**Urinary Tract Infections**

After this lecture and the reading, the student should be able to:

* Explain the pathophysiology of urinary tract infections (UTIs)
* Differentiate between complicated and uncomplicated UTIs
* Recognize objective and subjective clinical findings in patients with UTIs
* Identify the most common organisms responsible for each type of UTI
* Describe the spectrum of activity, role in therapy, adverse effect profile, and pharmacology of the antimicrobial agents commonly used in the treatment of UTIs
* Discuss the optimum duration of therapy and be familiar with the dosing of antimicrobials in complicated and uncomplicated UTIs
* Select empiric and definitive therapy for UTIs

**Explain the pathophysiology of urinary tract infections (UTIs)**

<http://www.merckmanuals.com/professional/genitourinary_disorders/urinary_tract_infections_uti/bacterial_urinary_tract_infections.html#v1052786>

The urinary tract, from the kidneys to the urethral meatus, is normally sterile and resistant to bacterial colonization despite frequent contamination of the distal urethra with colonic bacteria. Mechanisms that maintain the tract's sterility include urine acidity, emptying of the bladder at micturition, ureterovesical and urethral sphincters, and various immunologic and mucosal barriers.

About 95% of UTIs occur when bacteria ascend the urethra to the bladder and, in the case of acute uncomplicated pyelonephritis, ascend the ureter to the kidney. The remainder of UTIs are hematogenous. Systemic infection can result from UTI, particularly in the elderly. About 6.5% of cases of hospital-acquired bacteremia are attributable to UTI.

**Complicated UTI** is considered to be present when there are underlying factors that predispose to ascending bacterial infection. Predisposing factors include urinary instrumentation (eg, catheterization, cystoscopy), anatomic abnormalities, and obstruction of urine flow or poor bladder emptying

**Uncomplicated UTI** occurs without underlying abnormality or impairment of urine flow. It is most common in young women but also somewhat common in younger men who have unprotected anal intercourse, an uncircumcised penis, unprotected intercourse with a woman whose vagina is colonized with urinary pathogens, or AIDS. Risk factors in women include sexual intercourse, diaphragm and spermicide use, antibiotic use, and a history of recurrent UTIs. Even use of spermicide-coated condoms increases risk of UTI in women. The increased risk of UTI in women using antibiotics or spermicides probably occurs because of alterations in vaginal flora that allow overgrowth of Escherichia coli. In elderly women, soiling of the perineum due to fecal incontinence increases risk. Patients of both sexes with diabetes have an increased incidence and severity of infections.

**Differentiate between complicated and uncomplicated UTIs**

See above

**Recognize objective and subjective clinical findings in patients with UTIs**

* Subjective
  + Cystitis
* Dysuria
* Frequent urination
* Urgency to urinate
  + Pyelonephritis
    - CVA tenderness/ flank pain
    - N/V, malaise
    - Fever
    - Hematuria
  + Elderly
    - Altered mental status
  + Catheterized pts
* Lack lower S/Sx
* Objective
  + UA
    - **Leukocyte esterase**
    - +/- Blood
    - +/- Nitrite
    - pH
  + Urine microscopy
    - Bacteria
    - **WBCs**
  + Urine C&S
    - Midstream
    - Via catheter
    - Suprapubic bladder aspiration
  + WBCs - serum
  + Blood Cx
* Fever

<https://docs.google.com/viewer?a=v&q=cache:Hci9RGtQoW0J:www.medicaltextbooksrevealed.com/files/16775-53.pdf+most+common+bacteria+responsible+for+urinary+tract+infection&hl=en&gl=us&pid=bl&srcid=ADGEESgFoKvj_U8VkSTGItm8bqKxjlg0Y2YWh5pTdVKK2nzgz4eGWt4any338hd7OHrgrI8gxKPuK1DQGROEKza6NLV031KV7OQKaNzozIACKYLhZNuXrIDP5hxKzzClf5Kcmc400ANd&sig=AHIEtbT2hu6aLjZGP4_kg-QLRShaHTc2NA>

Lower urinary tract infection

Dysuria

Frequency

Suprabupic pain

Malodorous urine

Haematuria

Normal temperature

Upper urinary tract infection

Systematically unwell

Fever

Loin pain & tenderness

Nausea & vomiting

Hypotension or shock

Features of lower UTI

<http://www.aafp.org/afp/2005/0315/p1153.html>

<http://www.urology-textbook.com/urinary-tract-infection-diagnosis.html>

<http://library.med.utah.edu/WebPath/TUTORIAL/URINE/URINE.html>

Urine Analysis

*Macroscopic UA*

Direct visual observations for clarity, color, excessive cellular material or protein, crystallization or precipitation of salts upon standing at RT or in the refrigerator

*Dipstick Chemical Analysis*

pH ~ 5.6 – 6.5 ….. However, depending on the acid-base status, urinary pH may range from as low as 4.5 to as high as 8.0

Specific gravity (which is directly proportional to urine osmolality which measures solute concentration) measures urine density, or the ability of the kidney to concentrate or dilute the urine over that of plasma. Specific gravity between 1.002 and 1.035 on a random sample should be considered normal.

*Leukocyte esterase*

A positive leukocyte esterase test results from the presence of white blood cells either as whole cells or as lysed cells. Pyuria can be detected even if the urine sample contains damaged or lysed WBC's

Microscopic UA

Cell, cast, crystal & bacteria

Men normally have fewer than two white blood cells (WBCs) per high-powered field (HPF); women normally have fewer than five WBCs per HPF

Urine culture

Kass Criteria: In a properly obtainded midstream urine, 105 cfu/ml indicates significant urinary tract infection

* Asymptomatic bacteriuria
  + ≥105 CFU bacteria/mL x2 in asymptomatic pts?

**Identify the most common organisms responsible for each type of UTI**

<https://docs.google.com/viewer?a=v&q=cache:Hci9RGtQoW0J:www.medicaltextbooksrevealed.com/files/16775-53.pdf+most+common+bacteria+responsible+for+urinary+tract+infection&hl=en&gl=us&pid=bl&srcid=ADGEESgFoKvj_U8VkSTGItm8bqKxjlg0Y2YWh5pTdVKK2nzgz4eGWt4any338hd7OHrgrI8gxKPuK1DQGROEKza6NLV031KV7OQKaNzozIACKYLhZNuXrIDP5hxKzzClf5Kcmc400ANd&sig=AHIEtbT2hu6aLjZGP4_kg-QLRShaHTc2NA>

Community-acquired

E. coli 85% of UTIs

Klebsiella spp

Proteus mirabilis

Staphylococcus saprophyticus 5-15% of UTIs

Hospital-acquired

E. coli 50% of UTIs

Klebsiella spp

Citrobacter spp

Enterobacter spp

Pseudomonas aeruginosa

Enterococcus faecalis

<http://trihealth.adam.com/content.aspx?productId=10&pid=10&gid=000036>

**The bacterial strains that cause UTIs include:**

* *Escherichia (E.) coli* is responsible for most uncomplicated cystitis cases in women, especially in younger women. *E. coli* is generally a harmless microorganism originating in the intestines. If it spreads to the vaginal opening, it may invade and colonize the bladder, causing an infection. The spread of *E. coli* to the vaginal opening most commonly occurs when women or girls wipe themselves from back to front after urinating, or after sexual activity.
* *Staphylococcus saprophyticus* accounts for 5 - 15% of UTIs, mostly in younger women.
* *Klebsiella*, *Enterococci*, and *Proteus mirabilis* account for most of remaining bacterial organisms that cause UTIs. They are generally found in UTIs in older women.
* Rare bacterial causes of UTIs include *ureaplasma urealyticum* and *Mycoplasma hominis*, which are typically harmless organisms.

**Organisms in Severe or Complicated Infections**

* The bacteria that cause kidney infections (*pyelonephritis*) are generally the same bacteria that cause cystitis. There is some evidence, however, the *E. coli* strains in pyelonephritis are more virulent (able to spread and cause illness).
* Complicated UTIs that are related to physical or structural conditions are apt to be caused by a wider range of organism. *E. coli* is still the most common organism, but others include *Klebsiella*, *P. mirabilis*, and *Citrobacter*.
* Fungal organisms, such as *Candida* specie*s.* (*Candida albicans* causes the "yeast infections" that also occur in the mouth, digestive tract, and vagina.)
* Other bacteria associated with complicated or severe infection include *Pseudomonas aeruginosa*, *Enterobacter,* and *Serratia* species gram-positive organisms (including *Enterococcus* species).

**Describe the spectrum of activity, role in therapy, adverse effect profile, and pharmacology of the antimicrobial agents commonly used in the treatment of UTIs**

<http://en.wikiversity.org/wiki/Antimicrobial_Agents_II>

**Classification of antibiotics on a spectrum of their antimicrobial activity**

1. With the main influence on the gram-positive microbes: penicillins; **cephalosporins**; macrolides; reserve antibiotics (lincomycin, vancomycin).
2. With main influence on the gram-negative microbes: **aminoglycosides.**
3. Influencing both gram-positive and negative microbes: tetracyclines; levomycetin (chloramphenicol).
4. Influencing both gram-positive and negative microbes, and used locally: polymyxins; neomycin; monomycin; gramicidine.
5. Antifungal antibiotics: nystatin; griseofulvin; amphotericin B.
6. VI. Anticancer preparations: actinomycin, olivomycin, bruneomycin.

**Classification of sulfanilamides**

1. Sulfanilamides which are well absorbed from gastro-intestinal system, with resorbtive action:

*a) short acting (T1/2 about 8 h) - streptocidum, norsulfazolum (sulfathiazolum sodium), sulfadimezinum (sulfadimidine), urosulfanum (sulfacarbamid), aethazolum (sulfaethidole);*

*b) intermediate acting (T1/2 lesser 12-14 h) - sulfazinum (sulfadiazinum), me-tylsulfazinum, sulfamethoxazolum;*

*c) long action time (T1/2 about 24-28 h) – sulfapyridazinum (sulfamethoxypyridazine), sulfamonomethoxinum, sulfadimethoxinum;*

*d) ultralong action time (T1/2 about 65 h) –sulfalenum (sulfametopyrazine).*

B. Sulfanilamides which are badly absorbed from gastro-intestinal system, used for healing of intestinal infections - sulginum (sulfguanidine), phthalazolum (phthalylsulfathiazolum), phthazinum.

C. Combined preparations:  
*a) combination with salicylic acid for healing of non-specific ulceral colitis – salazopyridazinum (salazodin), salazolsulfapyridinum (sulfasalazin);*

*b) preparations containing trimethoprim – co-trimaxazole (biseptol), sulfatonum.*

D. Preparations for local use - sulfacylum-sodium (sodium sulfacetamide), maphenidum, sulfazini silver (silver sulfadiazine). Sodium salts of sulfanilamides.

**Trimethoprim / sulfamethoxazole (1:5 ratio)**

<http://www.antimicrobe.org/drugpopup/TMP-SMX%20rev%2011-08.pdf>

*Antimicrobial spectrum*

*Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Listeria monocytogenes*, *Nocardia asteroids*, *Mycobacterium fortuitum, Escherichia coli, Shigella dysenteriae, Salmonella typhi, Salmonella enteritidis, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Stenotrophomonas maltophilia, Haemophilus influenzae, Pasteurella multocida, Bordetella pertussis, Brucella melitensis, Neisseria gonorrhoeae, Neisseria meningitides*

*E. coli -*

*Staph +*

*Kleb -*

*Proteus -*

*Mechanism of action*

Sulfamethoxazole inhibits the synthesis of dihydrofolic acid. Trimethoprim inhibits thymidine and DNA synthesis. These two agents act synergistically in inhibiting folic acid synthesis.

*Role*

* + Acute uncomplicated cystitis – short course
  + Outpatient pyelonephritis
* Prostatitis

*Dose*

800/160mg tab PO q12h

*Adverse Effects*

GI – nausea, vomiting

Hematologic – pancytopenia, agranulocytosis, anemia, thrombocytopenia

Skin – toxic erythema, erythema nodosum, fixed local eruption, erythema multiforme, Lyell’s syndrome, Exfoliative dermatitis, urticaria, necrotizing vasculitis, photodermatitis, toxic erythema

Renal – transient blood urea and creatinine elevations, crystalluria, acute interstitial nephritis

CNS – headache, confusion, depression, aseptic meningitis

Electrolytes – Hyperkalemia (higher doses)

*Pregnancy* category C

*Pro & Cons*

* Pros
  + Very inexpensive
  + Good for short courses
  + Not a fluoroquinolone
* Cons
  + Resistance
  + Possible hypersensitivity

**Fluoroquinolones**

Cipro- Levo- O-floxacin

Ciprofloxacin

[*http://www.antimicrobe.org/drugpopup/Ciprofloxacin.pdf*](http://www.antimicrobe.org/drugpopup/Ciprofloxacin.pdf)

*Antimicrobial spectrum*

Gram-positive: methicillin-susceptible *Staphylococcus aureus* (MSSA) (lowest quinolone activity vs. MSSA), *Streptococcus pneumoniae*

Gram-negative: *Enterobacteriaceae, H. influenzae, other Haemophilus spp., N. gonorrhoeae, N. meningitides, M. catarrhalis, P. aeruginosa, S. maltophilia*

Atypicals: *Legionella pneumophilia*

*Staph +*

*Mechanism of action*

Inhibition of topoisomerase (DNA gyrase) enzymes, which inhibits relaxation of supercoiled DNA and promotes breakage of double stranded DNA.

*Role*

* Cystitis (no longer 1st line)
* Pyelonephritis
* Prostatitis

*Dose*

Uncomplicated UTI: 250mg PO q12h x 3 days

500mg extended release tablets q24h

Complicated UTI/Pyelonephritis: 500mg PO q12h / 400mg IV q12h x 7-14 days

*Adverse Effects*

CNS: headache, insomnia, dizziness; hallucinations, depression, psychotic reactions (rare)

Connective tissue: tendon injury

Renal: interstitial nephritis

Cardiovascular: QTC prolongation, torsades de pointes, arrhythmias

*Pregnancy* category C

*Pro & Cons for Fluoroquinolones in general*

* Pros
  + Generally well-tolerated
  + Many have daily dosing
  + Good for short courses
* Cons
  + Overutilized
  + Broad spectrum
  + Increasing resistance in *E. coli*

Levofloxacin

<http://home.intekom.com/pharm/aspen-p/a-levofl.html>

*Antimicrobial spectrum*

**Gram-negative organisms**: *Acinetobacter calcoaceticus, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Proteus mirabilis* and *Pseudomonas aeruginosa.***Gram-positive organisms**: *Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes* and *Streptococcus faecalis.***Other organisms**: *Chlamydia pneumoniae, Legionella pneumophila* and *Mycoplasma pneumoniae*.

*E. coli -*

*Staph +*

*Kleb -*

*Proteus -*

*Mechanism of action*

by inhibiting [DNA gyrase](http://en.wikipedia.org/wiki/DNA_gyrase), a type II [topoisomerase](http://en.wikipedia.org/wiki/Topoisomerase), and topoisomerase iv,[[98]](http://en.wikipedia.org/wiki/Levofloxacin#cite_note-97) which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division..

*Role for Fluoroquinolones in general*

* Cystitis (no longer 1st line)
* Pyelonephritis
* Prostatitis

*Dose*

Urinary tract infections, (complicated) and acute pyelonephritis: 250 mg once daily for 10 days.  
Urinary tract infections (uncomplicated) in women: 250 mg once daily for 3 days.

*Adverse Effects* <http://en.wikipedia.org/wiki/Levofloxacin#Adverse_effects>

* [P](http://en.wikipedia.org/wiki/Peripheral_neuropathy)eripheral neuropathy (irreversible nerve damage)
* T[endon](http://en.wikipedia.org/wiki/Tendon) damage
* Heart Problems (prolonged QT Interval / [Torsades de pointes](http://en.wikipedia.org/wiki/Torsades_de_pointes))
* Pseudomembranous colitis
* [Rhabdomyolysis](http://en.wikipedia.org/wiki/Rhabdomyolysis) (muscle wasting)
* Stevens-Johnson Syndrome

*Pregnancy* category C

*Pro & Cons for Fluoroquinolones in general*

* Pros
  + Generally well-tolerated
  + Many have daily dosing
  + Good for short courses
* Cons
  + Overutilized
  + Broad spectrum
  + Increasing resistance in *E. coli*

Ofloxacin

<http://en.wikipedia.org/wiki/Ofloxacin#Susceptible_bacteria>

*Antimicrobial spectrum*

**Aerobic Gram-positive microorganisms -** *Staphylococcus aureus (methicillin-susceptible strains), Streptococcus pneumoniae (penicillin-susceptible strains), Streptococcus pyogenes*

**Aerobic Gram-negative microorganisms -** *Citrobacter (diversus) koseri, Enterobacter aerogenes, Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Neisseria gonorrhoeae, Proteus mirabilis, Pseudomonas aeruginosa*

**Other microorganisms -** *Chlamydia trachomatis*

*E. coli -*

*Staph +*

*Kleb -*

*Proteus -*

*Citrobacter -*

*Mechanism of action*

by inhibiting [DNA gyrase](http://en.wikipedia.org/wiki/DNA_gyrase), a type II [topoisomerase](http://en.wikipedia.org/wiki/Topoisomerase), and topoisomerase IV,[[27]](http://en.wikipedia.org/wiki/Ofloxacin#cite_note-26) which is an enzyme necessary to separate (mostly in prokaryotes, in bacteria in particular) replicated DNA, thereby inhibiting bacterial cell division..

*Role for Fluoroquinolones in general*

* Cystitis (no longer 1st line)
* Pyelonephritis
* Prostatitis

*Dose* [*http://www.aafp.org/afp/1999/0301/p1225.html*](http://www.aafp.org/afp/1999/0301/p1225.html)

Acute uncomplicated urinary tract infections in women PO 200 mg twice daily x 3 days

Acute uncomplicated pyelonephritis PO 400 mg twice daily x 14 days

Parenteral 400 mg twice daily x 3 days

*Adverse Effects* <http://en.wikipedia.org/wiki/Levofloxacin#Adverse_effects>

* GI - diarrhea that is watery or bloody;
* CNS - seizure (convulsions), confusion, hallucinations, anxiety, feeling resltess, tremors, insomnia, nightmares, unusual thoughts or behavior
* CV - feeling light-headed, severe dizziness, fainting, fast or pounding heartbeat;
* Swelling or tearing of a tendon sudden pain, snapping or popping sound, bruising, swelling, tenderness, stiffness, or loss of movement in any of your joints;
* easy bruising or bleeding;
* fever, swollen glands, general ill feeling;
* Renal - urinating less than usual or not at all;
* numbness, burning pain, or tingly feeling in your hands or feet;
* pale skin, dark colored urine, fever, weakness, jaundice (yellowing of the skin or eyes);;
* Skin allergy - the first sign of any skin rash, no matter how mild; or severe skin reaction
* Allergic reactions - fever, sore throat, swelling in your face or tongue, burning in your eyes, skin pain, followed by a red or purple skin rash that spreads (especially in the face or upper body) and causes blistering and peeling.

*Pregnancy* category C

*Pro & Cons for Fluoroquinolones in general*

* Pros
  + Generally well-tolerated
  + Many have daily dosing
  + Good for short courses
* Cons
  + Overutilized
  + Broad spectrum
  + Increasing resistance in *E. coli*

**Nitrofurantoin**

Agents:

Macrobid

Macrodantin

*Antimicrobial spectrum*

[*http://books.google.com/books?id=gACeB8XCnpgC&pg=PA246&lpg=PA246&dq=antimicrobial+spectrum+of+nitrofurantoin&source=bl&ots=5NdjcJe-jh&sig=20Qw4Qy2-rDjmTTnzC4PGwNPz1Y&hl=en#v=onepage&q=antimicrobial%20spectrum%20of%20nitrofurantoin&f=false*](http://books.google.com/books?id=gACeB8XCnpgC&pg=PA246&lpg=PA246&dq=antimicrobial+spectrum+of+nitrofurantoin&source=bl&ots=5NdjcJe-jh&sig=20Qw4Qy2-rDjmTTnzC4PGwNPz1Y&hl=en#v=onepage&q=antimicrobial%20spectrum%20of%20nitrofurantoin&f=false)

*E. coli -*

*Staph +*

*Kleb -*

*Proteus -*

*Mechanism of action* [*http://en.wikipedia.org/wiki/Nitrofurantoin*](http://en.wikipedia.org/wiki/Nitrofurantoin)

The mechanism of action of nitrofurantoin is unique and complex. The drug works by damaging bacterial [DNA](http://en.wikipedia.org/wiki/DNA), since its reduced form is highly reactive. This is made possible by the rapid reduction of nitrofurantoin inside the bacterial cell by [flavoproteins](http://en.wikipedia.org/wiki/Flavoprotein) ([nitrofuran reductase](http://en.wikipedia.org/w/index.php?title=Nitrofuran_reductase&action=edit&redlink=1)) to multiple reactive intermediates that attack ribosomal proteins, DNA,[[7]](http://en.wikipedia.org/wiki/Nitrofurantoin#cite_note-6) respiration, pyruvate metabolism and other macromolecules within the cell. It is not known which of the actions of nitrofurantoin is primarily responsible for its bactericidal activity.

*Role*

* + Acute Uncomplicated Cystitis

*Dose*

100mg PO q12h (Macrobid) or 50mg PO q6h (Macrodantin)

*Adverse Effects*

Nausea and vomiting

Fever, rash

[Hypersensitivity pneumonitis](http://en.wikipedia.org/wiki/Hypersensitivity_pneumonitis)

[Pulmonary fibrosis](http://en.wikipedia.org/wiki/Pulmonary_fibrosis)

Drug-induced autoimmune hepatitis

*Pregnancy* category B

*Pro & Cons*

* Pros
* Narrow spectrum
* Little resistance
* Cons
  + Multiple daily dosing
  + Ineffective with CrCl <50 mL/min
  + Ineffective in short courses

**Fosfomycin**

*Antimicrobial spectrum* [*http://en.wikipedia.org/wiki/Fosfomycin*](http://en.wikipedia.org/wiki/Fosfomycin)

Fosfomycin has broad antibacterial activity against both Gram-positive and Gram-negative pathogens, with useful activity against *E. faecalis*, *E. coli*, and various Gram-negatives like Citrobacter and Proteus. Given a greater activity in a low pH milieu, and predominant excretion in active form into the urine, fosfomycin has found use for the prophylaxis and treatment of urinary tract infections caused by these uropathogens. Of note, activity against *S. saprophyticus*, Klebsiella and Enterobacter is variable and should be confirmed by MIC testing.

*E. coli -*

*Proteus -*

*Citrobacter -*

*Mechanism of action* [*http://en.wikipedia.org/wiki/Fosfomycin*](http://en.wikipedia.org/wiki/Fosfomycin)

Fosfomycin is bactericidal and inhibits bacterial cell wall biogenesis by inactivating the enzyme [UDP-N-acetylglucosamine-3-enolpyruvyltransferase](http://en.wikipedia.org/wiki/UDP-N-acetylglucosamine_enolpyruvyl_transferase), also known as MurA

*Role*

* + Acute Uncomplicated Cystitis

*Dose*

3gm PO x1

Some clinicians repeat daily x3

*Adverse Effects*

* diarrhea, nausea, stomach pain or upset;
* headache; dizziness; weakness;
* stuffy nose, sore throat;
* menstrual pain; vaginal itching or discharge
* back pain

*Pregnancy* category B

*Pro & Cons*

* Pros
* One-time dose
* Little resistance
* Activity vs. resistant organisms
* Cons
  + Higher failure rates with x1 dosing?
  + Lack of familiarity

**Ampicillin/Amoxicillin/Cephalexin**

*Antimicrobial spectrum*

**Amoxicillin** and **ampicillin** are bactericidal and relatively nontoxic, with a spectrum of antibacterial activity greater than that of penicillin G. They have excellent activity against staphylococci, streptococci, enterococci, and Proteus , and may achieve urinary concentrations high enough to be effective against E coli and Klebsiella

**Cefadroxil** and **cephalexin** are first-generation cephalosporins - they have greater activity against staphylococci and gram-negative bacteria. They have excellent activity against Staphylococcus , Streptococcus , E coli , Proteus , and Klebsiella

*E. coli -*

*Staph +*

*Kleb -*

*Proteus -*

*Mechanism of action* [*http://www.cancernewsnetwork.org/medications/rx/Cephalexin.html*](http://www.cancernewsnetwork.org/medications/rx/Cephalexin.html)

[*http://www.mims.com/USA/drug/info/ampicillin/?q=ampicillin&type=full#Actions*](http://www.mims.com/USA/drug/info/ampicillin/?q=ampicillin&type=full#Actions)

**Ampicillin** exerts its action by inhibiting the synthesis of bacterial cell wall.

**Cephalexin**, like the penicillins, is a beta-lactam antibiotic. By binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall, it inhibits the third and last stage of bacterial cell wall synthesis.

*Role*

* + Pyelonephritis
  + Healthcare-associated cystitis

*Dose*

variable

*Adverse Effects*

* GI - Onset of pseudomembranous colitis may occur during or after antibacterial treatment
* AlIergic reactions in the form of rash, urticaria, angioedema, and, rarely, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis
* Adverse reactions - Fever, colitis, aplastic anemia, hemorrhage, renal dysfunction, and toxic nephropathy

*Pregnancy* category B

*Pro & Cons*

* Pros
  + Safe to fetus
  + Narrow spectrum
* Cons
  + Resistance is common
  + Ineffective in short courses
  + Frequent dosing

**3rd Generation Cephalosporins**

**Anti-Pseudomonal**

Classification of Cephalosporins <http://www.emedexpert.com/compare/cephalosporins.shtml>

First Generation

* Cefadroxil
* Cephalexin
* Cephaloridine
* Cephalothin
* Cephapirin
* Cefazolin
* Cephradine

Second Generation

* Cefaclor
* Cefoxitin
* Cefprozil
* Cefuroxime

Third Generation

* [Cefcapene](http://en.wikipedia.org/wiki/Cefcapene)
* [Cefdaloxime](http://en.wikipedia.org/wiki/Cefdaloxime)
* [Cefdinir](http://en.wikipedia.org/wiki/Cefdinir) (Zinir, Omnicef, Kefnir)
* [Cefditoren](http://en.wikipedia.org/wiki/Cefditoren)
* [Cefetamet](http://en.wikipedia.org/wiki/Cefetamet)
* [Cefixime](http://en.wikipedia.org/wiki/Cefixime) (Zifi, Suprax)
* [Cefmenoxime](http://en.wikipedia.org/wiki/Cefmenoxime)
* [Cefodizime](http://en.wikipedia.org/wiki/Cefodizime)
* [Cefotaxime](http://en.wikipedia.org/wiki/Cefotaxime) (Claforan)
* [Cefovecin](http://en.wikipedia.org/wiki/Cefovecin) (Convenia)
* [Cefpimizole](http://en.wikipedia.org/wiki/Cefpimizole)
* [Cefpodoxime](http://en.wikipedia.org/wiki/Cefpodoxime) (Vantin, PECEF)
* [Cefteram](http://en.wikipedia.org/wiki/Cefteram)
* [Ceftibuten](http://en.wikipedia.org/wiki/Ceftibuten) (Cedax)
* [Ceftiofur](http://en.wikipedia.org/wiki/Ceftiofur)
* [Ceftiolene](http://en.wikipedia.org/wiki/Ceftiolene)
* [Ceftizoxime](http://en.wikipedia.org/wiki/Ceftizoxime) (Cefizox)
* [Ceftriaxone](http://en.wikipedia.org/wiki/Ceftriaxone) (Rocephin)

Third-generation cephalosporins with antipseudomonal activity:

* [Cefoperazone](http://en.wikipedia.org/wiki/Cefoperazone) (Cefobid)
* [Ceftazidime](http://en.wikipedia.org/wiki/Ceftazidime) (Fortum, Fortaz)

The following cephems are also sometimes grouped with third-generation cephalosporins:

[Oxacephems](http://en.wikipedia.org/wiki/Oxacephem): [latamoxef](http://en.wikipedia.org/wiki/Latamoxef) (moxalactam).

Fourth Generation

* Cefepime
* Cefluprenam
* Cefozopran
* Cefpirome
* Cefquinome

*Antimicrobial spectrum* [*http://www.fpnotebook.com/ID/Bacteria/Entrbctrc.htm*](http://www.fpnotebook.com/ID/Bacteria/Entrbctrc.htm)

Pseudomonas aeruginosa – negative rod

*E. coli -*

*Staph +*

*Kleb -*

*Proteus -*

*Mechanism of action* [*http://www.emedexpert.com/compare/cephalosporins.shtml*](http://www.emedexpert.com/compare/cephalosporins.shtml)

Cephalosporins disrupt the synthesis of the peptidoglycan layer of bacterial cell walls, which causes the walls to break down and eventually the bacteria die.

*Role*

* + Pyelonephritis
  + Healthcare-associated cystitis

*Dose*

* + ceftriaxone 1gm q24h, cefotaxime 1gm q8h

*Adverse Effects* [*http://www.uic.edu/pharmacy/courses/pmpr342/itokazu/cephalosporins.html*](http://www.uic.edu/pharmacy/courses/pmpr342/itokazu/cephalosporins.html)

* Hypersensitivity reactions manifested by rashes, eosinophilia, fever (1-3%); interstitial
* Thrombophlebitis - swelling (inflammation) of a vein caused by a blood clot.

*Pregnancy* category B

*Pro & Cons*

* Pros
  + Low resistance in E. coli
* Cons
  + Broad-spectrum
  + IV administration

**Antipseudomonal Drugs  
Beta-lactams**

* Agents
  + Ceftazidime
  + Piperacillin/tazobactam
  + Cefepime
  + Ticarcillin/clavulanate
  + Imipenem/cilastatin
  + Meropenem
  + Doripenem
  + Aztreonam

*Antimicrobial spectrum* [*http://www.neisslabs.com/doctors\_pdf/Ceftazidime.pdf*](http://www.neisslabs.com/doctors_pdf/Ceftazidime.pdf)

***Urinary Tract Infections*,** both complicated and uncomplicated, caused by *Pseudomonas aeruginosa* ; *Enterobacter* spp.; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus*; *Klebsiella* spp.; and *Escherichia coli*.

Pseudomonas aeruginosa – negative rod

*E. coli -*

*Kleb -*

*Proteus -*

*Mechanism of action* [*http://www.neisslabs.com/doctors\_pdf/Ceftazidime.pdf*](http://www.neisslabs.com/doctors_pdf/Ceftazidime.pdf)

Inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibit the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis

*Role*

* + Pyelonephritis in recently/currently hospitalized patients

*Dose*

* + variable

*Adverse Effects*

* Hypersensitivity reactions manifested by rashes, eosinophilia, fever (1-3%); interstitial
* Thrombophlebitis - swelling (inflammation) of a vein caused by a blood clot.

*Pregnancy* category B

*Pro & Cons*

* Pros
  + Broad-spectrum
  + Antipseudomonal
* Cons
  + Broad-spectrum
  + Expensive
  + Subject to abuse/overuse

**Aminoglycosides**

Agents:

[amikacin](http://en.wikipedia.org/wiki/Amikacin)

[arbekacin](http://en.wikipedia.org/wiki/Arbekacin)

[gentamicin](http://en.wikipedia.org/wiki/Gentamicin)

[kanamycin](http://en.wikipedia.org/wiki/Kanamycin)

[neomycin](http://en.wikipedia.org/wiki/Neomycin)

[netilmicin](http://en.wikipedia.org/wiki/Netilmicin)

[paromomycin](http://en.wikipedia.org/wiki/Paromomycin)

rhodostreptomycin

[streptomycin](http://en.wikipedia.org/wiki/Streptomycin)

[tobramycin](http://en.wikipedia.org/wiki/Tobramycin)

[apramycin](http://en.wikipedia.org/wiki/Apramycin)

*Antimicrobial spectrum* [*http://www.neisslabs.com/doctors\_pdf/Ceftazidime.pdf*](http://www.neisslabs.com/doctors_pdf/Ceftazidime.pdf)

***Urinary Tract Infections*,** both complicated and uncomplicated, caused by *Pseudomonas aeruginosa* ; *Enterobacter* spp.; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus*; *Klebsiella* spp.; and *Escherichia coli*.

Pseudomonas aeruginosa – negative rod

*E. coli -*

*Kleb -*

*Proteus -*

*Mechanism of action* [*http://en.wikipedia.org/wiki/Aminoglycoside*](http://en.wikipedia.org/wiki/Aminoglycoside)

Aminoglycosides have several potential antibiotic mechanisms

* They interfere with the [proofreading](http://en.wikipedia.org/wiki/Proofreading_(biology)) process, causing increased rate of error in synthesis with premature termination.
* Also, there is evidence of inhibition of [ribosomal translocation](http://en.wikipedia.org/wiki/Ribosomal_translocation) where the peptidyl-tRNA moves from the A-site to the P-site
* They can also disrupt the integrity of bacterial cell membrane

*Role*

* + Severe pyelonephritis
  + Resistant UTIs

*Dose*

* + Q8H dosing - peak 4, trough <1
  + Daily dosing – peak ~20, trough =0

*Adverse Effects* [*http://www.emedexpert.com/classes/antibiotics.shtml*](http://www.emedexpert.com/classes/antibiotics.shtml)

* + Ototoxicity
  + nephrotoxicity

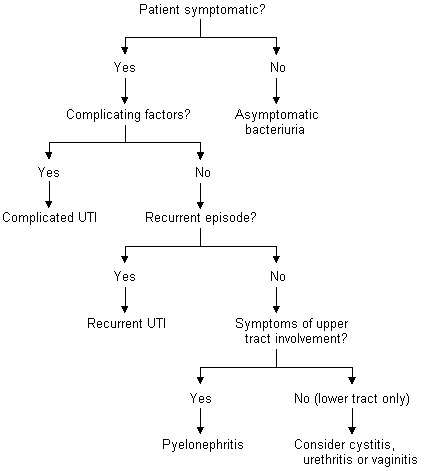
*Pregnancy* category D

*Pro & Cons*

* Pros
  + Excellent activity
  + Very low resistance
* Cons
  + Toxicity
  + IV only

**Adult Urinary Tract Infection**

<http://www.aafp.org/afp/1999/0301/p1225.html>



**FIGURE 1.**

Diagnostic approach to urinary tract infections in adults. (UTI = urinary tract infection)

**Acute Uncomplicated Cystitis**

***Antimicrobial Agents***

* + Preferred
    - Nitrofurantoin 100mg BID x 5 days
    - Trimethoprim/Sulfamethoxazole (TMP/SMX) 800/160 mg PO Q12H x 3 days
    - Fosfomycin 3gm PO x1 dose
  + Not preferred, but useful
    - Fluoroquinolones (FQ) PO x 3 days, low-doses
      * Levofloxacin 250mg daily; ciprofloxacin 250mg BID
    - Amoxicillin 500 mg PO BID x 3 days
    - Amoxicillin/clavulanate 500 mg PO TID x 3d
    - Other beta-lactams (cephalexin *et al*)
    - One-dose regimens

***Supportive measures***

* Hydration
* Urinary Analgesic
  + Phenazopyridine 100-200 mg PO Q8H x 2 days
  + Pain relief, not cure
* Cranberry juice?

**Recurrent Uncomplicated Cystitis**

* ≤3 episodes/year
  + Standard therapy
* >3 episodes/year
  + Relapse vs. recurrence
    - Relapse
      * 14 day course Rx
      * 2-4 week course Rx
      * 6 month course Rx
    - Recurrence
      * Re-infection
      * Retreat
      * Consider prophylaxis
  + Prophylaxis
    - Proper hygiene
    - ½ TMP/SMX 400/80mg daily or
    - TMP 100mg daily or
    - Nitrofurantoin 50-100mg daily or
    - 1 dose TMP/SMX post-coitus

Healthcare-associated UTIs - Etiology

* E. coli
* *Pseudomonas aeruginosa*
* Enterobacteriaceae
* Enterococci
* *Candida* sp.

Resistance is much more common

Healthcare-associated UTIs

* Associated with recent exposure to healthcare system
* Hospital admission
* Nursing home admission
* TMP/SMX not preferred due to likelihood of resistant organisms
* 7-10 day courses of therapy may be needed, depending on organism
* Narrow therapy when possible

**Complicated Cystitis**

* Criteria for ‘complicated’
  + Anatomic abnormalities
  + Catheterization
  + Male gender
* Often healthcare-associated
* Higher risk of systemic infections
* Organisms
  + *E. coli*
  + *Proteus mirabilis*
  + *Klebsiella pneumoniae*
  + *Pseudomonas aeruginosa*
  + Other GNR
  + Staphylococci*,* enterococci

**Treatment**

* Varies by resistance patterns
* Fluoroquinolone PO x 7-14 days
* TMP/SMX 800/160 mg PO Q12H x 7-14 days
* 3rd generation ceph?
  + Cefpodoxime
  + Not for men
* Culture before and after therapy
* Catheterized pts – change catheter

**Acute Pyelonephritis - Mild, Outpatient**

* PO Fluoroquinolone
  + Levofloxacin 750mg PO q24h x5 days
  + Ciprofloxacin 500mg PO q12h x7 days
  + Ciprofloxacin 1000mg ER PO q24h x7 days
* TMP/SMX 1 DS q12h x 7-14 days (if known susceptibility)
* Add 1x dose of ceftriaxone 1gm or aminoglycoside (5-7 mg/kg tobra or gent) in high-resistance areas
* Urine culture needed

**Acute Pyelonephritis - Severe, Inpatient**

* IV 3rd or 4th generation cephalosporin (ceftriaxone ideal)
* IV fluoroquinolone
* IV aminoglycoside +/- ampicillin
* Extended-spectrum penicillin (e.g. piperacillin/tazobactam)
* Carbapenem
* IV -> PO when stable, 7-14 days total Rx

**Acute Pyelonephritis**

* If patient has been hospitalized recently or is a LTCF resident:
  + Ceftazidime
  + Piperacillin/tazobactam
  + Cefepime
  + Ticarcillin/clavulanate
  + Aztreonam
  + Imipenem/cilastatin
  + Meropenem
  + +/- Aminoglycoside
* Follow blood and urine cultures to narrow therapy
* Patients should defervesce rapidly
* Phenazopyridine ineffective – use systemic pain meds (NSAIDs, APAP, etc)
* Transition to oral medications as patients improve

**Asymptomatic Bacteruria**

**UTIs in Pregnancy**

* Risks to fetus increased
* Asymptomatic bacteriuria needs treatment
* Treatment
  + Nitrofurantoin, PCNs, cephalosporins
  + 7 days of therapy
  + No FQs, TMP/SMX, tetracyclines, nitrofurantoin at term
* Follow-up culture in 1-2 weeks, then monthly

**UTIs in Children**

* Uncommon
* Signs/symptoms may be different
* Drugs used: cephalosporins, TMP/SMX
  + Not FQs, nitrofurantoin
* Duration of therapy: 7-14 days
* Need urologic workup
* Steroids may prevent damage in pyelonephritis

**Fungal Cystitis**

* Occurs mainly in ICU patients
* Related to catheterization
  + Tx: Remove catheter
  + If treatment truly needed: fluconazole
* Not effective: voriconazole, itraconazole, caspofungin

**Prostatitis**

* Etiology
  + *E. coli, P. mirabilis, K. pneumoniae,* other GNRs
  + Obstruction, anatomic problems can cause
* Common – up to 50% of males
* S/Sx
  + Acute – fever, chills, dysuria, hematuria, local pain
  + Chronic – urinary retention, frequent urination, dysuria, low back pain
* Diagnosis
  + Chronic – prostatic massage
  + Acute – no massage
* Therapy
  + PO FQ or TMP/SMX for 4-6 weeks
  + Chronic prostatitis likely to relapse, more therapy or surgery may be required

<http://www.aafp.org/afp/1999/0301/p1225.html>

Diagnostic approach to urinary tract infections in adults