Smyrna Tıp Dergisi ***Derleme***

Empirical Antibiotic Treatment of Uncomplicated Urinary Tract Infections: A Review
Komplike Olmayan İdrar Yolu Enfeksiyonlarının Ampirik Antibiyotik Tedavisi: Derleme

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Summary
This study aims to determine the choice of empirical antibiotics to be used for uncomplicated and mild-to-moderately complicated urinary tract infections (UTIs) in patients who do not require hospitalization. Characterizing UTIs as complicated and uncomplicated UTI is more practical than localizing into upper or lower UTIs.
Key words: Antibiotic treatment, empiric, pyelonephritis, urinary tract infections

Özet
Bu çalışma, hastaneye yatış gerektirmeyen hastalarda komplike olmayan ve hafif-orta komplike idrar yolu enfeksiyonlarında (İYE) kullanılacak ampirik antibiyotik seçimini belirlemeyi amaçlamaktadır. İdrar yolu enfeksiyonlarını karmaşık ve komplike olmayan idrar yolu enfeksiyonu olarak karakterize etmek, üst veya alt idrar yolu enfeksiyonlarını lokalize etmekten daha pratiktir.
Anahtar Kelimeler: Antibiyotik tedavisi, ampirik, piyelonefrit, idrar yolu enfeksiyonu

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Introduction

Urinary tract infections (UTIs) are commonly encountered in primary care (1,2), predominantly affecting women (40 times more in the 16-35 years age group), excluding the first 6 months postnatally (1). A study reported features of UTI in approximately 21% of patients who received antibiotics prescribed by general practitioners; of these 42.2% aged 15-65 years, while 55% were >65 years old (3).

About 95% of UTIs occur when bacteria that gain access through blood or lymphatic pathways (rarely through direct transmission) ascend the urinary tract and settle in the urethra and bladder (1,2,4,5). Mostly, a single causative pathogen is isolated in cultures, of which *Escherichia coli* is the commonest, causing 85% of the community-acquired and uncomplicated infections, and 50-60% of hospital-acquired and complicated infections (1,2,4,5,6,7,8).

Hitherto, studies conducted to localize the infection (upper or lower UTI), either clinically (50% accuracy) or through laboratory investigations, have been unsatisfactory. For instance, symptoms of fever, lumbar pain, and significant bacteriuria are present in both pyelonephritis and cystitis. Conversely, the upper urinary tract may be involved in patients with only bladder symptoms (1,5,7,9).

Therefore, family physicians must be able to delineate the infection as complicated or uncomplicated, rather than localizing the infection, while selecting the empirical antibiotic.

Diagnosis

Urine dipstick analysis and microscopic analysis are usually adequate in outpatient clinics to diagnose uncomplicated UTIs, sparing the need for urine culture which is the gold standard (1,8,9). Positive results for both nitrite and leukocyte tests in the dipstick analysis are adequately sensitive (80-90%) and specific (60-98%) for UTI. In microscopic urinalysis (at 100x), the presence of ≥ 5 leukocytes represents pyuria, and > 5 bacteria indicates infection (1,2,9). Above 10^5 cfu/ml in midstream urine

culture is confirmatory for UTI, whereas, $\geq 10^3$ cfu/ml in patients experiencing dysuria is sufficient for diagnosis (1,8,9).

Radiological studies are usually not required for diagnosis but are indispensable in complicated UTIs. Frequently used radiological methods include direct urinary system radiography, ultrasonography (USG), computed tomography (CT), and cystoscopy (2,5,7,9).

Classification of UTIs

UTIs are classified into 'complicated' and 'uncomplicated' based on clinical symptoms, anatomical level, infection severity, risk factors, and availability of the optimal antimicrobial treatment (10).

A. UNCOMPLICATED UTIs
   a) Uncomplicated Cystitis
   b) Uncomplicated Pyelonephritis
   c) Uncomplicated Recurrent UTI

B. COMPLICATED UTIs
   a) Complicated Cystitis
   b) Complicated Pyelonephritis
   c) Complicated Recurrent UTI
   d) Catheter-related UTI
   e) UTI in men
   f) Urosepsis

Adult asymptomatic bacteriuria (ABU) is excluded here since it is commensal colonization and not infection.

Features of Uncomplicated UTI

- Anatomically and functionally normal urinary system.
- Infection in adult patients (≥16 and ≤ 65 years, both genders) involving only the bladder.
- Non-pregnant female.
- *Escherichia coli* is the commonest pathogen.
- May occur and recur with sexual activity.
- Isolated or recurrent bacterial cystitis present in most patients.
- Reasonably effective short-term treatment with oral antibiotics is possible.

Features of Complicated UTIs

- Structural or functional disorder within the urinary tract.
- Extra-vesicular infection – in the kidneys, ureters, or perirenal tissues.
- Occurs in a pregnant female.
- More than 1 pathogen (E. coli is the commonest).
- Elderly patients (>65 years),
- All pediatric patients (<16 years) – Vesico-Urethral Reflux (VUR) is common in both genders.
- Poor general condition.
- Comorbidities causing immunocompromise – diabetes, kidney and liver failure, cancer, AIDS.
- Obstructive urinary symptoms – reduced urine flow strength or speed, hesitancy to initiate, intermittent urination, dripping after urination, and difficulty urinating or straining.
- Patients receiving urinary tract intervention, having a urinary catheter, or with residual urine >100 ml (detected by a catheter or on USG).
- Initial symptoms lasting > 7 days and non-responders to antibiotics within 48 hours.
- Hospital-acquired infections.

Complicated UTIs often occur from infection with highly virulent and antibiotic-resistant bacteria (1,2,14,4,6–9,11–13). These patients are difficult to follow up, requiring additional radiological or urological investigations. The indications for radiological assessment include – symptoms persisting or worsening even after 7 days of treatment; signs of complications and clinical deterioration; presence of atypical findings, recurrent infection, suspected pyelonephritic obstruction or renal papillary necrosis such as after using nonsteroidal anti-inflammatory drugs; male gender; patients with neuropathic bladder, diabetes mellitus, history of cancer, urolithiasis, genitourinary surgery, chronic renal failure, or the presence of polycystic kidney; and infection with unusual microorganisms (*Mycobacterium tuberculosis*), fungus, or proteus (2,5,7,9).

Risk factors for UTI

- Obstruction: Resultant urinary stasis increases the infection risk.
- VUR: Most common uropathy in pediatric UTI (30-40% of cases); VUR may cause renal failure due to renal scarring from frequent UTIs.
- Diabetes mellitus: Increases the frequency of ABU and UTI.

- Pregnancy: ABU occurs in 2-10% of pregnant women; if untreated, 1/3rd of these patients develop pyelonephritis.
- Urolithiasis: Obstruction and mucosal damage predispose to UTI.
- HIV: Increase the risk by 5 times.
- Renal papillary necrosis: Caused by infection, excessive use of analgesics, sickle cell anemia, and obstruction.
- Old age: UTI occurs frequently due to ABU, hygiene problems, neurogenic and obstructive bladder. Postmenopausal estrogen deficiency changes vaginal pH and microflora (lactobacilli disappear and *E. coli* colonize) leading to senile vaginitis and urethritis.
- Uncircumcision: About 85% higher incidence of UTI in uncircumcised men.
- Others: Nephrocalcinosis, chronic renal failure, urological interventions, gout, catheterization, renal transplantation, hyperphosphatemia, long-term steroid therapy, bladder prolapse, obesity, frequent sexual contact, anal intercourse, use of spermicides, and diaphragm (1,2,5,7,8,10,13).

Antibiotic treatment

It is essential to ascertain antibiotic sensitivity against regionally active microorganisms before initiating empirical treatment. Local antibiogram results (performed in regional hospitals) can help family physicians administer empirical treatment for UTIs with 95% accuracy (1,15). Further, the treatment efficacy depends upon the renal drug elimination rate and the duration for which the serum minimum inhibitory concentration (MIC) of the antimicrobial used is maintained (2).

Antibiotic treatment for UTI can be of three types (8):

I. *Empirical therapy:*
When the causative pathogen is not known, the antibiotic choice depends either on the local antibiogram results or the 'predicted possible infection' syndrome (8).
Considerations while selecting the appropriate antibiotic for a possible infection (8,14)**:**

1. Complicated or uncomplicated infection.
2. Can the infection be localized (upper or lower UTI)?
3. Is dipstick test or microscopic analysis sufficient for treatment planning?
4. When to go for a urine culture?
5. Most probable pathogen.
6. Will the antibiotics affect one or all pathogens?
7. Most suitable treatment setting - outpatient or inpatient; and the frequency of visits/controls if monitored in outpatient.
8. Monitoring maternal and feral toxicity in case of a pregnant patient.
9. Age of the patient.
10. Cost-effectiveness and duration of the empirical treatment.
11. Prior use of antibiotics by the patient and whether still using it.
12. Presence of any known antibiotic allergies and the available alternatives.
13. Alternative antibiotics to avoid gastrointestinal side effects (nausea, vomiting, abdominal pain, or diarrhea).
14. Alternative antibiotic if symptoms do not improve or worsen rapidly within 48 hours of antibiotic administration.
15. Probable drug interactions (other drugs used by the patient) with the antibiotics.
16. Whether the MIC achieved in the urine is adequate.
17. Whether patient's kidney and liver function may restrict antibiotic use.
18. Probable negative effects of the antibiotic on the vaginal and fecal flora: in women with recurrent UTIs (prolonged antibiotic use causes vaginitis).
19. Patient's ability (both physical and mental) to comply with antibiotic therapy.

II. *Pathogen-targeted*:
When the causative agent has been cultured, pathogen-targeted treatment is used. Meanwhile, the patient is monitored for the first 48 hours and empirical treatment is started until culture results are available. In the absence of an underlying undrained abscess or antibiotic resistance, the patient's symptoms will improve if the empirical treatment is appropriate; if they do not, the antibiotic treatment is changed based on the culture results.

If empirical treatment without culture yields an insufficient response within 48 hours, culture analysis should be commenced immediately. However, if the culture result is inconclusive, either the antibiotic is considered effective and continued with constant clinical monitoring, or the antibiotic is discontinued for 48 hours, and culture is restarted to determine the necessary antibiotics (8,14).

III. *Preventive/prophylactic antibiotic therapy*: Used in patients with recurrent UTIs; for instance, fosfomycin, TMP-SMX (Trimethoprim/sulfamethoxazole), nitrofurantoin, and cephalexin prophylaxis following sexual intercourse for recurrent bacterial cystitis in sexually active women (Table 1) (8,13).

Table 1. *Antibiotic treatment summary table*

First, MAKE THE DISTINCTION between complicated and uncomplicated UTI.
If complicated, IDENTIFY PATIENTS who can be followed up in the polyclinic.
SEPARATE complicated cases and uncomplicated patients that can be followed up from the outpatient clinic as 'possible' cystitis, recurrence, pyelonephritis.
GET CULTURE if possible.
Until the culture results come, if available, make the antibiotic selection by looking at the REGIONAL ANTIBIOGRAM RESULTS.
If there are no regional results, give the antibiotic according to the recommendations in the ANTIBIOTIC TREATMENT SUMMARY TABLE.
MAKE THE NECESSARY ARRANGEMENTS when the culture result comes.

Commonly used antibiotics for treatment of UTIs in primary care

1. Fluoroquinolones:

Ciprofloxacin is most commonly used for UTI. With an oral bioavailability of 70%, all fluoroquinolones (except moxifloxacin) are safely excreted by the kidneys, however, dose adjustment is required in renal failure with < 50 mL/min creatinine clearance (CrCl). Unlike other fluoroquinolones, Ciprofloxacin does not cause QT prolongation, and no dose adjustment is required in liver failure. Ensure adequate hydration during treatment.

Side effects: The commonest are mild gastrointestinal complaints (nausea, vomiting, and diarrhea) and neurological effects (peripheral neuropathy, cognitive impairments, dizziness, tremors, confusion, altered sensorium, tingling sensation, fatigue, psychiatric symptoms, vision and hearing problems, dysgeusia and altered smell). Additionally, photosensitivity, tendon rupture or tendonitis, muscle pain or weakness, joint pain, or swelling may occur. Neuropathy (persisting months to years, occasionally permanent) may occur at any time during or after the treatment.

Contraindications: Owing to its arthropathic effects, Ciprofloxacin is not recommended in pregnant or breastfeeding women, adolescents, and children <15 years. Not to be used in epileptic patients (1,8,9,13,16,17).

2. TMP-SMX (Trimethoprim/sulfamethoxazole:

Despite significant resistance in E. coli (10-70%), TMP-SMX can effectively treat UTIs with 100% oral bioavailability. It is also excreted via urine.

Side effects: Seen in 6-8% of cases; most common are gastrointestinal complaints (nausea, vomiting, diarrhea, and anorexia) and hypersensitivity; rarely, (1-2/thousand, 0.1%) toxic epidermal necrolysis and Stevens-Johnson syndrome may occur. Additionally, rash, exanthems, psoriasis, nail loss, vasculitis, central nervous system disorders, photosensitivity, hyperkalemia, raised serum creatinine levels (non-toxic effect, glomerular filtration rate (GFR) remains unaffected), or hematological toxicity (megaloblastic anemia, leukopenia, thrombocytopenia) can be seen.

Contraindications: Patients with folate and glucose-6-phosphate dehydrogenase (G6PD) defects, AIDS and pneumocystis pneumonia, and pregnant women (mainly 3rd trimester) (1,8,9,13,17).

3. Nitrofurantoin:

Frequently used in uncomplicated UTIs and prophylactic regimens, nitrofurantoin is recommended for upper UTI, complicated UTI, pyelonephritis, and prostatitis.

Side effects: Include gastrointestinal complaints, peripheral neuropathy, and hepatotoxicity (acute hepatotoxicity - 3/1 million, chronic hepatoxicity - 1/1500). It causes hemolytic anemia in G6PD-

deficient patients; prolonged use may induce a pulmonary hypersensitivity reaction.

Disadvantages and contraindications: Contraindicated in patients with <50 mL/min CrCl, peripheral neuropathy, or G6PD defects. Not suitable for use in the third trimester and children > 1 month of age (1,9,13,17–19).

4. Fosfomycin:
Fosfomycin resistance is present in 1% of *E. coli* and 19% of *Klebsiella* spp. It has 40% oral bioavailability and is excreted through the kidneys.

Side effects: Occur in 5% of cases, most common being diarrhea.

Disadvantages and contraindications: Safe to use during pregnancy (8,17,19).

5. Aminoglycosides:
They are poorly absorbed from the digestive tract, hence, the parenteral route is used in UTIs; also eliminated in urine. Gentamicin is the most preferred for UTIs owing to a higher concentration (50-100 times) in the urinary tract than blood. Drug allergy is extremely low.

Side effects: All aminoglycosides are ototoxic (hearing loss and vestibular toxicity) and nephrotoxic; high doses (treatment >5 days) in the elderly lead to renal failure. Gentamicin causes reversible nephrotoxicity (5-25%) and irreversible ototoxicity (1-5%); can also cause reversible neuromuscular blockage (with calcium gluconate) resulting in respiratory paralysis at very high doses.

Contraindications: Contraindicated in pregnancy, in patients with <50mL/min CrCl, with diabetes and liver failure, and in myasthenia gravis. Extreme caution to be taken when combining with other ototoxic and nephrotoxic drugs; pre-treatment hearing tests are advised, especially in elderly patients (1,8,9,13,17).

6. Cephalosporins:
They are generally excreted through the kidneys; however, ceftriaxone is excreted via the bile. For UTIs, 2nd (cefuroxime, axetil), 3rd (ceftriaxone, cefixime), and 4th (cefepime) generation cephalosporins can be used.

Side effects: Hypersensitivity, gastrointestinal complaints (especially diarrhea), local pain after intramuscular injection, thrombophlebitis after intravenous injection, pseudomembranous colitis, positive Coomb's test, hypoprothrombinemia, and bleeding disorders.

Contraindications: Approximately 10% of cephalosporin allergy is developed in penicillin-sensitive patients. Bile sludge may develop with ceftriaxone (1,8,9,13,17).

Possible drug interactions while treating UTI

a) TMP-SMX: with warfarin (markedly increases prothrombin time), methotrexate (increases concentration), phenytoin (half-life extended with TMP-SMX), rifampicin, thiazide and similar diuretics (increases the incidence of thrombocytopenia), primetamine (causes megaloblastic anemia; shortens the half-life of TMP-SMX when used for > 1 week) and pyrimethamine (1,8,9,13,17).
b) Nitrofurantoin: with fluoroquinolones, probenecid, and magnesium.
c) Fluoroquinolones: with theophylline (increases plasma theophylline), corticosteroids (risk of tendon rupture/tendinitis), antidiabetics (hypoglycemia or hyperglycemia), antacids containing magnesium or aluminum, sucralfate, iron, zinc (reduced oral absorption – use either 2 hours before or 4 hours after); warfarin (altered coagulation profile), and antiepileptics (reduced seizure threshold) (1,8,9,13,16,17).
d) Aminoglycosides with loop diuretics, other ototoxic and nephrotoxic drugs (nephrotoxicity increases as they are also excreted through the kidneys).
e) Cephalosporins with alcohol and alcohol-containing drugs (severe disulfiram-like reactions may occur with cefoperazone) (1,8,9,13,17).

Dose adjustment in renal failure

Clinically, GFR is considered while adjusting the dose in renal failure and creatinine clearance (in mL/min) is an indicator of GFR (normal range = 90-130 mL/min for adults; 60-90 mL/min for children and the elderly). No dose adjustment is

generally required for any of the aforementioned antibiotics unless CrCl is <50 mL/min (13).

Dose adjustment in liver failure

If serum bilirubin is <2 mg/dl, albumin is >3.5 g/dl, prothrombin time prolongation is <4s, and if there is no acidity and encephalopathy, outpatient treatment for UTI can be done (1,13).

Nitrofurantoin (prolonged use) and aminoglycosides are not suitable; TMP-SMX and cephalosporins (like ceftriaxone) should be used with caution. Fluoroquinolones and fosfomycin are safe (1,13).

Antibiotics for UTI in pregnancy

Aminopenicillins, cephalosporins, nitrofurantoin, fosfomycin 'B', fluoroquinolones, TMP-SMX, and aminoglycosides are included in category 'C' for pregnancy; hence, are not preferred because of high aminopenicillin resistance (ampicillin, bacampicillin, and amoxicillin). TMP-SMX, if given near delivery, may cause jaundice and/or kernicterus in the neonate, while nitrofurantoin can cause hemolytic anemia; therefore, neither is given in the third trimester (1,13).

Antibiotics for UTI in nursing mothers

Aminopenicillins, cephalosporins, TMP-SMX, and nitrofurantoin are safe during lactation because of their low passage into breast milk. Whereas, fluoroquinolones and aminoglycosides are not recommended (1,13).

Uncomplicated cystitis

Mainly related to sexual intercourse in young, sexually active women; *E. coli* is the commonest pathogen (75-90%). These patients can be categorized as non-pregnant women; and pregnant women, males (≥16 years), children (<16 years). It is diagnosed in women as – a non-pregnant female with a history of lower UTI symptoms (dysuria, frequent urination, and urgency requiring strong urination), no vaginal discharge or irritation, and a positive urine dipstick test. Risk factors for cystitis include using a spermicide, a new sexual partner, and maternal and childhood UTI (2,10).

Urine culture is advisable in these patients if there is – a male patient, suspected acute pyelonephritis, pregnant patient, female with atypical symptoms, or persisting or recurring symptoms within 4 weeks of treatment cessation (2,10).

In non-pregnant females, primarily, either fosfomycin (3 g single dose (OD) daily) or nitrofurantoin (100 mg twice daily (BD) or 50 mg 4 times a day (QD) for 3 days) is given. Either drug can be used in case of no improvement. Drug alternatives include TMP-SMX and cephalosporins – using cefadroxil 500 mg (BD) for 3 days, whereas TMP-SMX 160/800 mg in two doses for 3 days can be used if the local *E. coli* resistance rate is <20%. Aminopenicillins and beta-lactamase inhibitors combined with aminopenicillins (ampicillin/sulbactam or amoxicillin/clavulanic acid) are not recommended for empirical therapy due to high *E. coli* resistance. Fluoroquinolones should only be used as a replacement (10,14).

In pregnant women, cephalosporins (cephalexin), fosfomycin, and nitrofurantoin (except in G6PD deficiency and the 3rd trimester) can be used. Cephalexin (500 mg BD for a week), fosfomycin (3 g OD daily), or nitrofurantoin (100 mg BD or 50 mg QD for a week) can be given. Except for the 3rd trimester, TMP-SMX can be given in two doses of 160/800 mg for 7 days. Aminopenicillins can only be given with positive culture sensitivity; empirical treatment is avoided due to high resistance (10,14).

Prostate involvement in males can complicate the infection. TMP-SMX (160/800 mg BD) or fluoroquinolones (ciprofloxacin, 500 mg BD) for a week are used. Therapeutic levels of nitrofurantoin and fosfomycin are not achieved in the prostate, therefore, they are avoided (10,14).

Urinalysis and urine cultures are usually not indicated in asymptomatic patients, and a culture/antibiogram is required only when symptoms persist by the end of treatment or improve but recur within two weeks. In this case, it is assumed that the pathogen is not susceptible to the antibiotic used and a new antibiotic be used for seven days based on the antibiogram (Table 2) (10,14).

Asymptomatic bacteriuria in adults

Asymptomatic bacteriuria (ABU) is commensal colonization since bacteriuria without pyuria indicates contamination rather than infection. Sans urinary tract symptoms, ABU is the formation of ~10^5 colonies/ml in midstream urine culture taken twice consecutively in women and once in men. It is encountered in healthy premenopausal women (1-5%), healthy elderly (4-19%), diabetic patients (0.7-27%), pregnant women (2-10%), nursing home patients (15-50%), and in 23-89% of patients with spinal cord injury; rarely seen in young men and chronic bacterial prostatitis should be considered when detected. The bacterial spectrum in ABU is similar to complicated or uncomplicated UTIs (2,4,20,5–12).

Treatment: Same as in uncomplicated cystitis. Pregnant women, children >4 years, patients with severe diabetes, and proteus infection having ABU should always be treated even without symptoms (7). Unlike non-pregnant women, bacteriuria in pregnancy does not pass spontaneously (2,10). No treatment is required even with ≥10^5 cfu/mL in urine culture in – women without concomitant risk factors, postmenopausal women, elderly patients in nursing homes and well-controlled diabetes, recurrent UTIs, neurogenic bladder and spinal cord injury, catheter-related bacteriuria, or with a transplanted kidney (Table 2) (10,13).

Uncomplicated recurrent UTIs

UTI that occurs twice or more within 6 months, or thrice or more in a year, in non-pregnant patients without a urinary catheter is defined as recurrent UTI (2,5,8,9). Infected stones, chronic bacterial prostatitis, unilateral infected atrophic kidney, foreign bodies, infected renal cyst associated with renal calyces, papillary necrosis, ectopic ureter, and urethral diverticula frequently cause recurrent UTI; urine culture is necessary for diagnosis. Cystoscopy and radiological evaluation are usually not required. Risk factors for adolescent and pre-menopausal females are similar to uncomplicated cystitis; whereas, postmenopausal elderly women with a history of premenopausal UTI, urinary incontinence, senile vaginitis, cystocele, post-micturition residue, presence of a urinary catheter, and senile functional impairment are at risk (2,4,20,5–12).

Treatment: Includes risk factor avoidance, non-antimicrobial measures, and antimicrobial prophylaxis. Behavioral changes within the scope of non-antimicrobial measures include reducing fluid intake, practicing delaying urination, delaying urination after sexual intercourse, wiping from front to back after defecation, washing the area with antiseptics, using diapers in patients with fecal incontinence making urine alkaline (10,14). Although vaginal estrogen replacement therapy is partially beneficial in postmenopausal women, immunoactive prophylaxis (such as OM-89 or Uro-Vaxom R) can be used for all age groups.

Antibiotics same as in uncomplicated cystitis can be given as continuous low-dose prophylaxis (3-6 months) or post-intercourse prophylaxis. Nitrofurantoin (50 mg or 100 mg OD daily), fosfomycin (3 g once every 10 days), trimethoprim (100 mg OD daily), and cephalexin (125 mg or 250 mg OD daily) or cefaclor (250 mg OD daily) can be given during pregnancy. Post-sexual prophylaxis reduces UTI risk in pregnant women with a history of pre-conception recurrent UTIs. Self-diagnosis and short-term self-treatment with an antibiotic are allowed in eligible patients (Table 2) (10).

Uncomplicated pyelonephritis

Commonly presenting with fever (>38°C), chills, flank pain, nausea, vomiting, or costovertebral angle tenderness, pyelonephritis may present with typical symptoms of cystitis and vice versa. Pregnancy with acute pyelonephritis comes under complicated UTIs and may lead to premature birth or infant death (2,10).

The timely distinction between uncomplicated and complicated pyelonephritis is essential to prevent urosepsis. In urinalysis, leukocytes and bacteria clusters are usually seen, and leukocytosis, C-reactive protein, and erythrocyte sedimentation rate are monitored. A culture antibiogram, renal USG, and CT (magnetic resonance imaging in case of pregnancy) should be done (2,10).

Treatment: Patients >16 years of age, males or non-pregnant females, and those who do not require hospitalization are candidates for primary oral empirical treatment, which includes cephalosporins (cephalexin 500 mg BD/TD for 7-10 days) or fluoroquinolones (ciprofloxacin 500-750mg BD for 7 days). Based on positive culture sensitivity, co-amoxiclav (500/125 mg TD for 7-10 days) or TMP-SMX (160/800 mg BD for 14 days) can be given (2,10,21).

Table 2. *Arranging antibiotic treatment for some groups*

Asymptomatic Bacteriuria In Adults	It is the same as in uncomplicated cystitis.
Non-Complicated Cystitis	
Non-pregnant women	First choice: Fosfomycin or Nitrofurantoin. Second choice: TMP-SMX or Cephalosporins Third choice: Fluoroquinolones *Duration of treatment is 3 days, excluding Fosfomycin.*
Pregnant women	First choice: Cephalosporins or Fosfomycin or Nitrofurantoin * Second choice: TMP-SMX * *Duration of treatment is 7 days, excluding Fosfomycin.* ** Not used in the last trimester of pregnancy*
Males (≥16 years)	First choice: TMP-SMX or Fluoroquinolones *Duration of treatment is 7 days.*
Non-Complicated Recurrent UTI	The choice of antibiotics is the same as for uncomplicated cystitis, but the durations and doses of treatment are different. Usually once a day in low doses for 3-6 months.
Non-Complicated Pyelonephritis	
If the patient is ≥16 years of age, is a male or non-pregnant woman, and does not require hospitalization:	In oral use: First choice: Cephalosporins or fluoroquinolones, or Co-amoxiclav or TMP-SMX provided that the culture results are available and sensitive. *Duration of treatment is 7 days.* In intravenous (IV) use: First choice: Cephalosporins or fluoroquinolones or aminoglycosides
If the patient is ≥16 years of age, is a male or non-pregnant woman, and requires hospitalization:	Antibiotics in the above IV treatment are used in the same way.
If the patient is a pregnant woman over the age of 12	If the symptoms are mild and the patient is suitable for follow-up from the polyclinic: First choice: Oral cephalosporias *Duration of treatment is 7-10 days.* If hospitalization is required: First choice: IV Cephalosporins alone. Second choice: IV Cephalosporins in combination with aminoglycosides Third choice: Combination of IV aminoglycoside with ampicillin.
UTI Treatment In Children	
IV antibiotic options for children younger than 3 months	First choice: Ampicillin / amoxicillin with 3rd generation cephalosporin. Second choice: Ampicillin in combination with gentamicin.
Children ≥3 months and <16 years	Oral treatment choices: TMP-SMX, nitrofurantoin, cephalosporins, or amoxicillin (if the culture result is available and there is sensitivity) IV treatment choices: Cephalosporins, aminoglycosides *Duration of treatment is 7-14 days*

Intravenous (IV) treatment for patients managed without hospitalization includes cefuroxime (750 mg-1.5 g TD/QD), ceftriaxone (1-2 g daily), cephalosporins or ciprofloxacin (400 mg BD/TD), or gentamicin (initially 5-7 mg/kg OD, then according to serum concentration). This treatment is also valid for hospitalized patients.

Oral therapy is initiated when the patient improves and allows oral fluid intake (2,10,21).

In case the patient is pregnant, has mild symptoms, and is suitable for outpatient follow-up, oral cephalexin is preferred (500 mg BD/TD; in severe cases, 1-1.5 g TD/QD for 7-10 days). Severe cases require hospitalization; cefuroxime (750-1500 mg IV BD/QD) or ceftriaxone (2 g per day) alone or combined with aminoglycosides or with ampicillin can be used. If the patient improves, 7-10 days of oral treatment are started, followed by low-dose prophylaxis with nitrofurantoin, amoxicillin, or cephalexin. Approximately 95% of pregnant women improve within 24 hours (Table 2) (2,10,21).

Treatment of UTIs in children

The presenting features may be non-specific, varying with the child's age and the infection site. *E. coli* and *K. pneumoniae* are the most frequently isolated pathogens. Pediatric UTI (with 12-30% recurrence, and 25-33% incidence of VUR) is a complicated infection; therefore, urinary USG and VCUG (voiding cystourethrography) are used to determine underlying urological abnormalities. Children <3 years of age with VUR are prone to developing renal scarring with recurrent UTIs and inadequate treatment (8,22).

Treatment aims to improve acute symptoms and prevent complications and renal scarring that causes hypertension and chronic renal failure (4,8,22,23). Oral antibiotics are used in most children; if not possible, hospitalization and parenteral treatment are followed, which includes – (age <3 months) ampicillin/amoxicillin with 3rd generation cephalosporin (cefotaxime or ceftriaxone) or ampicillin with gentamicin. Oral therapy is started when the patient improves (8,24).

Primary oral antibiotics for non-high-risk children ≥3 months-16 years include amoxicillin, TMP-SMX, nitrofurantoin, or cephalosporins. If the culture results report sensitivity, amoxicillin 125 mg/250 mg TD is given till 5 years of age), and 500 mg TD for 5-15 years old.

For children aging >3months to 11 years, TMP-SMX (4 mg/kg BD, based on the trimethoprim dose) and nitrofurantoin dose of 750 mg/kg QD is given. For the 12-15 years group, TMP-SMX (160/800 mg BD) and nitrofurantoin (100 mg BD or 50 mg QD) are preferred. Cephalexin (12.5 mg/kg BD) can be given up to 11 years of age, and 500 mg BD for the 12-15 years group.

IV treatment options in children aged ≥3 months are cefuroxime (20 mg/kg TD, 50-60 g/kg TD/QD in severe cases), ceftriaxone (50-80 mg/kg OD, maximum 4 g/day), and gentamicin (initially 7 mg/kg OD, subsequent doses are adjusted based on serum gentamicin concentration).

Recommended treatment duration is 7 days for uncomplicated UTI (e.g., cystitis) and 14 days for pyelonephritis. Resistance rates are high (30-38% for *E. coli)* even with 3rd generation cephalosporins; therefore, antibiogram results should be considered (Table 2) (4,8,10,14,22,23).

Indications for Hospital Referral

If the symptoms worsen rapidly, no improvement within 48 hours, systemic deterioration, clinical features of sepsis, history of antibiotic use causing bacterial resistance, or the possibility of a different diagnosis (14).

Conclusion

Family physicians can effectively treat UTIs with empirical antibiotics; however, to prevent unnecessary drug use, regional antibiogram resistance results should be published annually by medical, educational, and research faculties. Additionally, differentiating between complicated and uncomplicated cases may help the physician decide on hospital referral.

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