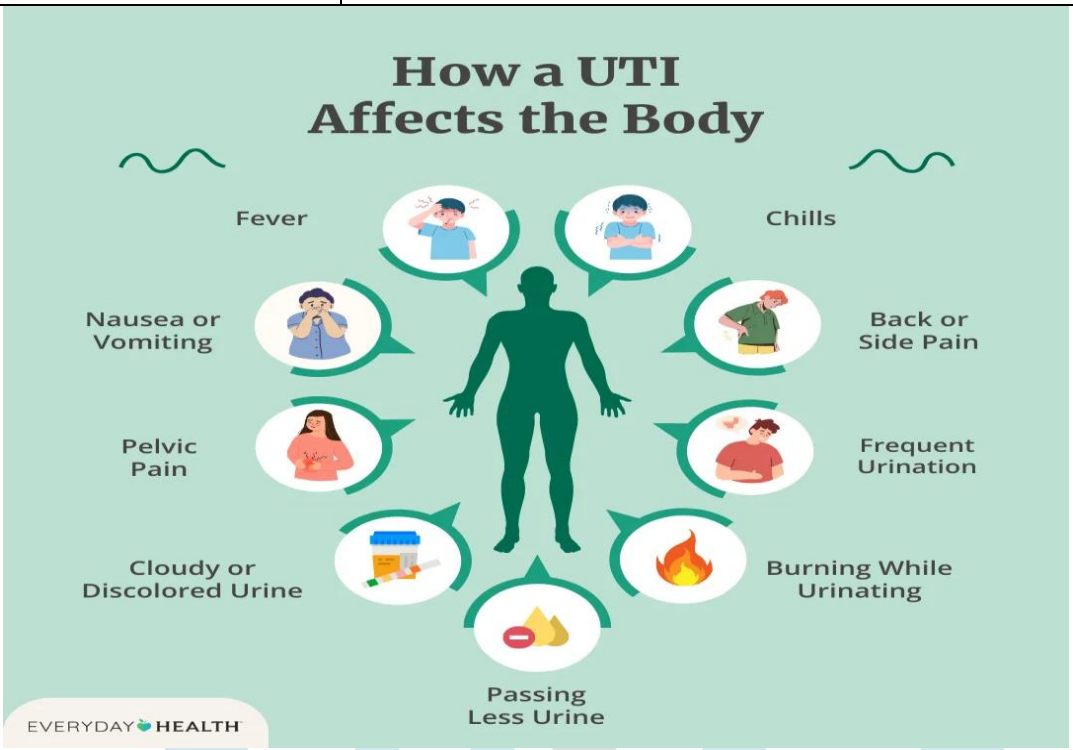
Individuals with symptomatic UTIs may experience symptoms such as a sudden increase in the frequency of urination and dysuria, along with burning sensations in the urethra while urinating, debilitating pubic pain in women, and feelings of pressure or pain in the rectum for men during and after urination. There can also be an unpleasant smell, cloudy urine, and visible blood in the urine. If the infection worsens, it can spread to the kidneys and uterus, leading to back pain, chills, fever, nausea, and vomiting.[9,10,11]

- **Commom symptoms in urinary tract infection -**

Table 1 : Common symptom in UTIs

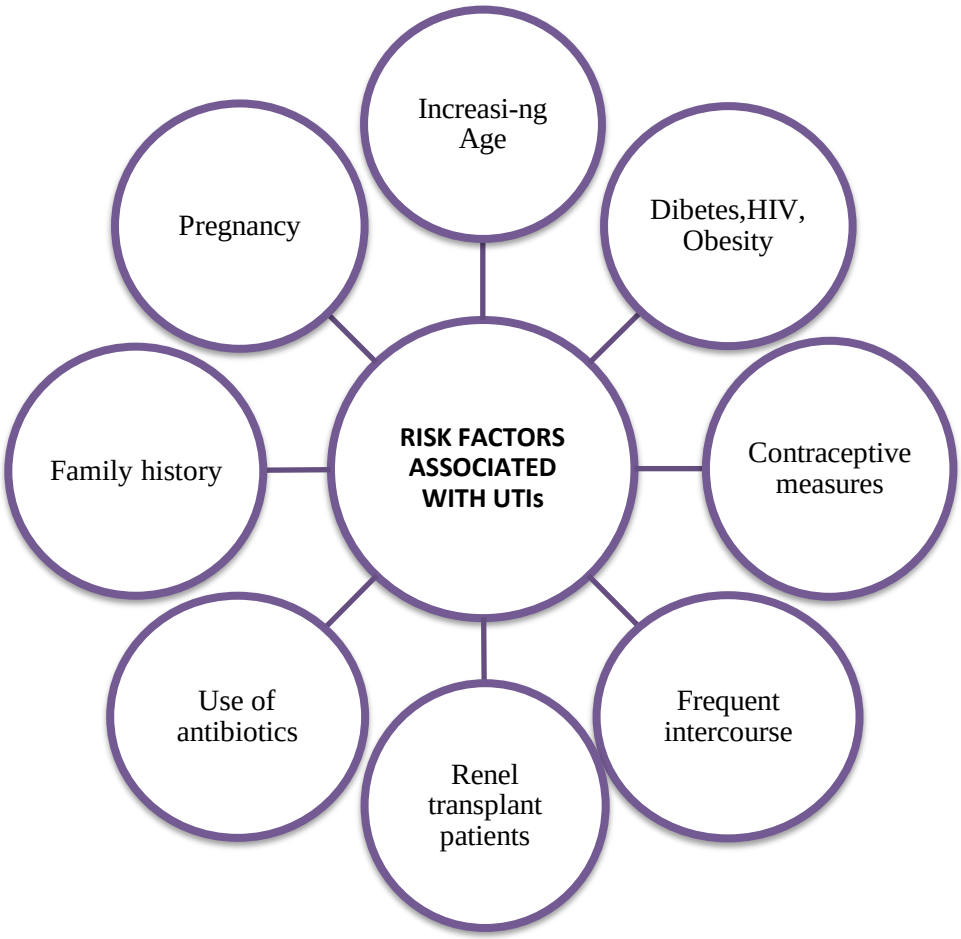
Symptoms in UTI	Meaning
Urgency	An unstoppable urge to urinate due to sudden involuntary contraction of the bladder muscles
Frequency	Urinating too often and at frequent intervals
Bacteriuria	Presence of bacteria in urine is called bacteriuria, while presence of >105 bacterial colonies/mL of urine is termed as significant bacteriuria
Pyuria	Presence of pus cells (WBCs) in the urine
Dysuria	Feeling of pain, discomfort or burning sensation while urinating
Nocturia	Frequently waking up at night to urinate because of UTI or bladder infection

Urinary incontinence	Loss of control of the bladder from a slight loss of urine following coughing, sneezing or laughing



❖ Risk factors of UTIs

- Special anatomical features or restrictions (for example, from vesicoureteral reflux, neuropathic bladder, mechanical or functional obstruction)
- Genetics – Certain cells on the vaginal mucosa and the urethra can express receptors that actually allow certain bacteria to attach and pull themselves into the bladder causing an increase risk of a UTI.
- Immunosuppression – There are a variety of causes of immune supression which decreases a person's ability to fight off infections.
- Personal Hygiene – Perineal contamination with faeces increases the risk of coliform bacteria in the vagina and near the urethra will increase the risk of urinary tract infections.
- Infrequent voiding – The bacteria spends a greater amount of time in the bladder allowing it time to replicate and take hold.



- **Causes of UTI:**

Normally urine is sterile. It is usually free of bacteria, viruses and fungi but does contain fluids, salts and waste products. An infection occurs when tiny organisms, usually bacteria from the digestive tract, cling to the opening of the urethra and begin to multiply. Most infections arise from one type of bacteria, E.coli which normally lies in the colon. The organisms most commonly responsible for catheter-associated UTIs are E.coli, Proteus mirabilis, P.aeruginosa, and Streptococcus faecalis, Staphylococcus aureus, Klebsiella, Pneumoniae, Mycobacterium tuberculosis, Actinomycetes, Nocardia, Candida etc can cause UTI. In addition Mycoplasma and Chlamydia may be associated with sexually transmitted UTI. [12]

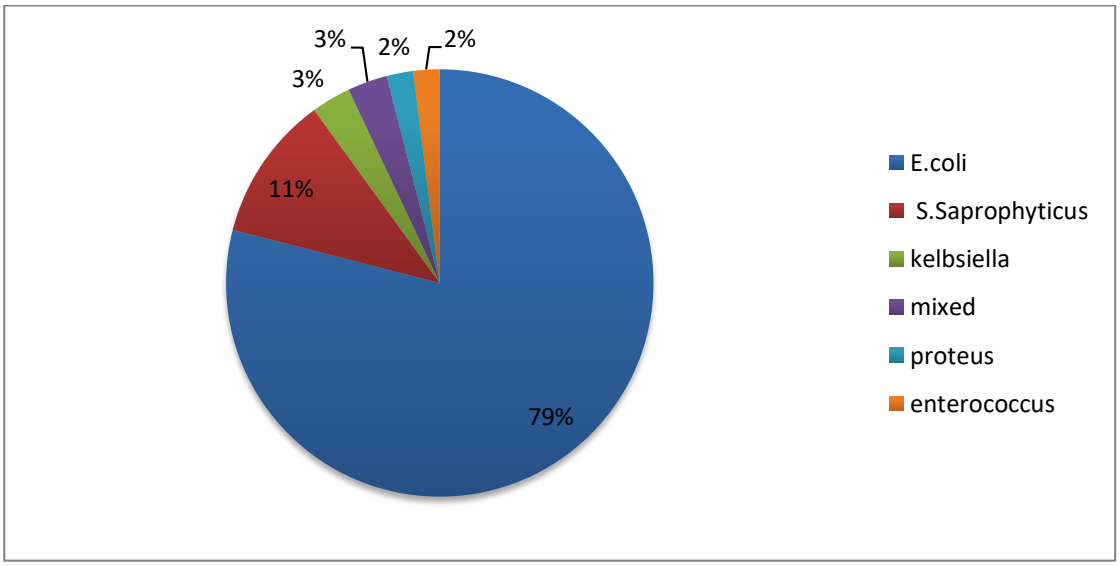


Figure.1. Diagram showing contribution of various microbes for causing the UTI: E. coli 79%, S. Saprophyticus 11%, Klebsiella 3%, Mixed 3%, Proteus 2%, Enterococcus 2%, others 2%.

❖ Etiology of bacterial UTIs-

The bacteria that most often cause cystitis and pyelonephritis are the following:

- Enteric, usually gram-negative aerobic bacteria (most often)
- Gram-positive bacteria (less often)

- **In normal genitourinary tracts**

E. Coli strains with particular attachment factors for the bladder and ureter's transitional epithelium make about 75–95% of cases in healthy genitourinary tracts. Pseudomonas aeruginosa and other enterobacteria, primarily Klebsiella or Proteus mirabilis, make up the remaining gram-negative urine pathogens. 5 to 10 percent of bacterial UTIs are caused by Staphylococcus saprophyticus, a gram-positive bacterium. Gram-positive bacteria that are less frequently isolated include Streptococcus agalactiae (group B streptococci) and Enterococcus faecalis (group D streptococci). These bacteria can be contaminants, especially if they were recovered from patients who had simple cystitis.

- **In hospitalized patients**

E. coli is responsible for around half of infections in hospitalized patients. The gram-positive bacterial cocci E. faecalis, S. saprophyticus, and Staphylococcus aureus make up the remaining 40%, while the gram-negative species Klebsiella, Proteus, Enterobacter, Pseudomonas, and Serratia make up around 40%.[19]

❖ Pathogenesis:-

Bacterial virulence factors significantly influence whether an organism will infect the urinary tract and the severity of the disease that results. Uropathogenic E. coli infects the urinary tract by employing a specific virulence factor that facilitates its colonization and attachment. The bacteria's adhesive properties, the reactive features of the urothelium, and the fluid present between the two surfaces are the three key ecological factors for microbial adherence. Most uropathogen adherence starts in the rectal flora and moves through the urethra, particularly in patients with indwelling catheters, with complications influenced by sex. In this way, the microbe is transported to the bladder, where it can then colonize. The effectiveness of colonization or elimination is determined by the interaction between the host and the microbe. Adhesions found on the surface of fecal bacteria play a role. At this stage, UPEC begins to produce toxins and proteases that act on host cells to obtain nutrients and generate siderophores for iron acquisition. [13]

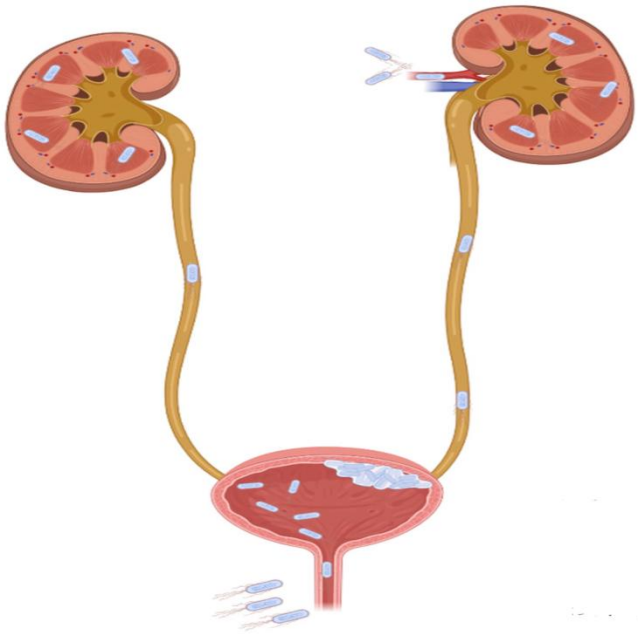


Diagram:1 The majority of UTIs are caused by intestinal flora-derived bacteria contaminating the periurethral region. After ascending the urethra, these bacteria settle in the bladder. Intracellular invasion and biofilm development result from this. If the microorganisms climb the ureters and invade the kidneys, the illness develops into pyelonephritis. Urosepsis can result from systemic dissemination in the kidneys, albeit this is uncommon.

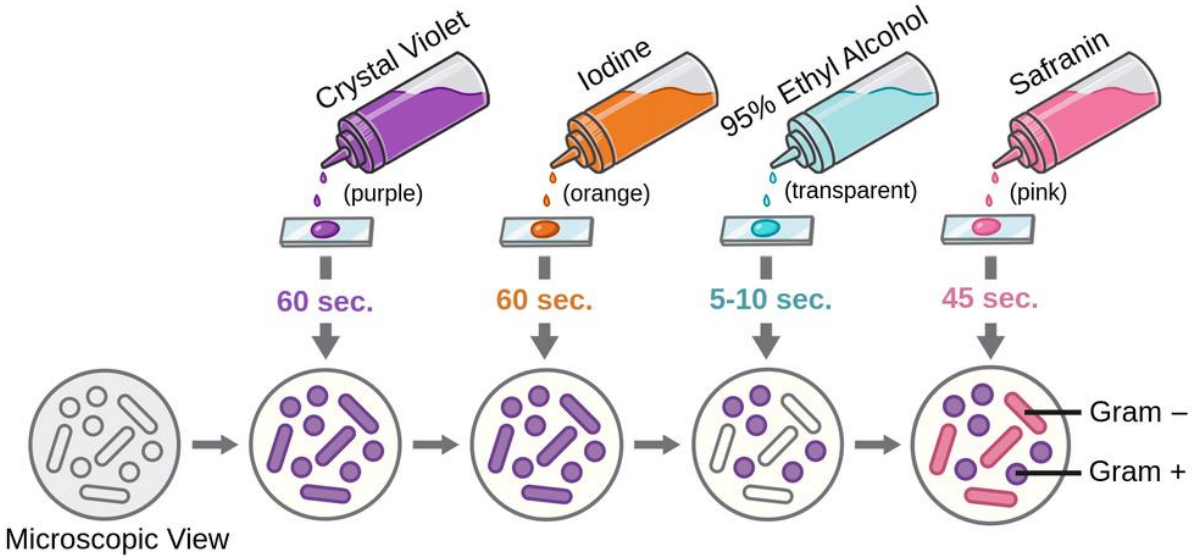
❖ Diagnosis of UTIs

- **Dipstick method :**

Dipsticks are the most frequently utilized tools when there is clinical evidence indicating that a patient may have a urinary tract infection (UTI). Generally, multiparameter dipsticks are employed, which can identify nitrite, leukocyte esterase, glucose, protein, and blood—factors that are crucial for diagnosing an infection. This test is known to be more affordable and serves as a quick alternative for evaluating biochemical parameters. However, the accuracy of these tests has not been established. They can identify positive results for nitrite and leukocyte esterase, which suggest the presence of bacteria and white blood cells (WBCs) in the urine, respectively. Most bacteria convert the nitrates found in urine into nitrites, which can be detected using dipsticks.[14,15]

- **Gram staining:**

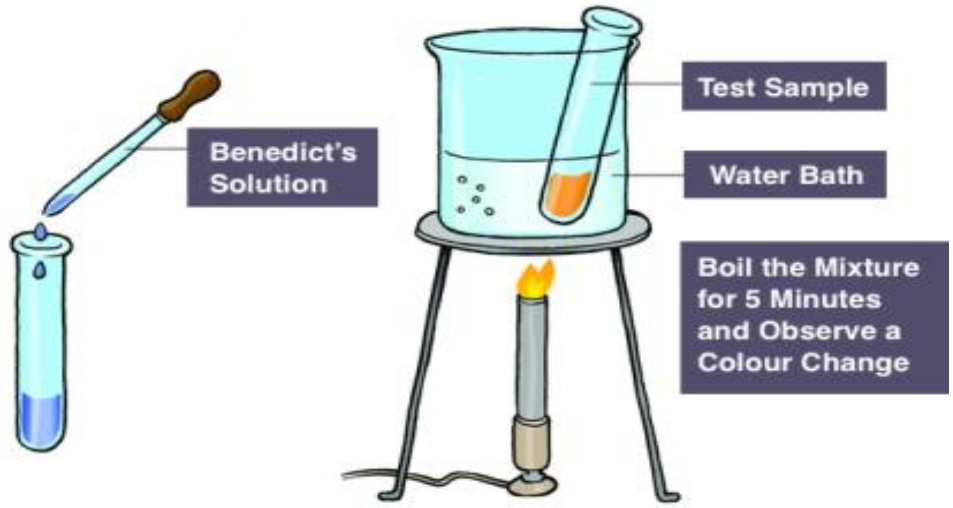
A smear of the isolate on a clean glass slide can be made, which is then air-dried and heat fixed by placing the glass slide over flame gently and Gram-stained in the end. This slide can be observed under a microscope that exhibits the staining of the bacteria. Gram positive bacteria are stained purple, whereas Gram-negative bacteria are stained pink.[16]



- **Biochemical tests :**

Biochemical tests can be used for the identification of various organisms by routine tests like carbohydrate fermentation, methyl red, citric acid utilization, hydrogen sulfide, etc. These tests require less amount of time to identify, along with decreased cost with the accuracy in the identification of microbes.[17]

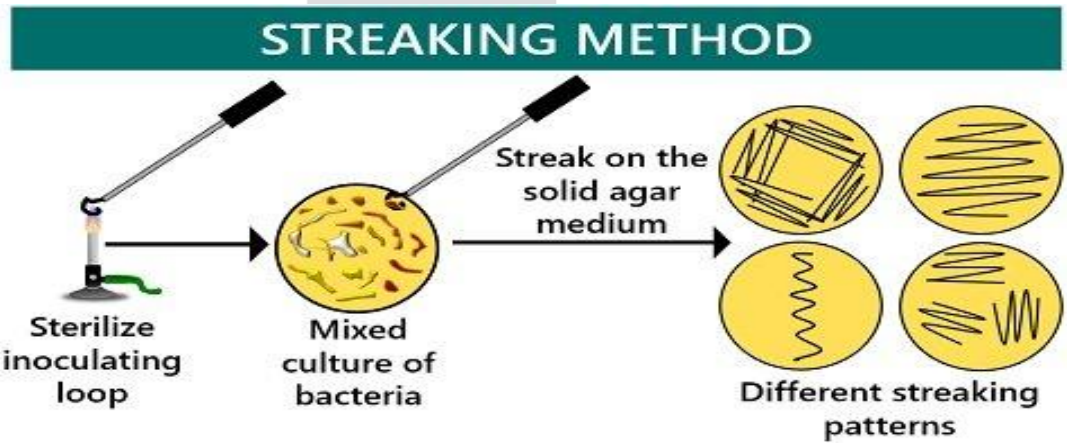
Example: Benedict's test, etc.



- **Urine culture:-**

Urine culture technique is considered the gold standard for the diagnosis of a urinary tract infection but is time-consuming and tedious. It either yields positive results i.e >105 CFU/ mL, or negative results. Lower counts of bacteria may be considered significant in elderly and immune compromised patients as it may lead to an infection.[15]

The culture of the urine is considered appropriate to detect asymptomatic bacteriuria during pregnancy. The samples of urine are generally collected through a clean catch of midstream urine, but catheterized specimens can also be obtained in some cases. The culture test of urine confirms the causative organism and its susceptibility to antimicrobials.[18]
Example: Streak plate method, etc.



- **Prevention:**

Altering lifestyle habits may assist in avoiding some urinary tract infections (UTIs). After menopause, women might apply estrogen cream to the vaginal area to lessen the risk of subsequent infections.

Bathing and hygiene:

- Options for sanitary pads rather than tampons, as some healthcare providers suggest that tampons may increase the likelihood of infections. Replace the pad every time you visit the bathroom.
- Avoid douching or using feminine hygiene sprays or powders. Generally, steer clear of any scented products in the genital area.
- Prefer showers over baths and refrain from using bath oils.
- Maintain cleanliness in the genital area. Wash both the genital and anal regions before and after engaging in sexual activities.
- Urinate both before and after sexual intercourse.
- Wipe from front to back following bathroom use.

Clothing:

- Steer clear of snug-fitting pants.
- Prefer cotton underwear and pantyhose, and ensure both are changed at least daily.

Diet:

- Stay well-hydrated by drinking ample fluids (2 to 4 quarts daily).
- Consume cranberry juice or take cranberry supplements, unless you have a personal or family history of kidney stones.
- Do NOT drink fluids that irritate the bladder, such as alcohol and caffeine.[12]

• Pharmacokinetics of Antibiotics

Antibiotics easily dissolves in water, does not strongly bind the protein in plasma, and is extensively released within human tissues. It is metabolized in two steps [20]. Antibiotics are quickly transferred to the prostate, kidneys, seminal vesicles, and bladder after digestion in the stomach [21]. Antibiotics penetrates the major neural, respiratory, and urine systems, providing cardiac support through anticystitis activity [21].

Antibiotic is released intact in the urine instead of breaking down [21, 22].As such, the dose of antibiotics must be adjusted for those with liver or kidney disease or who are pregnant [23]. Individuals with renal impairment have a higher max, a larger area under the curve (AUC), and low urine clearance; no dose adjustment is required for those with a creatinine clearance of less than 10 mL/min.

• Mode of Action

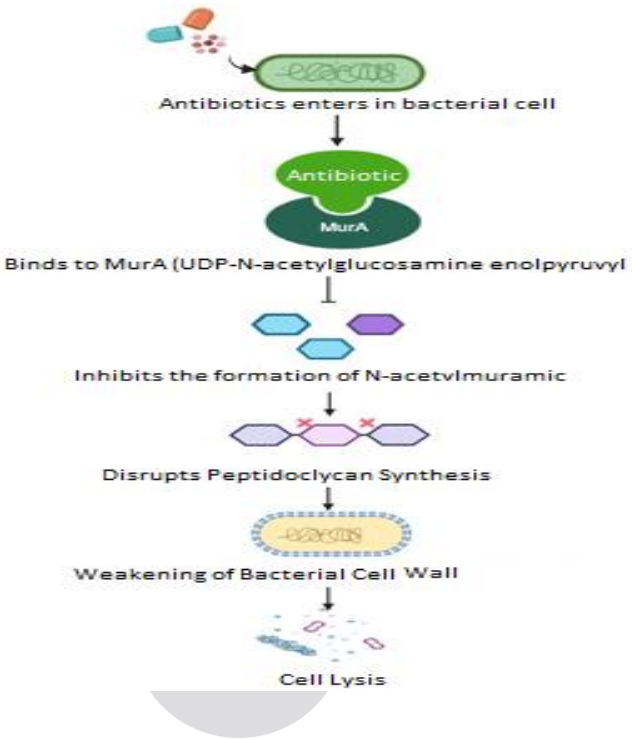
The transporters of glucose-6-phosphate and L-alpha glycerol-3-phosphate (UhpT and GlpT, respectively) are different membrane transporters that allow antibiotics to enter bacteria. It resembles glycerol-3-phosphate and glucose-6-phosphate, which are commonly transported across the bacterial membrane via UhpT and GlpT,

respectively. Cyclic AMP is required for the expression of genes encoding both transport systems. It achieves bactericidal activity by interfering with the initial step of peptidoglycan (PG) synthesis, which is the main building block of the bacterial cell wall (Fig. 2). UDP-N-acetylglucosamine enolpyruvyl transferase (MurA) is specifically inhibited.

Antibiotics inactivates MurA by forming a covalent bond with the cysteine thiol group. Consequently, UDP N-acetylmuramic acid (PG precursor) production is hindered, leading to the loss of the integrity of the peptidoglycan layer and then to cell lysis and death. It regulates the immune system by altering the levels of interleukins, leukotrienes, and tumor necrosis factor-alpha, in addition to its direct antibacterial action. It also affects the functioning of B cells, T lymphocytes, and neutrophils. Finally, Antibiotics reduces the adherence of bacteria to the urine and respiratory tract epithelia [24] .

Following is the diagram that shows the mechanism of action of Antibiotics

Fig. 2. Mode of action of Antibiotic. Antibiotic enters bacterial cell, binds to MurA, inhibits the formation of N-acetylmuramic acid, disrupts peptidoglycan synthesis, leading to the weakening of bacterial cell wall, and cell lysis.



❖ Treatment :-

Management of a urinary tract infection (UTI) should be tailored to each patient based on their unique medical history, the specific pathogens responsible for the infection, and the sensitivity of those pathogens to different treatments. Those who are severely ill typically need intravenous (IV) antibiotics and hospitalization, often due to a kidney infection (pyelonephritis) that could be advancing into the bloodstream. Other patients may experience milder infections (cystitis) and may recover swiftly with oral antibiotics. Additionally, some individuals may have UTIs linked to pathogens associated with sexually transmitted diseases (STDs)

- **Most commonly used Antibiotics for UTIs and its possible side effects:**

1.Macrodantin (Macrobid or Nitrofurantoin) –Side effects of long-term use may include fibrosis or scarring of the lungs and peripheral neuropathy.
Generally, the medication is considered safe during pregnancy, except with rare genetic metabolic deficiencies.

2.Bactrim (Septra or sulfa/TMP) –This drug should not be taken early during pregnancy and may affect the effectiveness of oral contraceptives.

3.Trimethoprim –It should not be taken during pregnancy.

4.Quinolones (Levaquin, Levofloxacin, or Cipro) - This drug should not be taken during pregnancy.

5.Cephalosporin (Keflex) – This may affect the effectiveness of oral contraceptives.

6.Doxycycline –It is not safe during pregnancy or breastfeeding.[12]

Table.1. Parenteral antibiotics used for the treatment of pyelonephritis and its side effects Antibiotic Dose (Adult)

Antibiotic	Dose (Adult)	Side effects
Cefuoxime	750 mg in every 8hr.	Diarrhea,Naysea,Allergic reactions
Ceftazidime	1g in every 8hr.	Diarrhea,Naysea,Allergic reactions
Co-amoxiclav	1.2g in every 8hr.	Nausea, diarrhoea, rashes, hepatitis, erythema multiforme
Gentamicin	80-120 mg in every 8hr.	Vestibular and hearing damage, nephrotoxicity
Ciprpfloxacin	200 mg in every 12hr.	Nausea ,vomiting, dizziness, headache, convulsions, hallucination, hepatitis, photosensitivity, blood disorder
Imipenem	500mg in every 8 hr.	Nausea, vomiting, diarrhoea, allergic reactions, convulsions, confusion .
Fosfomycin	2-3g once a day	Anorexia,Diarrhea,Epigastric,Discomfort, Headache,Nausea,Rash,Vomiting

❖ Conclusion

Urinary tract infections can vary in presentation, being asymptomatic, acute, chronic, or classified as complicated or uncomplicated. The clinical manifestations of UTIs depend on which part of the urinary tract is affected, the organisms responsible, the severity of the infection, and how the patient's immune system responds. Identifying the specific microbe causing the infection is essential, as it reduces both the cost and side effects associated with antibiotic treatment and helps mitigate the risk of developing antimicrobial resistance. Rapid diagnostic methods should be employed for swift diagnosis and suitable treatment of the pathogens involved. For minor uncomplicated UTIs, alternative treatments should be considered before resorting to immediate antibiotic prescriptions. Additionally, antimicrobial stewardship programs should be promoted to ensure the responsible use of antibiotics, which helps reduce the emergence of antimicrobial resistance in UTIs.

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