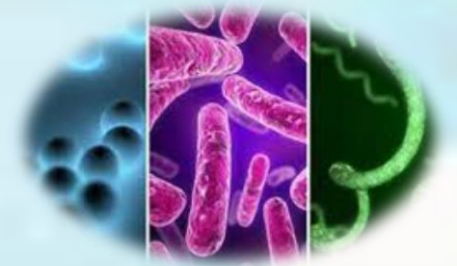


Urinary Tract Infections



13 Aban Drug and Poison Information Center

Dr. Nilofar Khoshnam Rad

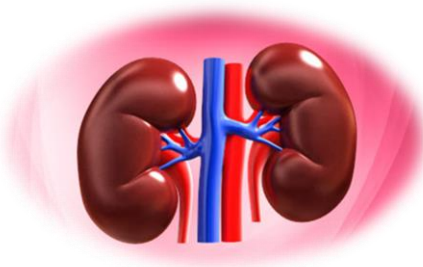
Pharm.D, Clinical pharmacist



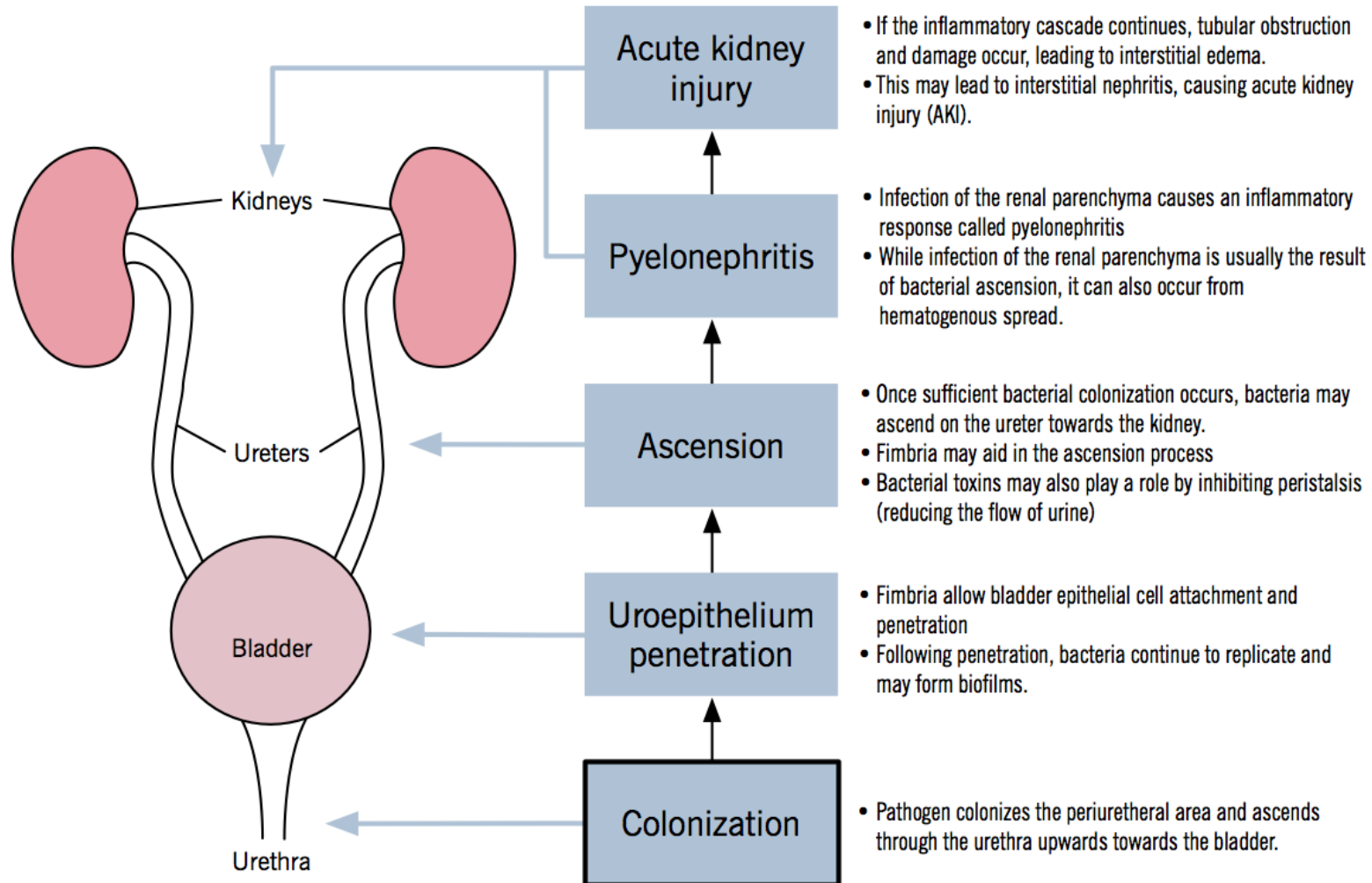
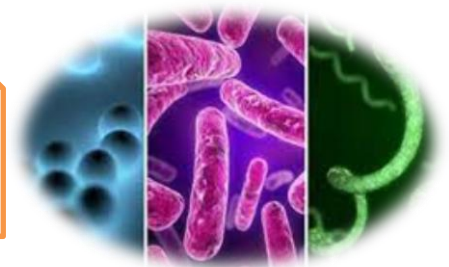
Definitions



- ❑ Among the **most common** bacterial infections
- ❑ Affecting **150 million people worldwide each year**
- ❑ Men and women may become infected
- ❑ UTIs are traditionally considered a disease of women, among whom **50%** will be affected during their lifespan
- ❑ Approximately 25% of women presenting with a first episode of bacterial cystitis go on to suffer recurrent UTI (rUTI) within 6 months, some having six or more infections in the year following the initial episode
- ❑ after 50: men are increasingly affected because of prostate problems



Pathophysiology



Introduction



Cystitis

Risk factors

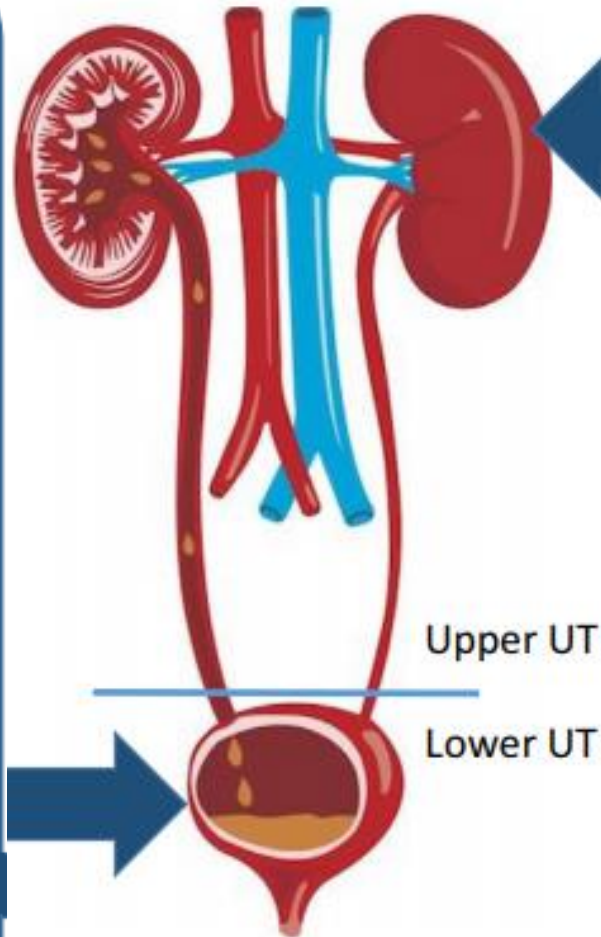
- Female sex, history of UTI
- Sexual activity
- Vaginal infection
- Diabetes, obesity, genetic susceptibility

Clinical symptoms

- Frequent and urgent urination
- Dysuria, suprapubic pain
- Nocturia, hematuria, malaise

Causative organisms

- UPEC
- *Klebsiella pneumoniae*
- *Staphylococcus saprophyticus*
- *Enterococcus faecalis*
- Others



Pyelonephritis

Risk factors

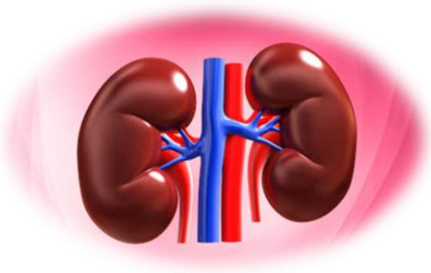
- Diabetes
- HIV/AIDS
- Iatrogenic immunosuppression
- Congenital or acquired urodynamic abnormalities

Clinical symptoms

- Back and/or flank pain
- Fever, chills, malaise
- Nausea, vomiting, anorexia

Causative organisms

- UPEC
- *Klebsiella pneumoniae*
- *Staphylococcus aureus*
- *Enterococcus faecalis*
- *Proteus* spp
- Others



Simple vs. Complicated



Approach to categorizing UTI in adults and adolescents

Acute simple cystitis

- Confined to the bladder
- No signs or symptoms that suggest an upper tract or systemic infection

Acute complicated UTI

Acute UTI accompanied by signs or symptoms that suggest extension of infection beyond the bladder:

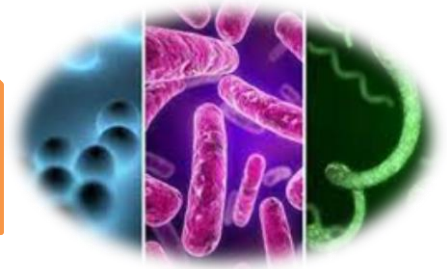
- Fever ($>99.9^{\circ}\text{F}/37.7^{\circ}\text{C}$)
- Chills, rigors, significant fatigue or malaise beyond baseline, or other features of systemic illness
- Flank pain
- Costo-vertebral angle (CVA) tenderness
- Pelvic or perineal pain in men

Special populations with unique management considerations

- Pregnant women
- Renal transplant recipients



Simple vs. Complicated



Underlying urologic Abnormalities:
nephrolithiasis,
strictures, stents, or
urinary diversions

Immunocompromising conditions:
such as neutropenia or
advanced HIV infection

**Poorly controlled
diabetes mellitus**

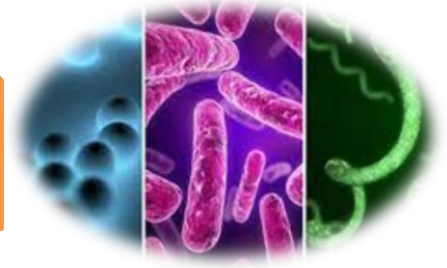
- If no concerning symptoms for upper tract or systemic infection
- Higher risk for more serious infection and have not traditionally been included in studies evaluating the typical antibiotic regimens
- Follow such patients more closely and/or have a low threshold to manage as complicated UTI

Acute simple cystitis in women

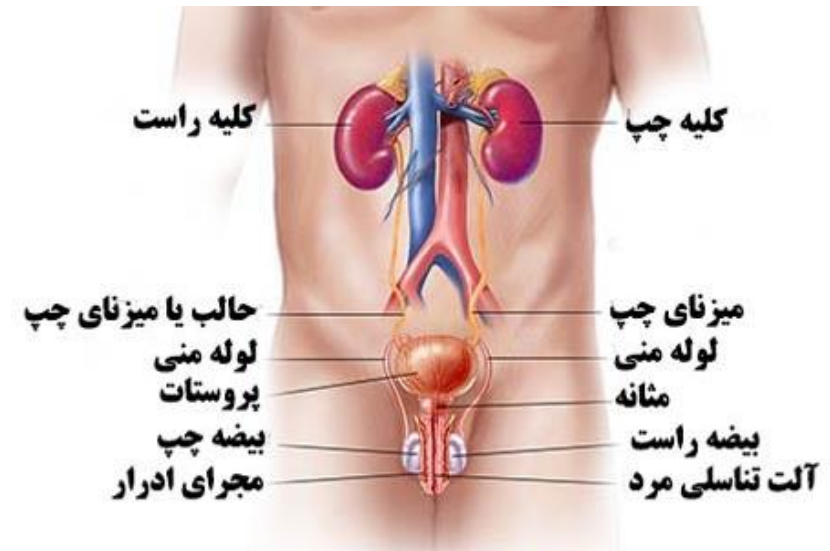
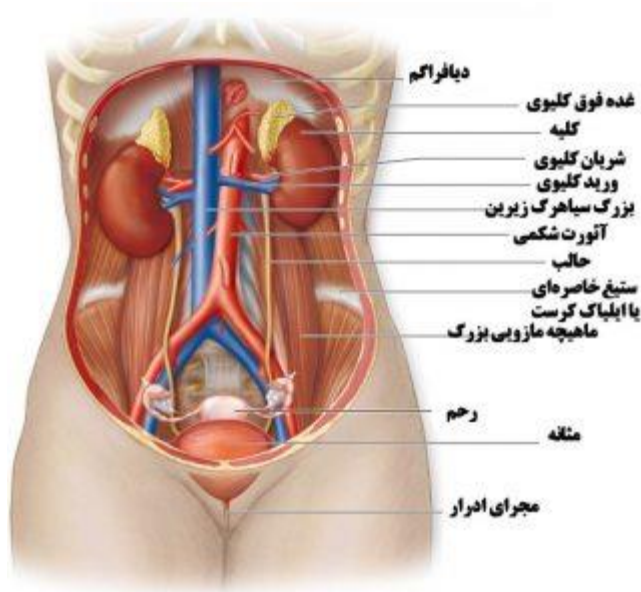




Risk factors



- Cystitis among women is extremely common.
- The shorter distance from the anus to the urethra
- Risk factors for cystitis include recent sexual intercourse and a history of UTI
- Use of spermicide-coated condoms, diaphragms, and spermicides alone are also associated with an increased cystitis risk.
- Diabetes mellitus and structural or functional urinary tract abnormalities





Microbiology



Common

- *Escherichia coli* (75 to 95%)
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Staphylococcus saprophyticus*

Resistant Risk Factors (prior 3 months)

- A multidrug-resistant gram-negative urinary isolate
- Inpatient stay at a health care facility
- Use of a fluoroquinolone, trimethoprim-sulfamethoxazole, or broad-spectrum beta-lactam
- Travel to parts of the world with high rates of multidrug-resistance

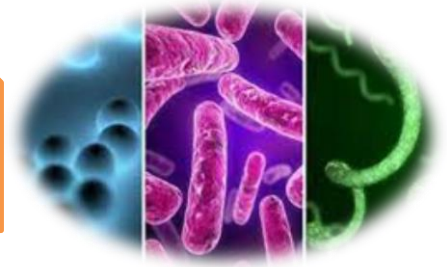
Contamination

- Lactobacilli enterococci
- Group B streptococci
- Coagulase-negative staphylococci other than *S. saprophyticus*

Among otherwise healthy nonpregnant women
May be appropriate to consider these organisms the likely causative agent in symptomatic women when found in voided midstream urine at high counts and with pure growth.



Signs & Symptoms



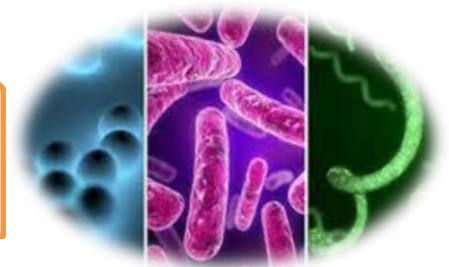
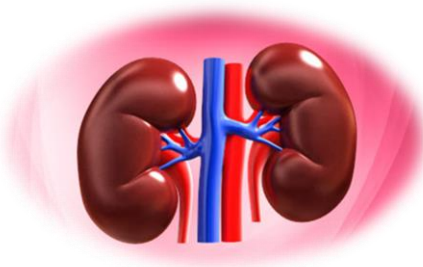
Classic

- Dysuria
- Urinary frequency,
- Urinary urgency,
- Supra-pubic pain
- Hematuria

Older women

- Chronic dysuria, urinary incontinence
- **Acute dysuria** (less than one week duration), **new or worsening** urinary urgency, new incontinence, frequency, gross hematuria, and suprapubic pain or tenderness
- Fever

Color and odor of urine are influenced by ingestion of certain foods, dehydration, and other noninfectious factors. Thus, increased fluid intake and careful observation are reasonable initial approaches to patients who complain of changes in odor or color of urine.

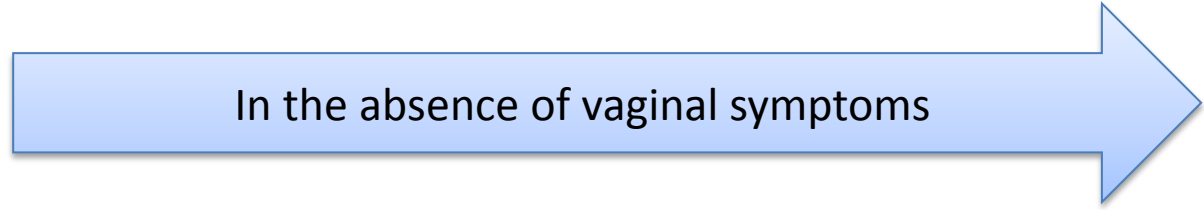


Clinical presentation

Suspicious
Dyssuria, urinary frequency or urgency, and/or suprapubic pain



50%



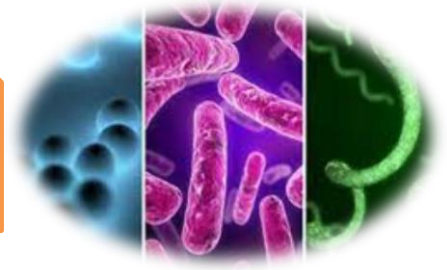
90%

× fevers/chills and flank pain ×

For most women with suspected acute simple cystitis, particularly those with classic symptoms, no additional testing is warranted to make the diagnosis.

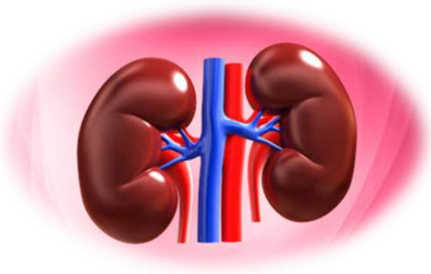


Physical examination



Costovertebral angle tenderness

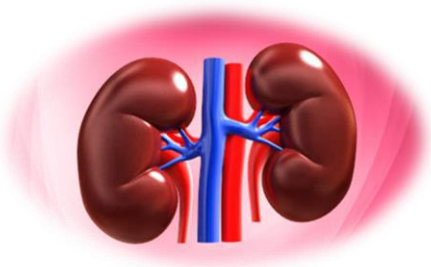




Urine analysis (U.A)



<i>Component</i>	<i>Result</i>	<i>Reference range</i>
Dipstick urinalysis		
Color	Pale yellow	—
Clarity	Clear	—
pH	6.5	—
Specific gravity	1.010	—
Glucose	Negative	Negative
Blood	1+	Negative
Ketones	Negative	Negative
Protein	Negative	Negative
Urobilinogen	Negative	Negative
Bilirubin	Negative	Negative
Leukocyte esterase	Negative	Negative
Nitrite	Negative	Negative
Urine microscopy		
White blood cells	1 per high-power field	0 to 5 per high-power field
Red blood cells	7 per high-power field	0 to 4 per high-power field
Squamous epithelial cells	None	None



U.A/U.C



Urinalysis

1

Macroscopic

Color	Yellow
Appereance	Semi clear
Specific Gravity	1010
pH	6
Protien	Neg.
Glucose	Neg.
Ketones	Neg.
Blood/Hb/Myoglobin	Neg.
Bilirubin	Neg.
Urobilinogen	Neg.
Nitrite	Neg

Microscopic

W.B.C	3-4
R.B.C	0-1
Epithelial Cells	4-6
Bacteria	Few
Crystal	1
Cast	1
Mucus	Neg
Pus Cell	Neg
Trichomonas	Neg

Bacteriology

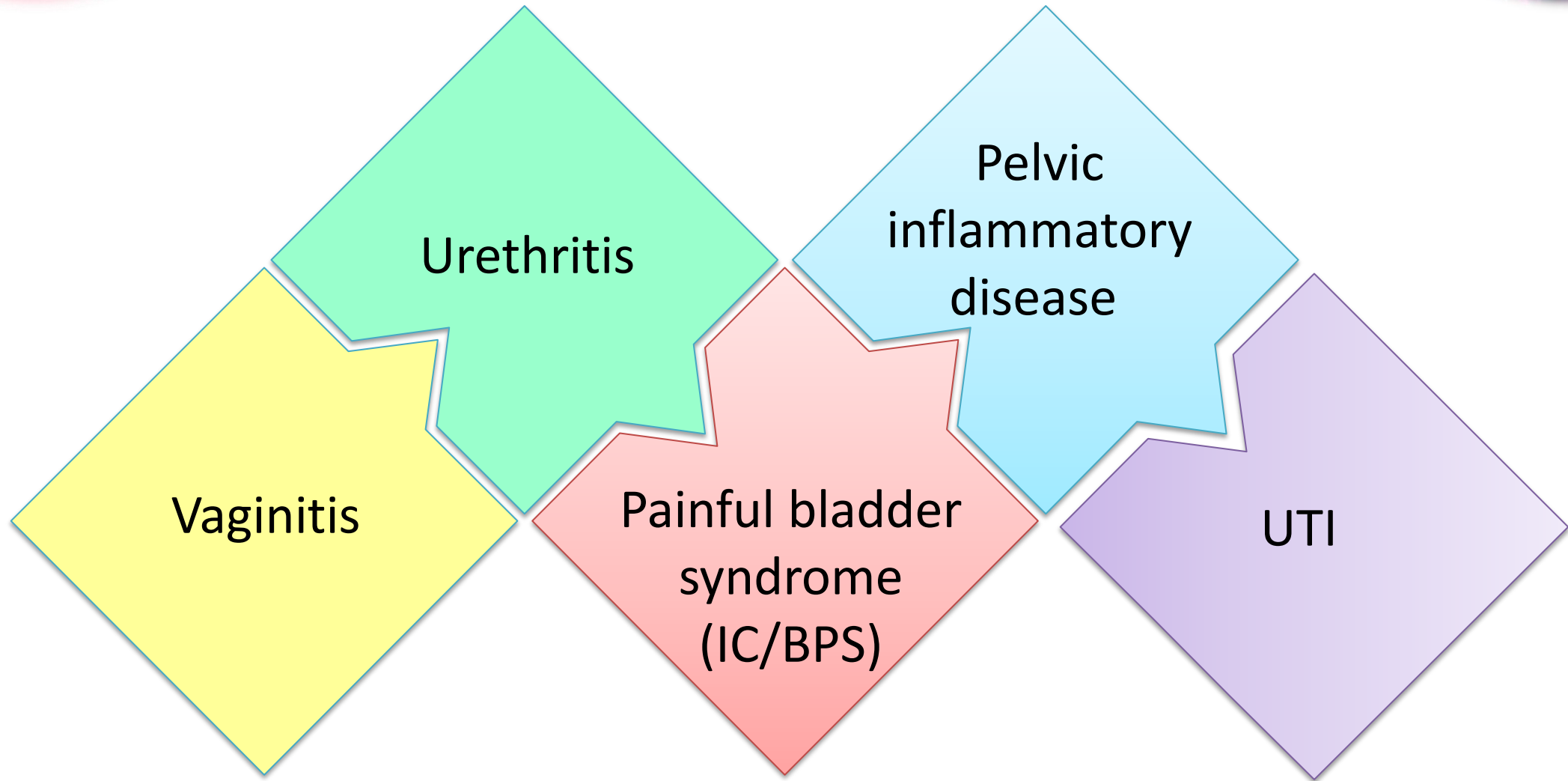
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Test : Urine Culture & S

Specimen	Urine
Colony Count	10000
Culture	Staphylococcus Epidermidis isolated.
Sensitive to	: Imipeneme; Ciprofloxacin; Nitrofurantoin;
Intermediate	: Gentamycin;
Resistant to	: Amoxycillin;



Differential diagnosis





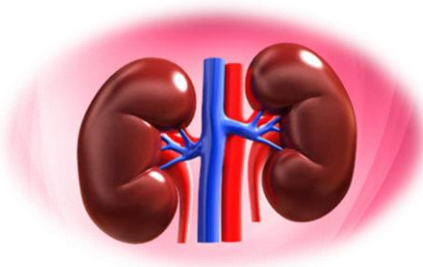
First line agents



Nitrofurantoin monohydrate/macrocrystal 100 mg BD for 5 days



GFR <30 mL/minute: Avoid use



First line agents



Trimethoprim-sulfamethoxazole (160/800 mg) orally twice daily for 3 days





First line agents



Fosfomycin 3 g orally single dose

Oral: Always mix with 3 to 4 oz (90 to 120 mL) cool water before ingesting; do not administer in its dry form or mix with hot water. May be administered without regard to meals.





Second line agents



Amoxicilline-clavunolate 625 mg for 5 to 7 days

Alternatives

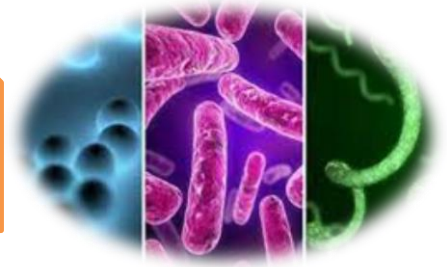
I. β -Lactams (Cefdinir, cefaclor, cephalixin, and cefpodoxime proxetil)
for 5–7 days

II. Fluoroquinolones (not moxifloxacin) for 3 days –
Because of serious adverse effects, avoid if there are other treatment options.

Ampicillin or amoxicillin should not be used for empiric treatment given the high prevalence of resistance to these agents



Deferring therapy



If none of these can be used because of resistance or other concerns, we defer antimicrobial therapy until a regimen can be selected based on results of culture and susceptibility testing.

For acute simple cystitis, studies among women without comorbidities have suggested that deferring antimicrobial therapy until these results are available is a safe strategy





Symptomatic therapy



- Symptoms should respond to antimicrobial therapy within 48 hours.
- Dysuria is usually diminished within a few hours after the start of antimicrobial
- For some patients with severe dysuria: oral phenazopyridine TDS as needed may be useful to relieve discomfort.
- A two-day course is usually sufficient
- Phenazopyridine should not be used chronically since it may mask clinical symptoms requiring clinical evaluation.



GFR \geq 50 mL/minute: 100 to 200 mg every 8 to 12 hours
GFR <50 mL/minute: Avoid use



Follow up



- Follow-up urine cultures are not needed in patients whose symptoms resolve on antimicrobials.
- For patients who had **hematuria** on initial presentation, a urinalysis should be repeated **several weeks** following antimicrobial therapy to evaluate for persistent hematuria.
- Persistent symptoms **after 48 to 72 hours** of empiric antimicrobial therapy or have **recurrent symptoms** within a few weeks of treatment should have additional evaluation.
- **Urine culture and empiric treatment with another antimicrobial agent**
- If symptoms persist in the setting of appropriate antimicrobial therapy, urologic assessment and radiographic imaging (CT) may be appropriate to evaluate for anatomic abnormalities.



Recurrent simple cystitis in women





Definitions



≥2 infections in six months or ≥3 infections in one year

Simple cystitis

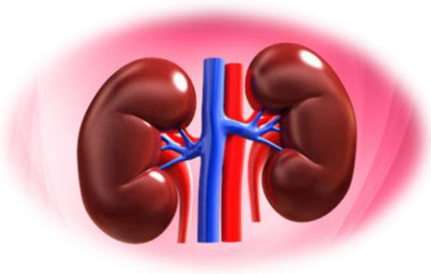
Reinfection

Behavioral risk factors

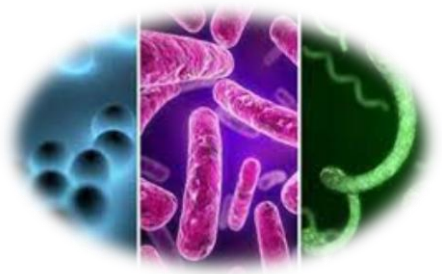
- Spermicide use during the past year
- Having a new sex partner during the past year
- Having a UTI at or before 15 years of age
- Having a mother with a history of UTIs

Urologic risk factors

- Urinary incontinence
- Presence of a cystocele
- Post-voiding residual urine
- Clonization



Evaluation

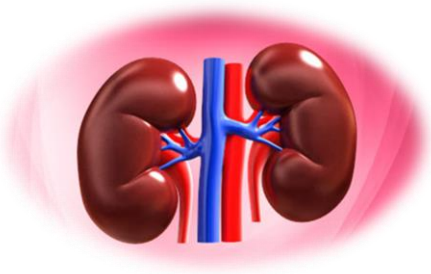


Recurrence?
2 weeks

Relapsing infection
Proteus spp
History of passing stones
Persistent hematuria

E. coli






Prevention



Liberal fluid intake

2 to 3 L/day




Contraception

Does not include a spermicide containing product

Post-coital voiding

May be helpful



Hygiene

From front to back

Topical estrogen

For postmenopausal women



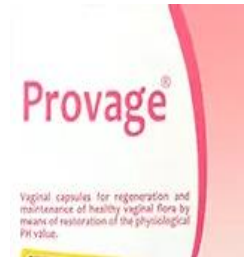
Optional strategies with uncertain benefit



Cranberry



Probiotics



Antiseptics





Antibiotics prophylaxis



Indications

Be sure that it is recurrent!
Very recurrent (2 or more in 6 months)
Who are bothered enough!
No symptoms that are not specific to urinary tract infection

Risk

Direct toxicities, selection of resistance, alteration of microbiome, and secondary Clostridioides [formerly Clostridium] difficile infection



Antibiotics prophylaxis



Antibiotic	Dosing for continuous prophylaxis	Dosing for postcoital prophylaxis
Nitrofurantoin	50 mg QD OR 100 mg QD	50 mg once OR 100 mg once
Trimethoprim-sulfamethoxazole	40 mg/200 mg (half a single-strength tablet) once daily OR 40 mg/200 mg (half a single-strength tablet) three times weekly	40 mg/200 mg (half a single-strength tablet) once OR 80 mg/400 mg (single-strength tablet) once
Trimethoprim	100 mg once daily	100 mg once
Cephalexin	125 mg once daily OR 250 mg once daily	250 mg once
Cefaclor	250 mg once daily	
Fosfomycin	3 g every 7 to 10 days*	

Duration

- 3 months

A conceptual illustration featuring a human hand holding a glowing purple orb that contains a fetus. The scene is set against a blue background with various pills and capsules scattered around. The text is centered over the hand and orb.

Urinary tract infections and asymptomatic bacteriuria in pregnancy



Epidemiology



Incidence

- The same as that in nonpregnant women
- Recurrent bacteriuria is more common
- The incidence of pyelonephritis is higher
- Typically occurs during early pregnancy

Risk factors

Prior UTI
Pre-existing diabetes mellitus
Increased parity
Low socioeconomic status

- Without treatment, 20 to 35 percent of pregnant women with asymptomatic bacteriuria will develop a symptomatic UTI, including pyelonephritis
- This risk is reduced by 70 to 80 percent if bacteriuria is eradicated
- Most cases of pyelonephritis occur during the second and third trimesters.



Pregnancy Outcome



- No correlation has been clearly established between acute cystitis of pregnancy and increased risk of low birth weight, preterm delivery, or pyelonephritis, perhaps because pregnant women with symptomatic lower UTI usually receive treatment.
- Pyelonephritis, however, has been associated with adverse pregnancy outcomes (anemia, sepsis, respiratory distress)
- Not related to trimester

Screening

- First prenatal visit
- Rescreening?



Diagnostic criteria



- For asymptomatic women, bacteriuria is formally defined as two consecutive voided urine specimens with isolation of the same bacterial strain in **quantitative counts of $\geq 10^5$ colony-forming units (cfu)/mL** or a single catheterized urine specimen with one bacterial species isolated in a quantitative count of $\geq 10^2$ cfu/mL
- As most clinical laboratories do not routinely quantify urine isolates to 10^2 cfu/mL, it is reasonable to use a quantitative count **$\geq 10^3$ cfu/mL in a symptomatic pregnant woman** as an indicator of symptomatic UTI.
- If bacteria that are not typical uropathogens (such as lactobacillus) are isolated, the diagnosis of cystitis is typically made only if they are isolated in high bacterial counts ($\geq 10^5$ cfu/mL).



Treatment in pregnancy



Antibiotic	Dose	Duration (days)	Notes
Nitrofurantoin	100 mg BD	5 to 7	Does not achieve therapeutic levels in the kidneys so should not be used if pyelonephritis is suspected. Avoid use during the first trimester and at term if other options are available.
Amoxicillin	500 mg TDS 875 mg BD	5 to 7	Resistance may limit its utility among gram-negative pathogens.
Amoxicillin-clavulanate	500 mg TDS 875 mg BD	5 to 7	
Cephalexin	250 to 500 mg QID	5 to 7	
Cefpodoxime	100 mg BD	5 to 7	
Fosfomycin	3 g single dose		Does not achieve therapeutic levels in the kidneys so should not be used if pyelonephritis is suspected.
Trimethoprim-sulfamethoxazole	800/160 mg BD	3	Avoid during the first trimester and at term.



Antibiotics to avoid

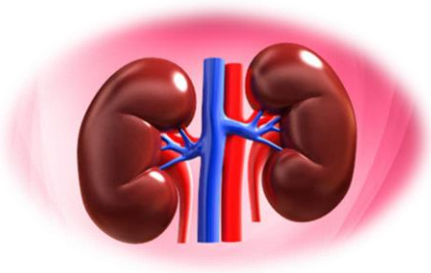


- Tetracyclines (adverse effects on fetal teeth and bones)
- Aminoglycosides (ototoxicity following prolonged fetal exposure)
- Fluoroquinolones; avoid during pregnancy and lactation (toxic to developing cartilage)
- Trimethoprim-sulfamethoxazole; avoid during first and third trimester
- Nitofurnatoin; avoid during first and third trimester

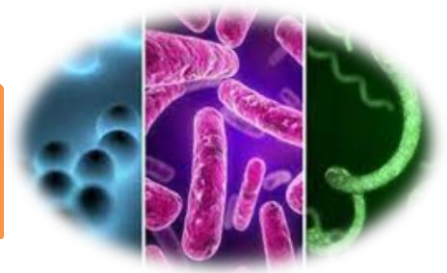


Complicated UTI





Simple vs. Complicated



Approach to categorizing UTI in adults and adolescents

Acute simple cystitis

- Confined to the bladder
- No signs or symptoms that suggest an upper tract or systemic infection

Acute complicated UTI

Acute UTI accompanied by signs or symptoms that suggest extension of infection beyond the bladder:

- Fever ($>99.9^{\circ}\text{F}/37.7^{\circ}\text{C}$)
- Chills, rigors, significant fatigue or malaise beyond baseline, or other features of systemic illness
- Flank pain
- Costo-vertebral angle (CVA) tenderness
- Pelvic or perineal pain in men

Special populations with unique management considerations

- Pregnant women
- Renal transplant recipients



Complications



Complications

- Bacteremia
- Sepsis
- Multiple organ system dysfunction
- Shock
- Acute renal failure

Risk factors

- Urinary tract obstruction
- Recent urinary tract instrumentation
- Urinary tract abnormalities
- Elderly
- Diabetes mellitus

Acute pyelonephritis can also be complicated by progression of the upper urinary tract infection to renal corticomedullary abscess, perinephric abscess, emphysematous pyelonephritis, or papillary necrosis.

Risk factors for such complications include urinary tract obstruction and diabetes mellitus (particularly for emphysematous pyelonephritis and papillary necrosis)



Diagnostic approach



- Acute complicated urinary tract infection (UTI) should be suspected in patients with dysuria, urinary frequency or urgency, or suprapubic pain who also have fever, chills, flank pain, pelvic or perineal pain (in men), or who otherwise appear clinically ill.
- Acute pyelonephritis, specifically, should be suspected in patients presenting with fever and flank pain, even in the absence of typical symptoms of cystitis.
- Acute complicated UTI is also often suspected in patients with non-localizing fever or sepsis. Evaluation includes examination to assess for other causes of illness and urine studies.
- Xanthogranulomatous pyelonephritis



Microbiology



Common

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Staphylococcus aureus* (MRSA, MSSA)
- *Pseudomonas*
- *Staphylococcus saprophyticus*
- *Candida spp.*

MDR risk factors

- An MDR, gram-negative urinary isolate
- Inpatient stay at a health care facility (eg, hospital, nursing home, long-term acute care facility)
- Use of a fluoroquinolone, TMP-SMX, or broad-spectrum beta-lactam (eg, third- or later-generation cephalosporin)
- Travel to parts of the world with high rates of MDR organisms



Management

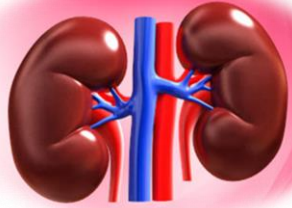


Hospitalization

- Septic
- Critically ill
- Persistent high fever ($>38.4^{\circ}\text{C}/>101^{\circ}\text{F}$)
- Severe pain
- Marked debility
- Inability to maintain oral hydration or take oral medications

Outpatient

- Mild to moderate
- Can be stabilized with rehydration and antibiotics



Empiric



ICU/ critically ill

- Vancomycin 15 to 20 mg/kg IV every 8 to 12 hours with or without a loading dose
plus
- An antipseudomonal carbapenem:
 - Imipenem 500 mg IV every 6 hours or
 - Meropenem 1 g IV every 8 hours or
 - Doripenem 500 mg IV every 8 hours

Linezolid/ daptomycin

Plazomycin

Cefiderocol

Parenteral fosfomycin

Imaging

Obstruction/critically ill



Empiric



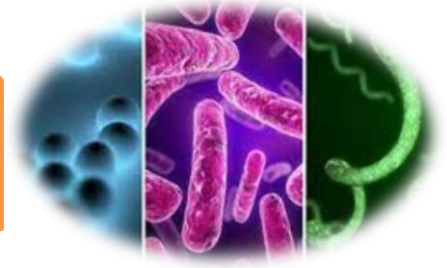
Other hospitalized-No risk factor for MDR

- Ceftriaxone 1 g IV once daily or
- Piperacillin-tazobactam 3.375 g IV every 6 hours or
- Alternatives:
 - Levofloxacin 750 mg IV or orally daily
 - Ciprofloxacin 400 mg IV twice daily
 - Ciprofloxacin 500 mg orally twice daily
 - Ciprofloxacin extended-release 1000 mg orally once daily

- If Enterococcus or Staphylococcus species are suspected (based on prior isolates or gram-positive cocci on urine Gram stain), piperacillin-tazobactam is preferred.
- If Pseudomonas is suspected (based on prior isolates), piperacillin-tazobactam or a fluoroquinolone is preferred.



Empiric



Other hospitalized + risk factor for MDR

- Piperacillin-tazobactam 3.375 g IV every 6 hours or
- An antipseudomonal carbapenem:
 - Imipenem 500 mg IV every 6 hours or
 - Meropenem 1 g IV every 8 hours or
 - Doripenem 500 mg IV every 8 hours

- If VRE or MRSA are suspected (based on prior isolates or gram-positive cocci on urine Gram stain), vancomycin (for MRSA) or daptomycin or linezolid (for VRE) is added.



Empiric



Outpatients- No risk for MDR- No concern for FQ

- For patients with low risk of fluoroquinolone resistance/toxicity:
 - Ciprofloxacin 500 mg orally twice daily for 5 to 7 days or
 - Ciprofloxacin extended-release 1000 mg orally once daily for 5 to 7 days or
 - Levofloxacin 750 mg orally once daily for 5 to 7 days

- If the community prevalence of fluoroquinolone resistance in Escherichia coli is known to be >10%, give one dose of a long-acting parenteral agent prior to the fluoroquinolone:
 - Ceftriaxone 1 g IV or IM once
 - Ertapenem 1 g IV or IM once
 - Gentamicin 5 mg/kg IV or IM once
 - Tobramycin 5 mg/kg IV or IM once



Empiric



Outpatients- No risk for MDR + concern for FQ

- **One dose of a long-acting parenteral agent:**
- Ceftriaxone 1 g IV or IM once
- Ertapenem 1 g IV or IM once
- Gentamicin 5 mg/kg IV or IM once
- Tobramycin 5 mg/kg IV or IM once
- Cefadroxil 1 g orally twice daily for 10 to 14 days



- TMP-SMX one double-strength tablet PO BD for 7 to 10 days
- Amoxicillin-clavulanate 875 mg PO BD for 10 to 14 days or
- Cefpodoxime 200 mg PO BD for 10 to 14 days or
- Cefdinir 300 mg orally twice daily for 10 to 14 days or
- Cefadroxil 1 g orally twice daily for 10 to 14 days

- ❑ In outpatients who are systemically ill or are at risk for more severe illness, we favor continuing the parenteral agent until culture and susceptibility testing results can guide selection of an appropriate oral agent.



Empiric



Outpatients-Risk for MDR

- Ertapenem 1g IV or IM once



- Ciprofloxacin 500 mg orally twice daily for 5 to 7 days or
- Ciprofloxacin extended-release 1000 mg orally once daily for 5 to 7 days or
- Levofloxacin 750 mg orally daily for 5 to 7 days

- If the patient cannot take a fluoroquinolone or has high risk for fluoroquinolone resistance (fluoroquinolone-resistant isolate or fluoroquinolone use in prior three months): Ertapenem 1 g IV or IM once daily until cultures and susceptibility testing return



Culture based therapy

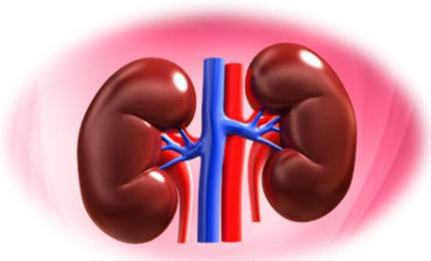


In many cases, broad-spectrum empiric regimens can be replaced by a more narrow-spectrum agent.



- Levofloxacin (750 mg once daily)
- Ciprofloxacin (500 mg twice daily or 1000 extended release once daily)
- Trimethoprim-sulfamethoxazole (160 mg/800 mg tablet orally twice daily)

- Oral beta-lactams?
- If Enterococcus is isolated, amoxicillin (500 mg orally every eight hours or 875 mg twice daily) is the agent of choice if the organism is susceptible.
- Use of nitrofurantoin, fosfomicin, and pivmecillinam should generally be avoided in the setting of acute complicated UTI because they do not achieve adequate tissue levels outside the bladder



Duration of therapy

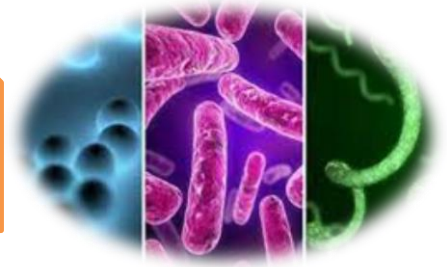


Class	Duration
Fluoroquinolones	5 to 7 days
Cotrimoxazole	7 to 10 days
Beta-lactams	10 to 14 days

- Longer durations may be warranted in patients who have a nidus of infection (such as a nonobstructing stone) that cannot be removed.
- The duration of antimicrobial therapy need not be extended in the setting of bacteremia in the absence of other complicating factors; there is no evidence that bacteremia portends a worse prognosis



Follow up



- Among patients treated as outpatients, those who had pyelonephritis should have close follow-up either face-to-face or by telephone within 48 to 72 hours.
- Persistent symptoms **after 48 to 72 hours** of empiric antimicrobial therapy or have **recurrent symptoms** within a few weeks of treatment should have additional evaluation.
- **Urine culture and empiric treatment with another antimicrobial agent**
- If symptoms persist in the setting of appropriate antimicrobial therapy, urologic assessment and radiographic imaging (CT) may be appropriate to evaluate for anatomic abnormalities.
- For patients who had **hematuria** on initial presentation, a urinalysis should be repeated **several weeks** following antimicrobial therapy to evaluate for persistent hematuria.





Special groups

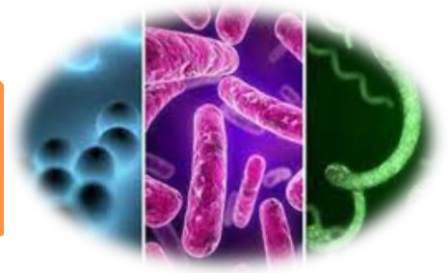


Cystitis in Men

- Cystitis in men without involvement of the prostate is uncommon and should be classed as a complicated infection. (EAU-2021)
- Treatment with antimicrobials penetrating into the prostate tissue is needed in males with symptoms of UTI.
- A treatment duration of at least seven days is recommended, preferably with trimethoprim sulfamethoxazole or a fluoroquinolone if in accordance with susceptibility testing.



Special groups



Cystitis in renal insufficiency

- The choice of antimicrobials may be influenced by decreased renal excretion; however, most antimicrobials, have a wide therapeutic index.
- The exception of antimicrobials with nephrotoxic potential, e.g. aminoglycosides.
- The combination of loop diuretics and a cephalosporin is nephrotoxic.
- Nitrofurantoin is contraindicated in patients with and $eGFR < 30 \text{ ml/min/1.73m}^2$ as accumulation of the drug leads to increased side effects as well as reduced urinary tract recovery, with the risk of treatment failure.



Special groups



Lactating mothers

- Trimethoprim/sulfamethoxazole: has a high success rate in eradicating bacteriuria for women with UTI and is compatible with breastfeeding
- Quinolones are effective and probably compatible with breastfeeding. (many investigators based on arthropathy in animal studies)
- A 7-day course of nitrofurantoin has similar efficacy to TMP/SMX and is compatible with breastfeeding, but it should be avoided in populations at risk for G6PD deficiency

