

Pharmacology of UTI

UTI is an infection affecting part of the urinary system

It is one of the most commonly occurring bacterial infections, especially in females of childbearing age

Approximately 60% of females will develop a UTI during their lifetime with about one fourth having a recurrence within a year

UTIs are classified into upper and lower UTIs

Upper tract infection, also known as pyelonephritis, is an infection involving the kidneys whereas lower tract infections correspond to bladder infection or cystitis

UTIs are designated as uncomplicated or complicated

Uncomplicated infections occur in individuals who lack structural or functional abnormalities of the urinary tract that could interfere with the normal flow of urine or voiding mechanism

Complicated UTIs are usually the result of a predisposing lesion of the urinary tract, such as a congenital abnormality or distortion of the urinary tract, a stone, indwelling catheter, prostatic hypertrophy and obstruction

Most common bacteria involved in the etiology of UTI is E.coli

Other frequently isolated organisms include Klebsiella pneumoniae, Pseudomonas aeruginosa , staphylococci...

**Patients with pyelonephritis may complain of:
Fever, flank pain, frequency, nausea and
vomiting**

Patients with cystitis may complain of:

**Burning on urination (dysuria), frequent
urination, urgency, suprapubic pain, blood
in the urine (hematuria) and back pain**

Most effective antibiotics in UTIs:

Trimethoprim-sulfamethoxazole (co-trimoxazole)

Cephalosporins

Quinolones and Fluoroquinolones

Nitrofurantoin

Fosfomycin...

Quinolones; Fluoroquinolones

Inhibitors of microbial DNA synthesis (inhibit bacterial DNA replication by inhibiting bacterial gyrase enzyme which is a type II topoisomerase)

Most widely used antibiotics in 2002 but their use has been recently reduced due to toxicity, development of resistance and the introduction of safer new macrolides

Chemotherapeutic agents (synthetic)

Cidal

Broad spectrum (effective against pseudomonas)

■ **Quinolones are classified into:**

1st generation

Nalidixic acid **Pipemidic acid** **Oxolinic acid**

2nd generation

Ciprofloxacin **Ofloxacin** **Norfloxacin**
Enoxacin **Lomefloxacin** **Nadifloxacin**

3rd generation

Levofloxacin **Sparfloxacin** **Gatifloxacin**

4th generation

Moxifloxacin **Prulifloxacin** **Gemifloxacin**

- 1st generation e.g. Nalidixic acid effective more in G+ve infections and only in UTI's (urinary tract antiseptic). Has little activity against E. coli; Proteus; Shigella, Enterobacter and klebsiella. No effect against Pseudomonas
- 2nd generation exhibit more activity against G-ve bacteria
- 3rd & 4th generations have good activity against pseudomonas and anaerobic microorganisms
- Most widely used quinolones include:
Ciprofloxacin (2nd); levofloxacin (3rd); moxifloxacin (4th)

Quinolones are orally effective and well absorbed but affected by food containing Ca^{++} and iron

Mainly (particularly Ciprofloxacin & levofloxacin) used in complicated UTI's, respiratory infections, invasive external otitis, bacterial prostatitis and cervicitis, bacterial diarrhoea caused by shigella, salmonella and E. coli

■ Mechanisms of bacterial resistance to quinolones:

- Some types of bacterial efflux pumps can act to decrease intracellular quinolone concentration
- Production of certain proteins especially by Gram-ve bacteria that can bind to DNA gyrase, protecting it from the action of quinolones
- Mutations in DNA gyrase or topoisomerase which could lead to a decrease in quinolones binding affinity and hence decreasing their effectiveness

■ Quinolones side effects:

- GIT irritation; photosensitivity
- Cardiac toxicity (many may be associated with prolongation of QT interval) (many were withdrawn because of this side effect)
- Some are not recommended in children or during pregnancy because they may interfere with cartilage development
- Some have been reported to be carcinogens

Nitrofurantoin

Synthetic, bactericidal orally effective antibiotic

It is effective against G+ve & G-ve bacteria

Has good activity against G-ve bacteria particularly E. coli

Highly effective in UTI's (cystitis) (known as UT antiseptic)

■ Nitrofurantoin MOA (multiple):

It is converted by bacterial reductases into many reactive intermediates leading to direct damaging effect of bacterial DNA, disruption of RNA and protein synthesis and also interfering with many metabolic processes in bacteria

- Development of resistance to nitrofurantoin is rare, due to multiple sites of action (the bacteria that is sensitive to it remain sensitive forever)
- Pulmonary fibrosis is a major side effect to nitrofurantoin
- Nitrofurantoin is contraindicated in patients with G-6-PD deficiency

Fosfomycin

It is a broad-spectrum bactericidal drug primarily used to treat lower UTI (cystitis) and occasionally is used for prostate infections

It disrupts cell wall synthesis by inhibiting phosphoenolpyruvate synthetase and thus interferes with the production of peptidoglycan

Fosfomycin has a broad spectrum of activity against both gram-positive and gram-negative organisms, including many antibiotic-resistant organisms

It is available in 3g oral powder dosage form for reconstitution

Use of fosfomycin is commonly restricted to only a single dose because of rapid microbial resistance

Fosfomycin is well tolerated but may lead to the following side effects:

- Metallic taste
- Stomach upset
- Dizziness
- Stuffy nose
- Back pain
- Vaginal itching or discharge