Clinical, Etiological and Treatment Profile of Urinary Tract Infection in Women

Rajarajan S1*, John Flamitha J2, Juguna Joseph2, Chandrasekaran V2, Dr. Senthil Selvi R2
1. Professor, Department of Pharmacy Practice, The Erode College of Pharmacy, Erode, Tamilnadu, India.
2. Student of Pharm.D, Department of Pharmacy Practice, The Erode College of Pharmacy, Erode, Tamilnadu, India.
*Corresponding author’s E-mail: rajarajannba@gmail.com

ABSTRACT
Urinary tract infections are one of the most common infection affecting both males and females in all age groups. The prevalence is more common among females. The females are affected during their childhood, adult and child-bearing age. The most important cause is the anatomical structure of the female and pathogens. Based on the classification of infection in the upper or lower part of the urinary tract it is named as cystitis, urethritis, and pyelonephritis. Dysuria, frequent or urgent urination and abdominal pain are the common symptoms and other symptoms are oliguria, vomiting, and bloody urine. Diagnosis is based on the culture and sensitivity test and it is commonly used to identify the type of causative organism depending upon these antibiotics were prescribed. The most commonly used antibiotic class and suitable dose are an important part of treatment for the children, adults and pregnant women. The resistance and sensitivity development is important for the selection of antibiotic and course of treatment. The aim of this review is to analyze the common causes, risk factors, diagnosis of UTI including their treatment profile for women.

Keywords: Urinary tract infection, Classification, Cause, Symptoms, Diagnosis, Pathogens, Antibiotic.

INTRODUCTION
Urinary tract infection (UTI) is one of the most common bacterial infections in the world1. Women are most commonly affected with UTI once in their lifetime because of their shorter urethra. Urinary tract infection is most commonly caused by microbes such as bacteria, other nonbacterial pathogens are fungi (usually candida species), and less commonly by mycobacteria viruses and parasities2.

Nonbacterial pathogens usually affect immune compromised patients who are associated with a condition of diabetes, obstruction or structural urinary tract abnormalities or have recent Urinary tract instrumentation. Urinary tract infections are also due to some behavioural factors like delay in micturition, sexual activity, poor hygiene and use of diaphragms and spermicides3. The main symptoms of urinary tract infection are abdominal pain, vomiting, dysuria, oliguria. Urinary tract infections are divided into upper and lower infection. The upper urinary tract infection involves kidney and the ureters, and the lower urinary tract involves bladder and the urethra4. Females are mostly affected at their adult age and child bearing age. Antibiotics are most commonly used to treat acute uncomplicated urinary tract infection and they are selected based on the culture and sensitivity test. The aim of this study is to know about etiology, risk factors, common diagnostic procedures and treatment profile of urinary tract infection5, 6.

OBJECTIVE
This review article is a detailed study of urinary tract infection including their major symptoms, most common uropathogens causing UTI, dose and dosage form for pediatrics, pregnant women and general female patients, and the prescribing pattern of antibiotics for different types of UTI.

Urinary tract infection is the second most common infectious disease next to the respiratory tract infection and affecting most commonly women of all age groups, including neonate and geriatric age groups. In pediatric age groups 0.7% of febrile illness is due to the urinary tract infection7. In emergency departments, 14% of children are admitted due to UTI either due to direct infection or indirectly due to its associated complication8. Almost all the women have at least one symptomatic UTI during their lifetime. Young and sexually active women have the highest incidence of UTI at the age of 18-24 years9. In case of pregnant women beginning of the 6th week and 22nd and 24th week of gestation, there is an increased risk of urinary stasis and vesicoureteric reflux due to ureteric dilatation. So, 90% of the pregnant women had a risk of developing urinary tract infection10.

EPIDEMIOLOGY
CLASSIFICATION
Based on Anatomical Level of Infection, Severity of Infection and Risk Factors12
1. Complicated UTI - Genitourinary tract infection, Structural or functional abnormality of the genitourinary tract, Immunocompromised patients.
2. Uncomplicated UTI - Episodes of acute cystitis and acute pyelonephritis.

4. **Lower UTI** - Cystitis, Urethritis, and Prostatitis.

5. **Cervicitis** - Infection affecting cervix caused by sexually transmitted agents like Neisseria gonorrhoea and chlamydia trachomatis.

6. **Cystitis** - Infection involving the bladder and presenting with dysuria, urinary frequency and, urgency.

7. **Prostatitis** - Infection of the prostate. Fever is the main symptom.

8. **Pyelonephritis** - Infection in the kidney with a symptom of fever, chills, vomiting, Lower back pain.


10. **Urosepsis** - Sepsis syndrome induce urinary tract infection.

11. **Relapse** - Recurrence of infection with the same microorganism.

12. **Reinfection** - Recurrence of infection with different microorganism.

**Based on Site of Infection**

- **Upper UTI** - It involves renal parenchyma and ureters with Pyelonephritis and ureteritis.
- **Lower UTI** - It involves the bladder (cystitis), the urethra (urethritis) and in males the prostate (prostatitis).

<table>
<thead>
<tr>
<th>Types</th>
<th>Causes</th>
<th>Risk factors</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated UTI</td>
<td>Antibiotic-susceptible bacteria</td>
<td>Female gender, Previous infection, Diabetes, Sexual activity, Obesity, Heredity</td>
<td>Cystitis, Urethritis, Pyelonephritis</td>
</tr>
<tr>
<td>Complicated UTI</td>
<td>Structural or functional abnormalities</td>
<td>Urinary obstruction, Retention, Spinal cord injuries, Immunosuppression, Renal failure</td>
<td>Cystitis, Pyelonephritis</td>
</tr>
</tbody>
</table>

**ETIOLOGY AND RISK FACTORS**

The microorganism is the major cause of UTI infection. These microorganisms invade into the urinary tract and form colonies. The most common microorganism that causes UTI includes gram-negative bacteria and as well as gram-positive bacteria.

Common uropathogens causing UTI infection

**Uncomplicated UTI**

- *E. coli*
- *S. saprophyticus*
- *Enterococcus spp*
- *K. pneumoniae*
- *P. mirabilis*

**Complicated UTI**

- *P. aeruginosa*
- *Acinetobacter baumannii*
- *Enterococcus species*

**Candida spp**

**Recurrent UTI**

- *K. pneumonia*
- *Enterobacter spp*
- *Enterococcus spp*
- *Staphylococcus spp*

Escherichia coli and staphylococcus and saprophyticus accounts for about 80% of community acquired uncomplicated urinary infection (UTI). *E. coli* is a common UTI pathogen in younger women. They colonize well in a rectum and to lesser extend in a cervix and urethra. Gram-negative pathogens, including Pseudomonas spp, Enterobacter spp, Serratia spp, Citrobacter spp, urease-producing Klebsiella spp, Proteus spp, Corynebacterium urealyticum, and Providencia spp are also involved in this type of infection. By Aspergillus spp and Cryptococcus neoformans increasing number of fungal UTI were reported. In one study, positivity for Candida spp was found in 5% of urine specimens from a general hospital and in 10% from a tertiary-level care center.
RISK FACTORS

Premenopausal women of any age

- **Diabetes**
  The risk factor for asymptomatic bacteriuria includes peripheral neuropathy, microalbuminuria and longer duration of diabetes\(^2\). The risk factor for symptomatic UTI includes type 2 diabetes, higher age, and microalbuminuria\(^3\).

- **Diaphragm use especially those with spermicide\(^2\)**
  The use of diaphragm is a risk factor for urethritis in uncomplicated UTI and it cause symptomatic reactions.

- **History of UTI or UTI during childhood**
  In case of recurrent UTI and pyelonephritis the major risk factor is a family history. This supports the idea of a genetic influence on defense mechanisms in the urogenital tract\(^4\). The development of a symptomatic UTI depends on the balance between pathogen virulence and the host response to the pathogen\(^5\).

- **Intercourse related issues**
  During sexual intercourse there is a chance of developing UTI due to pre and Post coital voiding patterns, frequency of urination, delayed voiding habits, wiping patterns, douching, and use of hot tubs, frequent use of pantyhose or tights, or body mass index\(^6\).

POSTMENOPAUSAL AND OLDER ADULT WOMEN

- **Estrogen deficiency**
  Estrogen secretion in the ovary is significantly reduced after menopause and this reduction cause the growth of lactobacillus in the vaginal layer\(^7\). Due to this vaginal pH get reduced and the bacteria continuously grows to induce UTI\(^8\,\(^9\).

- **Anatomical impairment**
  A change in the anatomical structure is the major risk factor for UTI. The impairment in the anatomical structure will easily invade bacteria into the urethra and the infection develops\(^10\).

- **History of UTI before menopause**
  The women's during their pregnancy they develop UTI because of the stasis of urine in the ureters which delays bladder emptying and also due to vesicoureteral reflux\(^11\).

- **Urinary catheterization**
  During catheterization there is an increased risk of infection especially at the urethra, it causes uncomplicated UTI with a symptomatic bacterial infection\(^12\).

- **Urinary incontinence**
  Increased external sphincter cause incomplete bladder emptying which cause the bacteria to grow in a bladder which is the major risk factor for cystitis\(^13\).

Figure 1: Pathophysiology of urinary tract infection

Complicated UTI

Structural and functional abnormality of urinary tract which causes obstruction of urine flow, persons having frequent urinary infection, immunocompromised patients, having a history of diabetes or chronic kidney disease and catheterization is the common criteria for the complicated UTI\(^14\).

Uncomplicated UTI

Pregnant women and persons not having any serious comorbidity are the general reasons, the common infection due to common microorganism are involved in this category. Persons with unhygienic are also comes under uncomplicated UTI, unprotected anal intercourse is also the reason for UTI\(^15\).
CLINICAL MANIFESTATION

Cystitis
Dysuria, urinary frequency, urgency, nocturia, hesitancy, suprapubic discomfort, hematuria, unilateral back or flank pain, fever32.

Pyelonephritis
The symptoms are low grade fever, rigors, nausea, vomiting and flank or loin pain33.

Acute bacterial prostatitis
The symptoms are dysuria, frequency and pain in the prostatic pelvic or perineal area, fever and chills33.

Chronic Bacterial Prostatitis
Recurrent episodes of cystitis, pelvic and perineal pain are the symptoms of chronic bacterial prostatitis32, 33.

Other common signs and symptoms include
- Burning micturition
- Frequent urination
- Urgency of urination
- Incomplete bladder emptying
- Cloudy urine
- Fever
- Chills
- Back pain or loin pain34.

DIAGNOSIS

Clinical Examination
The initial step in UTI diagnosis is evaluation of patient signs and symptoms. Dysuria, frequent and urgent urination are the common symptoms of acute bacterial cystitis and also cause abdominal pain or hematuria. Depending upon the age of the child the signs and symptoms may differ. Vomiting, fever, oliguria and sepsis are the symptoms of newborns. In infants and young children typical signs and symptoms is fever. The bacteria that cause acute urethritis includes Neisseria gonorrhoea and chlamydia trachomatis and herpex simplex virus develop symptoms of fever, chills, flank pain mainly in case of upper UTI35. When severe flank pain radiating to the groin it indicated renal calculi and it is a cause of pyelonephritis. Asymptomatic UTI was seen in elders and having a risk of septic shock. Sometimes they experience a symptom of difficulty in urination or have any combination of these symptoms34.

Laboratory Evaluation
Leukocyte esterase or nitrate is a rapid and inexpensive method to diagnose bacteriuria the method used is urine dipstick testing. Dipstick tests include leukocyte esterase, nitrate blood, and protein. Urinalyses are used to detect pyuria36. When both Pyuria and bacteriuria are detected on microscopic examination indicates the risk of UTI. The use of a postvoid residual volume measure, urodynamic testing, cysstourethroscopy or radiologic imaging is not cost-effective in women unless they have evidence of a complicated infection or renal calculi. These are rarely necessary to diagnose acute uncomplicated cystitis and pyelonephritis37.

Urine Culture
The urine culture test is important to identify the effective antibiotic against microorganism. Urine culture and antimicrobial susceptibility are the important tests; mainly it is used to identify acute pyelonephritis. Empirical therapy is preferred as an initial treatment followed by that susceptibility test will conduct and based on this antibiotic are selected38, 39.

Other Tests Include
Intravenous Pyelogram - A series of X-ray of the bladder kidneys and ureters after a special dye is injected.

Ultrasound - A test that uses sound waves to analyze internal organs.

Cystoscopy - A test that uses a special instrument fitted with a lens and a light source to see the bladder inside the urethra.

TREATMENT

Goals of Treatment40
- Empirical antibiotic therapy meant for symptomatic relief.
- Check the improvement of the patient in case of cystitis relives within 24 hrs and in case of pyelonephritis relives within 48-72 hrs.
- If no improvement the patient is diagnosed by using imaging studies.
- The treatment should be started with low toxicity drugs and low potential of changing the bowel flora.
- The antibiotic started after culture sensitivity test and antibiotic prescribed according to the pathogens.
- Continuously monitor the patient and give better lifestyle modifications.

Antibiotic Selection
The patient condition is categorized as complicated and uncomplicated UTI and in uncomplicated, hospitalization is not needed but in case of complicated UTI the patients were admitted and parenteral antibiotics were started. Then urine culture and sensitivity were done to identify the bacteria and according to that, the antibiotics were selected. The antibiotics are given in regular and appropriate interval. When the patient condition is improved the antibiotics are given in a tablet form41.
Nitrofurantoin

Cystitis is mainly treated by nitrofurantoin. It is active against E.coli and it has only 0.9% resistance. It achieves high urinary concentration but does not penetrate well into the renal parenchyma; therefore it should not be used for the treatment of pyelonephritis. Creatinine clearance of 60mL/minute or less or nitrofurantoin is contraindicated. The common adverse effects are peripheral neuropathy, epigastric pain, hemolytic anemia, and pulmonary reaction. The colour of urine turns to dark brown on exposure to air for the patients who are taking nitrofurantoin. Dose available is 50 mg, 100 mg tablet, and 25mg/5ml suspension.

Trimethoprim/ Sulfamethoxazole

It is a highly effective agent for the treatment of uncomplicated cystitis and having high curative rates. Its action is related to the inhibition of dihydrofolate reductase. It is mainly active against salmonella typhi, enterobacter, klebsiella. 20% resistance rates have been recommended. Megaloblastic anemia, vomiting, stomatitis, are the common side effects. Patient with renal disease may develop uremia. So, dosage adjustment is needed. An elderly patient is at high risk of bone marrow toxicity. Dose available is 80mg+400mg tablet 2 BD for 2days, 40mg+200mg per 5ml suspension.

Fluoroquinolones

Levofloxacin and ciprofloxacin are commonly used fluoroquinolones. It is commonly used for the treatment of uncomplicated pyelonephritis and complicated UTIs, including urosepsis. They are acted by inhibiting enzyme bacterial DNA gyrase, which nicks double stranded DNA, introduces negative supercoils and then reseals the nicked ends. The increasing resistance is reported to the bacteria of salmonella, pseudomonas.

Ciprofloxacin - It is active against a broad range of bacteria and it is highly susceptible against E.coli, K.pneumonia, Enterobacter, Salmonella typhi. Ciprofloxacin has a good safety record the available doses are 250mg, 500mg, 750mg tablet, 200mg/100ml IV infusion.

Norfloxacin - It is less potent than ciprofloxacin; it attains lower concentration in tissues. It is metabolized as well as excreted unchanged in the urine. It is available as 200mg, 400mg, and 800mg tablet.

Ofloxacin - It is mainly active against gram-negative bacteria. It is active against chlamydia and mycoplasma. It is available as 100mg, 200mg, 400mg tablet and 200mg/100ml IV infusion.

Beta Lactam Antibiotics

It is an alternative treatment for the management of uncomplicated UTI. Due to resistance problems, the penicillins should not be used unless the infection is known to be sensitive. They are safe to use during pregnancy and lactation and are relatively inexpensive. Diarrhoea, skin reactions, genital itching, and vaginal problems are some of the adverse effects. Co-amoxiclav has a broader spectrum of action than amoxicillin alone but is considerably more expensive and should be used as a second-line agent. It has been used during pregnancy and is probably safe but the experience is limited.

Ampicillin - It is the first choice of initial treatment of acute infections with bacteriological data but higher failure and relapse rates are reported because of emergence rates of ampicillin resistance strains of E.coli.

Piperacillin /carbenicillin - It is used to treat serious pseudomonas treatment with an indwelling catheter or chronic obstruction.

Cephalosporins

Cephalosporins are the class of antibiotic which are commonly used in UTI. Characteristics of individual cephalosporins may vary. Cephalexin, cefradine, cefaclor, and cefadroxil may be used with caution during pregnancy and lactation. Hypersensitivity is the main adverse effect. The resistance of the organism is isolated mainly in institutional settings or multiple antibiotic exposures. It is mainly used in the treatment of klebsiella and proteus infection.

Phenazopyridine

It is an azo dye with local analgesic and anesthetic effects on the urinary tract. The exact mechanism of action is not known and it gives sudden relief from pain, burning, urgency, and frequency of urination. It is used as an adjuvant and it is available as 500 mg tablets.

Antibiotic Prophylaxis

The prophylaxis treatment is common for urinary retention; uropathogens are acting as a reservoir in the rectal flora because of the several anatomical factors. Minardi et al reported a reduction in the recurrence rate after pelvic floor re-education with biofeedback, supporting the hypothesis that emptying disorders play an important role in the recurrence of UTI in women. When all attempts at modification of patient behavior and lifestyle have failed to resolve the problem of recurrence, it may be necessary to start antimicrobial prophylaxis. The antibiotics of choice for this purpose are nitrofurantoin, cotrimoxazole, cephalosporins and quinolones, all at lower than therapeutic dosages. In all cases, a prophylactic regimen should be initiated only after complete eradication of the original infection is confirmed by a negative urine culture, performed 1–2 weeks after the conclusion of primary therapy.

Fungal Infections

Fungal infection due to candida species is mainly considered. The presence of candida in the urine is called candiduria. The finding of Candida in the urine can frequently be the result of contamination during the collection of urine samples from patients with Candida resident on the external genitalia. Candiduria is a...
condition most often found in elderly, hospitalized, or immunocompromised patients. The mainstay of antibiotic treatment for candiduria is the azolic compounds, mainly fluconazole 200 mg orally daily for 2 weeks. The use of amphotericin B, which is more toxic, is to be regarded as second-line and for intravascular irrigation in certain settings, because it does treat potential fungal spread to the upper urinary tract (or even worse, systemic spread). Treatment of UTI in Children Amoxicillin is used as a first-line choice of drugs in UTI but it has an increased resistance over E. coli and followed by this the highest cure rates of trimethoprim or sulphamethoxasole is used. A Cochrane review analyzing short-duration (two to four days) versus standard-duration (seven to 14 days) oral antibiotics in 652 children with lower UTI found no significant difference in positive urine cultures between the therapies immediately after treatment (eight studies: relative risk = 1.06; 95% confidence interval, 0.64 to 1.76) or 15 months after treatment (10 studies: relative risk = 0.95; 95% confidence interval, 0.70 to 1.29). The conclusion indicates that there is no difference between the short and standard-duration therapies in the development of a resistant organism at the end of treatment.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosing</th>
<th>Common adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/clavulanic (Augmentin)</td>
<td>25 to 45 mg per kg per day, divided every 12 hours</td>
<td>Diarrhea, nausea/vomiting, rash</td>
</tr>
<tr>
<td>Cefixime (Suprax)</td>
<td>8 mg per kg every 24 hours or divided every 12 hours</td>
<td>Abdominal pain, diarrhea, flatulence, rash</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>10 mg per kg every 24 hours or divided every 12 hours</td>
<td>Diarrhoea, Nausea, Rash, Abdominal pain</td>
</tr>
<tr>
<td>Cefprozil (Cefzil)</td>
<td>30 mg per kg every 24 hours or divided every 12 hours</td>
<td>Diarrhoea, Nausea, Rash, Abdominal pain</td>
</tr>
<tr>
<td>Cephalexin (Keflex)</td>
<td>25 to 50 mg per kg per day, divided every 6 to 12 hours</td>
<td>Diarrhea, headache, nausea/vomiting, rash</td>
</tr>
<tr>
<td>Trimethoprim/sulphamethoxasole (Bactrim, Septra)</td>
<td>8 to 10 mg per kg per day, divided every 12 hours</td>
<td>Diarrhea, nausea/vomiting, photosensitvity, rash</td>
</tr>
</tbody>
</table>

Duration of Treatment

Thus, a two to four-day course of oral antibiotics appears to be as effective as a seven to 14 day, course in children with lower UTIs. A single-dose or Single-day course may be less effective compared to two-four day course. In children’s fluoroquinolones are not commonly used because of their risk of affecting developing joints.

Special Consideration

In children, the risk of renal scarring is such that UTI should be diagnosed and treated promptly, even if symptomatic. Quinolones are contraindicated in children because of the theoretical risk of causing cartilage and joint problems. Dosage consideration is important to prevent toxicity, the children treatment is started after taking culture and sensitivity test. The children are continuously monitored to check any abnormalities are present. Constipation should be addressed in children and infants who are taking a treatment course of antibiotics.

Treatment of UTI in Non-pregnant Women

Uncomplicated UTI

In clinical practice, the most commonly applied recommendation is guidelines prepared by the Infectious Disease Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases (ESCMID). These guidelines recommend treatment of uncomplicated cystitis with nitrofurantoin (100 mg every 12 hours for 5 days), fosfomycin (a single dose of 3 g) and if local resistance rate is under 20% of isolates, TMP-SMX (160 mg and 800 mg, twice a day for 3 days). The second line of treatment consists of fluoroquinolones (ciprofloxacin, 250 mg twice daily for 3 days; levofloxacin, 250 mg or 500 mg once daily for 3 days). The guidelines also list some of the β-lactam agents especially the drugs like amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil in 3-7-day regimen as choices for therapy when other antibiotics are not used.

Treatment of Complicated UTI

Complicated Cystitis:

1. Ciprofloxacin 500mg PO bid or levofloxacin 250mg PO q day
2. Trimethoprim-sulphamethoxasole 160/800 mg (one DS tablet) bid

Alternatives with less data or less activity:

1. Agents such as oral 2nd and 3rd generation cephalosporins are more active than oral cephalaxin or amoxicillin.
2. Nitrofurantoin 100 mg PO BID (not recommended in patients with concern for pyelonephritis or those with poor renal function)45.

Complicated pyelonephritis

Patients requiring hospitalization: Fluoroquinolones and TMP/SMX are not recommended for return patients admitted with pyelonephritis due to high rates of resistance (~20%). When susceptibilities results return patients may be de-escalated to an FQ or TMP/SMX if they are susceptible.

No risk factors for multi-drug resistant organisms:
1. Ceftriaxone 1g IV q24h (2g if > 80kg).
2. Severe beta-lactam allergy: Aztreonam 2g IV q8h43.

TREATMENT OF UTI IN PREGNANT WOMEN

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Pregnancy Category</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalexin (Keflex)</td>
<td>B</td>
<td>250 mg two or four times daily</td>
</tr>
<tr>
<td>Nitrofurantoin (Macrodantin)</td>
<td>B</td>
<td>50 to 100 mg four times daily</td>
</tr>
<tr>
<td>Sulfisoxazole (Gantrisin)</td>
<td>C*</td>
<td>1 g four times daily</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>B</td>
<td>250 mg four times daily</td>
</tr>
<tr>
<td>Fosfomycin (Monorol)</td>
<td>B</td>
<td>One 3-g sachet</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>C†</td>
<td>160/180 mg twice daily</td>
</tr>
</tbody>
</table>

To eradicate the infectious microorganism(s) 10-day course of treatment is sufficient. Some authorities have advocated shorter courses of treatment even single-day therapy. The pregnant women with UTI are treated with a short course of antibiotics. Masterton demonstrated a cure rate of 88 percent with a single 3-g dose of ampicillin in ampicillin-sensitive isolates55. A single dose of amoxicillin, cephalexin (Keflex) or nitrofurantoin was less successful in eradicating microorganism with curative rates of 50-78 percent54, 55. A single dose of 3g sachet of Fosfomycin is effective. The other classes of antibiotics have not been used in the treatment of UTIs, research studies are necessary to determine the other antibiotic uses in UTI and also to determine the effective short course, treatment of antibiotic compared to traditional course treatment. A repeat culture test should be obtained to determine the complete eradication of bacteriuria 56.

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