Chemotherapeutics IV – UTI therapy and prevention 2023
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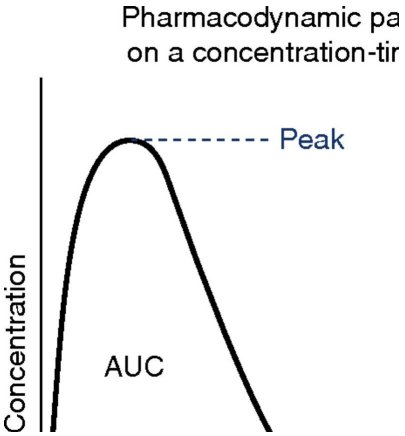
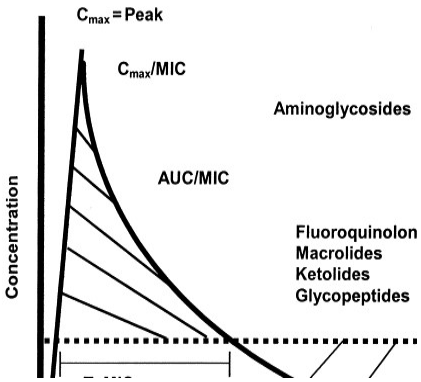
I. Quinolones:
I generation (non-fluorinated quinolones) - nalidixic acid (old generation)
II generation (fluorinated quinolones): ciprofloxacin, norfloxacin, ofloxacin
III generation (fluorinated quinolones): gati-, levofloxacin
IV generation (fluorinated quinolones): gemi-, moxi-, trova-, delafloxacin

Mechanism of action: inhibition of DNA gyrase and Topoisomerase IV
Pharmacokinetics:
Absorption: very well from GI
Food does not impair the absorption of most quinolones. However, quinolones chelate with cations such as aluminum, magnesium, calcium, iron, and zinc = reduced absorption and bioavailability, resulting in lower serum drug concentrations and less target-tissue penetration
Distribution: very good into most tissues (poor CSF penetration into uninflamed meninges, but ciprofloxacin, ofloxacin and trovafloxacin − are known to penetrate to a moderate extent in the presence of inflammation)
Protein binding – low/moderate
Metabolism: liver (primarily by glucuronides conjugation)
Elimination: urine (glomerular filtration and tubular secretion) or bile (moxifloxacin, trovafloxacin)
Postantibiotic effect





Quinolones: concentration-dependent and dose-dependent antibiotics with persistent postantibiotic effect.

Antimicrobial activity:
Gram negative aerobics (inc. Pseudomonas) - All of FQ,
Streptococci – levo-, gati-, moxifloxacin
Staphylococci (exc. MRSA) - All of FQ, delafloxacin has activity against MRSA
Atypical bacteria - All of FQ,
Mycobacterium – cipro-, ofloxacin
Anaerobes – gemifloxacin

Indications:

- UTI (complicated UTI, in uncomplicated UTI – only pyelonephritis): cipro-, norflo-, levofloxacin
- respiratory tract infections (community-acquired pneumonia in patients with intolerance to beta-lactams and macrolides, exacerbation of COPD, legionella community-acquired pneumonia, nosocomial pneumonia due to P. aeruginosa (with no risk to MRSA)): ciprofloxacin, moxifloxacin, levofloxacin, delafloxacin
- traveler's diarrhea: ciprofloxacin
- prostatitis: cipro-, levofloxacin
- conjunctivitis: cipro-, moxi-, levo-, oflo-, gatifloxacin
- severe marrow and bone infections: ciprofloxacin
- skin and its appendages infections: cipro-, oflo-, dela-, levofloxacin
- drug resistant tuberculosis: moxi-, levo-, gatifloxacin
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Adverse effects:

- neuropathy- dizziness, hallucinations, seizures
- phototoxic and fotoallergic reactions
- headache
- prolongation of thr QT wave (especially moxifloxacin)
- tendonitis and tendon rupture
- cartilage damage
- dysglycemia
- **risk of aortic dissecting aneurysm!**

Contraindications: pregnancy, prepuberal children, lactation (exc. exacerbation of cystic fibrosis due to *P. aeruginosa*, inhalation anthrax – levo-, ciprofloxacin)

<u>The recommendation is that fluoroquinolones should not be used in the following situations:</u>

- patients who previously had serious side effects with a fluoroquinolone
- for treatment of uncomplicated self-limiting infections (for example throat infections)
- for prevention of recurring urinary tract infection
- for prevention of infection e.g. traveller's diarrhoea
- for uncomplicated lower urinary tract infection (exsc. pyelonephritis) - unless guided by susceptibility testing that indicates that no safe alternative is likely to be effective.
- for mild or moderately severe infections (unless guided by susceptibility testing that indicates that no safe alternative is likely to be effective)

<u>The recommendation is that fluoroquinolones should be used with caution especially for:</u>

- elderly
- patients with kidney problems
- patients who have had an organ transplantation or those who are being treated with a systemic corticosteroid

These patients are at higher risk of tendon injury caused by fluoroquinolones and quinolones antibiotics.

II. Sulfonamides (sulfadiazine, sulfacetamide, sulfamethoxazole, co-trimoxazole)
Mechanism of action: inhibition of folic acid synthesis

Antibacterial activity: Strep. pyogenes, pneumoniae, Haemophilus influenzae, Nocardia, Actinomyces, Chlamydia trachomatis

Resistance: Neisseria meningitidis, Pseudomonas aeruginosa, Staphycolocci

Pharmacokinetics:

- well absorbed from GI
- variable absorption from the skin, vagina
- bound to plasma protein in varies degree
- distributed throughout all tissues and fluids incl. CSF
- metabolized in the liver (acetylation!), excreted in the urine partly as unchanged, partly as active substances

Indications:

- ocular infections – topical ocular sulfacetamid
- urinary tract and prostatic infections – sulfametoxazole (co-trimoxazole)
- burn infections – silver sulfadiazine
- malaria (resistant to meflochine *Plasmodium falciparum*) - sulfadoxin + pyrimethamine
- toxoplasmosis - sulfasalazine + pyrimethamine

Co-trimoxazole (sulfamethoxazole-trimethoprim)

Activity:

- Chlamydia
- Neisseria meningitidis
- Brucella
- Nocardia
- Yersinia
- Pneumocystis carinii (jiroveci)

Limited activity against: streptococcus, staphylococcus, Gram - aerobic

Resistant strains: Pseudomonas aeruginosa, Bacteroides, enetrococci

USES:

- Therapy and prevention of UTI
- bronchitis (exacerbations)
- GI infections – traveler diarrhea, typhoid fever, shigellosis
- nocardiosis
- Pulmonary infections - Pneumocystis carinii (jiroveci)

Adverse effects:

- hypersensitivity reactions (skin rashes, erytema multiform, Stevens-Johnson syndrome)
- kernicterus
- agranulocytosis, acute aplastic, hemolytic anemia (glucose-6-phosphate dehydrogenase deficiency)

III. Metronidazole, tynidazole

Mechanism of action: Metronidazole is reduced by low-redox-potential electron transfer proteins (e.g. nitroreductases such as ferredoxin) to unidentified polar product(s) which lack the nitro group. The reduction product(s) appears to be responsible for the cytotoxic and

antimicrobial effects of the drug which include disruption of DNA and inhibition of nucleic acid synthesis.

Spectrum :

Anaerobic bacteria: Clostridium, Bacteroides,Fusobacterium
Trichomonas vaginalis
Giardia lamblia, Entamoeba histolytica

Pharmacokinetics :

absorption: very well in GI and from the skin
protein binding – poorly 20%)
metabolism –hepatocytes,
distribution- widely penetrate into most tissues (inc. CSF)
elimination - urine 80%

USES:

- infections caused by anaerobic bacteria

(abscess, postoperative infections, skin infections, bones, CNS, vaginitis) – therapy/prevention - metronidazole

- pseudomembranes collitis - metronidazole
- giardiasis, amoebiasis - tynidazole
- genital trichomoniasis - tynidazole
- sepsis - metronidazole
- periodontal infections, zapalenia dziąseł - metronidazole
- Ulcers - metronidazole
- eradykation *H. pylori* – metronidazole

Adverse effects:

- vomiting, nausea, diarrhea
- metalic taste,
- leukopenia, trombocytopenia,
- neuropathy (dizziness, vertigo, paresteshia)
- discoloration of urine
- glossitis, ulcerations in the oral cavity
- teratogenic effect

UTI prevention of reccurences

- Nalidixic acid and cinoxacin
- Co-trimoxazole
- Nitrofurantoin
- Methenamine

IV. Nitrofuran derivatives – nitrofurantoin, furazidin

Mechanism of action: reduction of nitric group by bacterial flavoproteins to reactive intermediates which inactivate or alter bacterial ribosomal proteins and other macromolecules. As a result of such inactivations, the vital biochemical processes of protein synthesis, aerobic energy metabolism, DNA synthesis, RNA synthesis, and cell wall synthesis are inhibited. Nitrofurantoin is bactericidal in urine at therapeutic doses.

Spectrum:

Aerobic gram + i gram - bacteria: Staphylococcus, Escherichia, Proteus, Salmonella, Shigella, Community-acquired only
Resistant: Pseudomonas, Acinetobacter

Pharmacokinetics

- Bioavilability: interaction with food (protein rich food increases 50%)
- Absorption – very well,
- Metabolism – liver, kidney
- Elimination – very rapidly (high concentration in urine!!!)

Urine pH !!!
Acidic - convertion to lipophilic metabolites, TOXICITY!!!
alkaline – inactivation,

Indications: uncomplicated infections of urinary tract
Side effects:

- GI irritation, nausea, vomiting, diarrhea
- Megaloblastic, hemolytic anemia (G-6-P dehydrogenase deficiency),
- Peripheral neuropathy (paresthesia, confusion, vertigo)
- hypersensitivity reactions (Stevens-Johnson Syndrom),
- Urine discoloration - brown,
- Pulmonary fibrosis !!!!

V. Methenamine
Mechanism of action: hydrolysis to formaldehyde and ammonia in acidic urine; formaldehyde has nonspecific bactericidal action
Activity and therapeutic use: nearly all bacteria, attention: urea-splitting bacteria
Pharmacokinetics:
absorbed from GI, when in enteric capsules,
excretion - nearly negative – decomposes in low pH (mandelate or hippurate)
Adverse effects:
gastrointestinal distress, albuminuria, hematuria, rashes
Contraindications: hepatic failure (ammonia), renal failure(acids – crystallization of methenamine)

VI. Fosfomycin
Mechanism of action: interferes with early stage of bacterial cell wall synthesis by inhibiting phosphoenolpyruvate transferase.
Activity: Aerobic gram + i gram – bacteria require *N*-acetylmuramic acid for cell wall synthesis: *Escherichia, Proteus, Klebsiella, Salmonella, Enterobacter, Citrobacter*, Community-acquired only
Therapeutic use: asymptomatic bacteriuria, uncomplicated UTI, surgical prophylaxis
Pharmacokinetics:
absorbed partially in the small intestine, binds to plasma proteins at only negligible levels and is distributed widely into a variety of tissues; in addition to serum, elimination: unchanged in the urine
Adverse effects: diarrhea, headache, vaginitis
Contraindications: hypersensitivity reactions