ANTIBIOTICS AND ANTISEPTICS FOR URINARY TRACT INFECTIONS

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INTRODUCTION (1)

- UTIs are very commonly found in medical practice
- Gram (–) pathogens, especially *E. coli*, are the most prevalent etiology
- UTIs include acute uncomplicated cystitis, acute and chronic pyelonephritis, acute and chronic prostatitis
- In acute stage with signs of systemic infections → use systemic antimicrobial agents
To prevent recurrent infection → use urinary antiseptics

Urinary antiseptics may be effective to cure uncomplicated lower UTI, but not for UTIs with signs of systemic infections
OBJECTIVES

- To understand the difference between urinary antiseptics and antibiotics used for UTI
- To understand the indications, mechanism of action, pharmacokinetics, side effects, contraindications, precautions, and interactions of antimicrobial agents commonly used for the treatment of UTI
ANTIBIOTICS COMMONLY USED IN UTI

Antimicrobials for systemic infections:
1. Trimethoprim-sulfamethoxazole
2. Fluoroquinolones
3. Betalactams: Penicillins and Cephalosporins
4. Aminoglycosides

Urinary antiseptics:
1. Nitrofurantoin
2. Methenamine
3. Fosfosmycin
ANTIMICROBIALS
COMMONLY USED FOR UTIs
WITH SYSTEMIC INFECTIONS
TRIMETHOPRIM – SULFAMETHOXAZOLE (COTRIMOXAZOLE)
COTRIMOXAZOLE (1)

Mechanism of action:

pteridine + PABA

Enz. dihydropteroate synthetase

dihydrofolic acid

Enz. dihydrofolate reductase

sulfonamides

trimethoprim

tetrahydrofolic acid

synthesis of amino acids, purines, and pyrimidines
Spectrum: wide, mainly active against Gram (-) pathogens

Pharmacokinetics:
- Rapidly absorbed
- High tissue concentration in prostate

I: UTI, typhoid fever, shigellosis, typhoid fever, lower respiratory tract infection, *Pneumocystis carinii* infection

SE: hypersensitivity reactions, Stevens-Johnson’s syndrome, bone marrow depression, hemolytic anemia, crystalluria
FLUOROQUINOLONES
FLUOROQUINOLONES (1)

MA:

1. Inhibits topoisomerase II (= DNA gyrase) which plays a role in the relaxation of the supercoiled DNA during transcription

2. Inhibits topoisomerase IV which plays a role during the separation of the newly formed chromosomal DNA after the replication
FLUOROQUINOLONES (2)

Derivatives: ciprofloxacin, ofloxacin, levofloxacin, norfloxacin, moxifloxacin

Pharmacokinetics:
- Effective for systemic infections
- Long $T_{1/2}$

Interactions:
- Absorption through gastrointestinal tract is reduced by antacids
- Fluoroquinolones inhibit metabolism of theophylline
The ‘respiratory quinolones’ (moxifloxacin, levofloxacin):

- active against pathogens causing lower respiratory tract infections (including Gram positive bacteria and ‘atypical’ pathogens), i.e.: *S. pneumoniae, H. influenzae, M. catarrhalis, S. aureus, M. pneumoniae, C. pneumoniae*
FLUOROQUINOLONES (4)

Spectrum:
- Mainly Gram (-) pathogens
- *P. aeruginosa* (only ciprofloxacin)
- Less active against Gram (+) (except moxifloxacin)
- Inactive against anaerobes

SE: gastro-intestinal and CNS, phototoxicity, prolongation of QT interval → *Torsades de pointes*, tendinitis, hepatotoxicity

CI: pregnant women and children → possible joint damage
PENICILLINS
PENICILLINS (1)

Structure:

Betalactamase (penicillinase) breaks the betalactam ring → loss of antibacterial activity

Betalactamase (penicillinase) breaks the betalactam ring → loss of antibacterial activity
MA:

- Binds to the Penicillin-binding proteins (PBPs), i.e. transpeptidases → blocks the cross-linking process in the synthesis of cell wall

- This is followed by the activation of autolysin → cell lysis
PENICILLINS (3)

Classification based on antibacterial spectrum:

1. Natural penicillin: penicillin G, fenoksimetil-penisilin
2. Aminopenicillin: amoxicillin, ampicillin (commonly used in UTI, often in combination with a betalactamase inhibitor)
3. Anti-staphylococcal penicillin: dicloxacillin, flucloxacillin
4. Anti-pseudomonal penicillin: ticarcillin
5. Ureidopenicillin: piperacillin
PENICILLINS (4)

Mechanism of resistance:
- production of betalactamase
- modification of PBP
- reduction of cell wall permeability

SE:
- Hypersensitivity reactions: urticaria, skin rash, asthma, fever, serum sickness, anaphylaxis
- Toxic reactions: CNS stimulation
PENICILLINS (5)

Indications:

Infections due to susceptible pathogens in:

- Upper and lower respiratory tract infections
- **Urinary tract infections**
- STD: syphilis, gonorrhoe
- Skin and soft tissue infections
- Others: tetanus, anthrax, actinomycosis, clostridium, bacterial meningitis
Penicillins commonly used in UTI:

- Ampicillin:
  - Oral ampicillin → for uncomplicated lower UTI
  - Intravenous ampicillin + an aminoglycoside → for UTI with systemic infection

- Amoxicillin-clavulanic acid and ampicillin-sulbactam:
  - Indicated for UTI with systemic infections caused by betalactamase-producing Gram (-) pathogens
CEPHALOSPORINS
CEPHALOSPORINS (1)

MA: see penicillins

Spectrum:

- Generation 1: mainly active against Gram (+) pathogens
- Generation 2: mainly active against Gram (-) pathogens
- Generation 3: active against Gram (-) and (+) pathogens
- Generation 4: active against ESBL-producing pathogens
Examples:

- Gen 1: cefazolin, cephradine, cephalexin, cephadroxil
- Gen 2: cefamandole, cefuroxime, cefoxitin
- Gen 3: cefotaxime, ceftriaxone, ceftazidime
- Gen 4: cefepime

Note: all generations can be used for UTI, but generation 1 has limited antibacterial activity
CEPHALOSPORINS (3)

Indications:
- Respiratory tract infections
- **Urinary tract infections**
- Skin and soft tissue infections
- Nosocomial infections
- Intra-abdominal infections
- Surgical prophylaxis (cefazolin)
- Gonorrhea (ceftriaxone)
- Meningitis due to G (-) pathogens (only the 3rd generation cephalosporins)
CEPHALOSPORINS (4)

SE:

- Hypersensitivity reactions: 5-10% cross-hypersensitivity with penicillins
- Nephrotoxicity
- Bleeding associated with hypoprothrombinemia (associated with methyl thiotetrazole group, e.g. cefoperazone, cefamandole)
- Leukopenia
- Superinfection
AMINOGLYCOSIDES
AMINOGLYCOSIDES (1)

Derivatives:
- Gentamicin, tobramycin, amikacin, kanamycin, streptomycin

MA: Inhibits protein synthesis (ribosome subunit 30S) of bacteria

Bactericidal

Commonly combined with the betalactams in the treatment of many serious infections caused by susceptible Gram (-) pathogens
AMINOGLYCOSIDES (2)

Spectrum:

- Active against Gram (-) pathogens such as: *P. aeruginosa, Klebsiella, Proteus, E. coli*
- Streptomycin: not effective against *P. aeruginosa*. Only indicated for the treatment of tuberculosis
- Amikacin: still effective for infections due to gentamicin-resistant Gram (-) pathogens.
Mechanism of resistance:

- To produce enzymes capable of destroying the drug (e.g., acetyltransferase). This is transferable via plasmids.
- To decrease drug uptake.
- To modify the drug receptor.
Pharmacokinetics:
- Highly polar $\rightarrow$ not absorbed via GI tract
- Unable to penetrate the blood brain barrier
- Highly concentrated in the kidneys and the inner part of ear $\rightarrow$ causing nephro- and oto-toxicity
- Not metabolized
- Excretion: glomerular filtration. In renal insufficiency $\rightarrow$ drug accumulation $\rightarrow$ requiring dosage reduction
AMINOGLYCOSIDES (5)

Indications:
- Gentamicin, netilmicin, tobramycin, amikacin: For serious infections by Gram (-) pathogens eg., UTI, sepsis
- Streptomycin: for tuberculosis, brucellosis, plague

SE:
- Ototoxicity: hearing loss, tinnitus, vertigo
- Nephrotoxicity
- Respiratory paralisis due neuromuscular blockade (rare)
Caution:

- The elderly and patients with renal insufficiency
- Concomitant treatment with other ototoxic drugs (furosemide, ethacrinic acid)
- Aminoglycosides are not indicated for trivial infections

Note: blood level monitoring is required to adjust dose in patient with impaired renal function
AMINOGLYCOSIDES (7)

Gentamicin (prototype)
- Effective for serious infections due to Gram-negative pathogens including such as *P. aeruginosa*, *Proteus*, *Klebsiella*, *Serratia*, *E. coli*, *Enterobacter*
- A once-daily dose is more preferable than the divided dose.
- Not recommended for topical use in hospital, except for burns
AMINOGLYCOSIDES (8)

- Amikacin:
  - Is still effective against gentamicin-resistant pathogens

- Tobramycin:
  - Shares the same indication with gentamicin

- Streptomycin:
  - Only indicated for tuberculosis, brucellosis, and plague
URINARY ANTISEPTICS
NITROFURANTOIN (1)

MA: damages the DNA of susceptible pathogens

Spectrum: Gram (+) and (-) pathogens.

No cross resistance with other drugs but ineffective against *P. aeruginosa*

Pharmacokinetics:
- well absorbed through the GI tract
- metabolism and excretion are very rapid → no systemic antibacterial action
- urine pH should be kept at < 5.5
NITROFURANTOIN (2)

- **Indication**: - uncomplicated lower UTI (esp. in women) and prophylaxis of cute exacerbation in chronic UTI

- **SE**: gastric irritation, neuropathy, hemolytic anemia (in G6PD-deficient patients). Rarely: lung fibrosis

- **CI**: renal insufficiency

- **Interaction**: antagonizes nalidixic acid
METHENAMINE

- At pH < 5.5 methenamine → releases formaldehyde (antibacterial)

- *Proteus* splits urea → releases ammonium hydroxide → pH ↑ → methenamine loses its activity

- SE: gastric irritation, albuminuria

- CI: impaired renal and/or hepatic function

- Interaction: sulfonamide should not be combined with methenamine because it may form insoluble compound with formaldehyde released by methenamine
FOSFOMYCIN

- **MA:** inhibits cell wall synthesis in the early stage
- **Spectrum:** *E. coli* and other Gram (+) and (−) pathogens, but not *P. aeruginosa*
- **SE:** nausea, diarrhea, headache
- **I:** uncomplicated lower UTI
- **Dose:** 3 g in single administration
- This drug appears to be safe for use in pregnancy
THANK YOU