**MACROLIDES**

Spectrum

- Aerobic gram-positive cocci
- Gram-negatives: Haemophilus, N. meningitidis, N. gonorrhoe, Moraxella, Bordetella pertussis, Helicobacter pylori, Campylobacter, Rickettsia, Treponema, Borrelia burgdorferi
- Atypical bacteria: Mycoplasma, Legionella, Chlamydia
- Anaerobes excl. Bacteroides
- Corynebacterium diph., Listeria
- Protozoa: Toxoplasma gondii

Erythromycin – older macrolide

Clarithromycin, azitromycin, roxitromycin – modern macrolides

Differences: spectrum and pharmacokinetics

Pharmacokinetics:

modern macrolides –large volume of distribution, penetrate well into abscesses

macrolides cannot penetrate into CSF

protein binding 50-90%

metabolized in the liver – erythromycin - whole, moderna macrolides – in part

renal elimination significant for clarithromycin

General therapeutic use:

- infections caused by atypical bacteria
- to eradicate the diphtheria carrier state/prophylaxis
- pertussis
- streptococcal infections and tetanus in patients with allergy to penicillin
- to eradicate the Helicobacter pylori
- gonoccocal urethritis
- Campylobacter infections

Use in dentistry:

- Prophylaxis against bacterial endocarditis in susceptible patients who are allergic to penicillin

Adverse effects:

- allergic reaction fever, eosinophilia, skin eruptions,
- cholestatic hepatitis
- epigastric distress
- cardiac arrythmias

**KETOLIDES** - Thelitromycin

Spectrum – Gram positive aerobics, like macrolides, more effective againts macrolide-resistant strains, inc. multidrug-resistant Strep. pneumonia, atypical bacteria, Moraxella cathrarralis

Well absorbed, extensively proteins bound, metabolized in the liver (CYP450), excreted renally

Adverse effects: GI problems, slowed accomodation, confusion, loss of consciousness, reversible hepatic imparement, QT **prolongation**

**CLINDAMYCIN**

Antibacterial activity

- Gram-positive aerobic cocci incl. Staph. aureus
- anaerobes
- Actinomyces and Nocardia
- Pneumocystis carini, Toxoplasma gondii, Plasmodium

Pharmacokinetics

- nearly completely absorbed
- widely distributed in many tissues (inc. bones) and fluids (exc. CSF), accumulates in activated leukocytes and alveolar macrophages and in abscesses
- 90% is bound to proteins
- metabolized in the liver in 90%, excreted in the bile

General therapeutic use

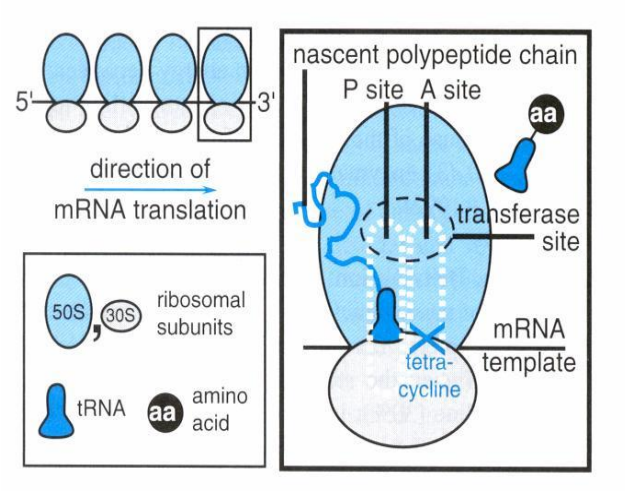
- aspiration pneumonia, lung abscessus, pelvic abscessus, peritonitis
- Pneumocystis carini pneumonia
- topically or orally in acne, bacterial vaginitis

Use in dentistry

- The third choice for treatment of orodental infections (purulent osteitis – when penicillins or macrolides are ineffective)
- An alternative antibiotic for prophylaxis against bacterial endocarditis

Adverse effects: diarrhea, skin rashes, erythrema multiforme, granulocytopenia

**TETRACYCLINES**




Spectrum

- Rickettsia, Coxiella, Vibrio cholerae, Brucella, Franciscella, Yersinia pestis
- Atypical bacteria !!!
- Spirocheta (Borrelia, Treponema, Leptospira)
- Anaerobes excl. Bacteroides, Propionibacterium acne
- Actinomyces and Nocardia
- A significant number of gram-positive cocci and gram-negative bacilli are resistant !!!

Old generation: chlortetracycline, oxytetracycline, tetracycline
Modern tetracyclines: doxycycline, minocycline

Pharmacokinetics:

- absorption varies among generations
- widely distributed including tissues and secretions incl. CSF
- highly concentrated in gingival fluid
- metabolized in the liver - enterohepatic circulation, excretion – renal and/or hepatic

General therapeutic uses

- Atypical infections of respiratory tract
- Sexually-transmitted diseases: chlamydial infection, syphilis
- Rocky Mountain spotted fever, recrudescent epidemic typhus, murine typhus, scrub typhus, Q fever
- Brucellosis, tularemia, cholera
- Actinomycosis, nocardosis, leptospirosis, borreliosis, plague
- Acne

Use in dentistry:
Certain types of periodontal disease (juvenile periodontitis – Actinobacillus actinomycetemcomitans).
Used subgingivally (paste, monofilament cords).

Adverse effects:

- gastrointestinal irritation and diarrhea
- photosensitivity
- hepatic toxicity, renal toxicity (exaggeration of existing renal insufficiency or outdated prep.)
- depression the bone growth (tetracycline-calcium orthophosphate complex)
- vestibular toxicity (minocycline)
- hypersensitivity reactions - skin reactions
- pseudomembranous colitis
- suprainfections (prolonged clotting time)
- antianabolic effect, hyperkalemia

- hypoplasia of enamel (during dentition – pitting formation, cusp deformation, increased susceptablity to caries)
- brown discoloration the affected teeth (oxidation of the tetracycline)- gingival 1/3 of the teeth
- discoloration of teeth due to minocycline (the incisal ½ to ¾ of the crowns) fully mineralized dentition – complexes with iron

**GLYCYLCYCLINES** - Tigecycline
Gram positive aerobics (Staph., Strep, Enterococci) including multidrug-resistant strains *(Enterococcus faecalis* – VRE, *Enterococcus faecium* - VRE), *Enterobacteriacae , Acinetobacter baumannii , Stenotrophomonas maltophilia*
Atypical bacteria
Anaerobes

- Pharmacokinetics: limited hepatic metabolism, large volume of distribution, extensively protein bound.

- Therapeutic use: skin and skin structure infection, complicated intraabdominal infection
- Well tolerated: GI problem, rare- pancreatitis; possible adverse effects typical for tetracyclines

**CHLORAMPHENICOL**

- Gram-positive aerobics
- Gram-negative aerobics
- Brucella, Bordetella pertussis, Vibrio
- Atypical bacteria
- Anaerobes

Pharmacokinetics

- well absorbed and distributed in body fluids inc. CSF
- may accumulate in brain tissue
- metabolized in the liver )glucuronic transferase)
- eliminated by the kidney mainly as unactive metabolites

Therapeutics uses:

- Typhoid fever and other types of salmonella systemic infections
- Bacterial meninigitis and brain abscesses
- Severe anaerobic infections
- Brucellosis
- Rickettisial diseases

Adverse effects

- hematologic toxicity: depression of the bone marrow: dose-related and dose-independent idiosyncratic response (aplastic anemia, pancytopenia)
- hypersensitivity reactions
- nausea, vomiting, unpleasant taste, peritoneal irritation, optic neuritis
- „gray baby" syndrome

**STREPTOGRAMINES**

Quinupristin (Streptogramin B)/dalfopristin (Streptogramin A)

- Gram-positive aerobics incl. S. pneumoniae SPPR, Enterococci VRE, Staph. MRSA
- Atypical bacteria
- Anaerobes

Pharmacokinetics: metabolized in the liver,inhibitors of P450, biliary excretion

Therapeutic use: VRE infections, MRSA infections, infections caused by multidrug resistant gram-positive strains

Adverse effects: arthralgias, myalgias

**OXALIDINONES** – LINEZOLID

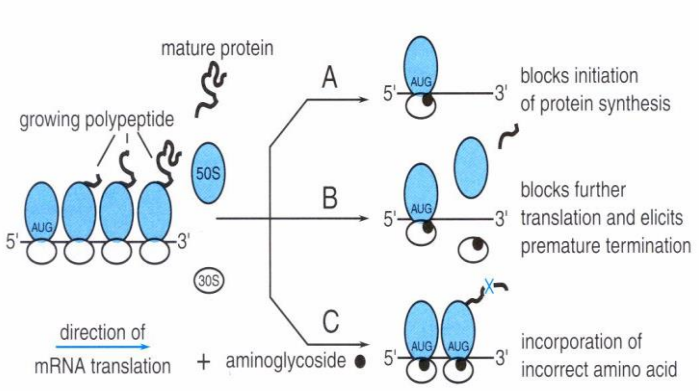
- Gram-positive aerobics incl. MRSA, VRE, SPPR
- Gram-positive anaerobes

Pharmacokinetics: well absorbed abd distributed, metabolized in the liver, excreted renally, mainly as metabolites.

Therapeutic use: nosocomial infection due to susceptible strains

Adverse effects: GI symptoms, rash, thrombocytopenia

**AMINOGLYCOSIDES**




Antibacterial activity: aerobic gram-negative bacilli.

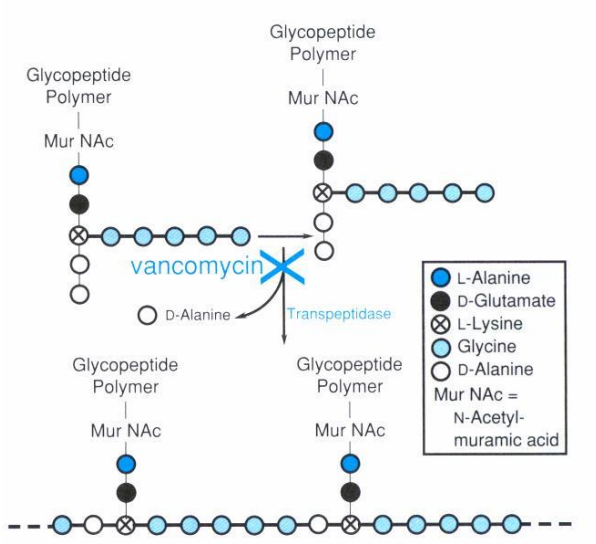
Pharmacokinetics:

- poorly absorbed from GI tract
- volume of distribution=volume of extracellular fluid
- penetration to CSF is inadequate
- eliminated generally by glomerulal filtration, in large fraction as unchanged drugs

Gentamicin, neomycyn, streptomycin

Adverse effects: ototoxicity, nephrotoxicity, neuromuscular blockade

## VANCOMYCIN




Antimicrobial activity:

- Aerobic Gram-positive bacteria (Staph. incl. strains resistant to methicillin)
- Anaerobic Gram-positive bacteria (Clostridium difficile)

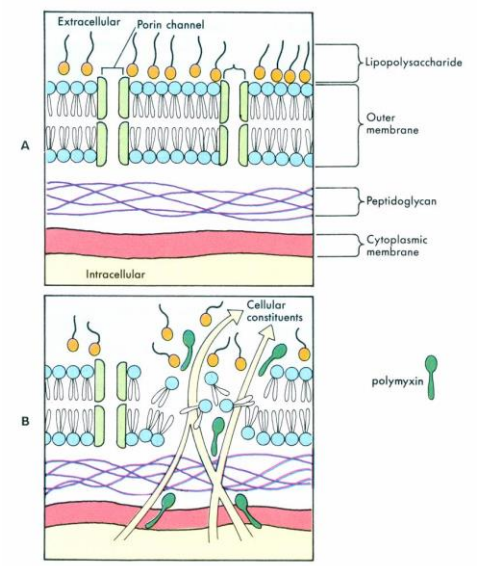
Pharmacokinetics:

- poorly absorbed, given i.v.
- distributed in body fluids (inc. CSF- when the meninges are inflamed)
- excreted in urine in 90%

Adverse effects:

- hypersensitivity reactions, chills, fever, infusion related erythrematous, urticariae reaction
- tachycardia, hypotension
- „red-men" or „red-neck" syndrome
- ototoxicity
- nephrotoxicity

## POLYMYXINES




Antibacterial activity: restricted to aerobic Gram-negative bacteria

Pharmacokinetics: are not absorbed from GI tract, from any mucosa and surface of lesions

Adverse effects

- nausea, vomiting, diarrhea, when taken orally
- nephrotoxicity (renal tubules) - when given parenterally
- neurotoxicity (peripheral)

## QUINOLONES

- Gyrase – continious introduction of negative supercoils into DNA
- Topoisomerase IV – separates interlinked (catenated) doughter DNA molecules

Unfluorinated QUINOLONES

Nalidixic acid, cinoxacin

Antibacterial activity: community-aquired Gram-negative bacteria

Pharmacokinetics:

readily absorbed, in 90% proteins bound, metabolized and excreted in the urine

FLUORINATED QUINOLONES

Antibacterial activity of FQ – wide and differs among preparations

| | |
|---|---|
| **Gram negative aerobics (inc. Pseudomonas)** | **all of FQ** |
| **streptococci** | **levo-, gati-, moxi-** |
| **staphylococci exc. MRSA** | **all of FQ** |
| **atypical bacteria** | **all of FQ** |
| **mycobacteria** | **cipro-, peflo-, oflo-** |
| **anaerobes** | **gareno-, gemi-** |

Pharmacokinetics

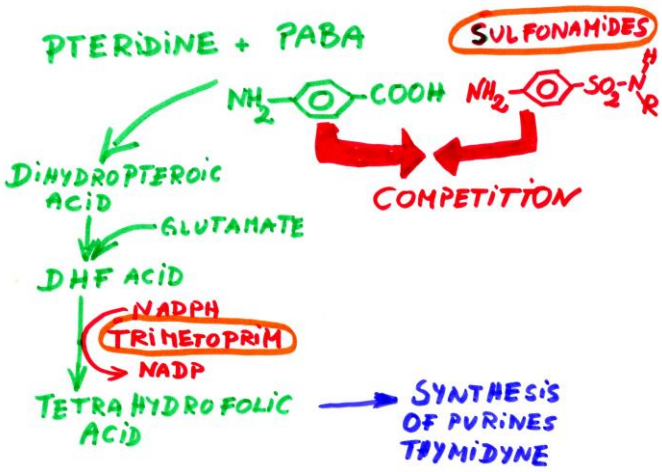
| | GI | CSF | Tissues | Urine | Phagocytes | M | E |
|---|---|---|---|---|---|---|---|
| Nor | 1 | 0 | 0 | 1 | 1 | N | K |
| Pe | 1 | 1 | 1 | <1 | 1 | M | L> K |
| Cipro | 1 | 1 | 1 | <1 | 1 | P | K> L |
| Spar | 1 | 1 | 1 | <1 | 1 | M | L> K |
| Grepa | 1 | 1 | 1 | 0 | 1 | M | L |
| Trova | 1 | 1 | 1 | 0 | 1 | M | L |

Therapeutic use
- urinary tract infections
- prostatitis
- sexually transmitted diseases (exc. Treponema)
- gastrointestinal and abdominal infections
- respiratory tract infections
- bone, joint and soft tissue infections
- tuberculosis, tularemia

Adverse effects:
- CNS effects: seizures, hallucinosis
- photosensitivity
- arthralgias and joint swelling in children

Contraindicated: in pregnancy, in prepubertal children (exception – cystic fibrosis)

**SULFONAMIDES**




Spectrum: Strep. pyogenes, pneumoniae, Haemophilus influenzae, Nocardia, Actinomyces, Chlamydia trachomatis Neisseria meningitidis? Shigella? E. coli?

Pharmacokinetics:
- well absorbed from GI
- distributed throughout all tissues and fluids incl. CSF
- metabolized in the liver (acetylation!), excreted in the urine partly as unchanged, partly as active substances

Poorly absorbed sulfonamides
Sulfasalazine
Agents absorbed rapidly and excreted rapidly
Sulfisoxazole, sulfamethoxazole, sulfadiazine, sulfamethizole
Long-acting sulfonamides
Sulfadoxine
Only topically used sulfonamide
Sulfacetamide , sulfadiazine, mafenide
Therapeutic use:
- topically used: eyes - sulfisoxazole, sulfacetamide, wounds, burns – mafenide (carbonic anhydrase inhibitor), sulfadiazine
- urinary tract infections – sulfisoxazole?
- nocardiosis - sulfisoxazole, sulfadiazine
- toxoplasmosis - sulfadiazine in combination with pyrimethamine
- malaria - sulfadoxine with pyrimethamine

Adverse effects

- crystalluria (old type)
- acute hemolytic anemia, aplastic anemia, agranulocytosis
- hypersensitivity reactions
- necrosis of the liver
- anorexia, nausea, vomiting
- kernicterus

Co-trimoxazole: sulfamethoxazole + trimetoprim

Spectrum

- Chlamydia
- Neisseria meningitidis
- Brucella
- Nocardia
- Yersinia

– wider than old-type sulfonamides

Therapeutic uses:

- urinary tract infections
- exacerbations of chronic bronchitis
- acute otitis media, acute maxillary sinusitis
- shigellosis, a second-line drug in typhoid fever
- nocardiosis
- pneumonia caused by Pneumocystis carinii (jiroveci)

**NITROFURANTOIN**

Spectrum: Enterococci and Gram negative aerobics (Proteus?, Pseudomonas? Klebsiella?)

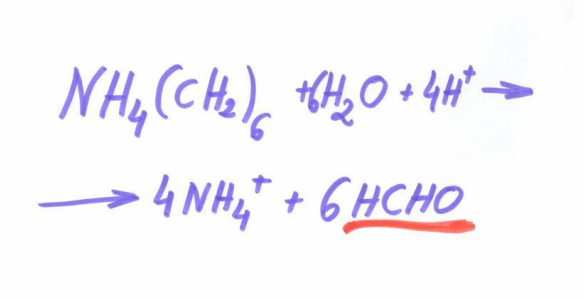
Pharmacokinetics:

well absorbed, metabolized only in 60%, and excreted rapidly, low pH of urine!!!

Adverse reactions:

- nausea, vomiting, diarrhea - common
- chills, fever, leukopenia, hemolytic anemia ( G-6-P dehydrogenase deficiency), cholestatic jaundice, hepatic damage, acute pulmonitis – hypersensitivity reactions
- interstitial pulmonary fibrosis – free radicals
- polyneuropathies, vertigo, drowssiness, muscular aches
- urine – brown!

**METHENAMINE**




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)

**METRONIDAZOLE**

Activity:

anaerobes

protozoa

(Trichomonas, Amoeba, Giardia)

Pharmacokinetics:

well absorbed, widely distributed, penetrates into CSF, metabolized in the liver

Therapeutic uses

- anaerobic or mixed infections
- vaginitis
- antibiotic-associated enetrocolitis
- abscesses
- preparation for colon surgery
- amebiasis, giardiasis, trichomoniasis, balantidiasis

Adverse effects

- nausea, vomiting, dry mouth, metallic taste
- dark urine
- vomiting, diarrhea, stomatitis
- agranulocytosis

is mutagenic, carcinogenic, teratogenic

## ANTIFUNGAL AGENTS

| Classification | Site infected | Example |
|---|---|---|
| Superficial | Skin, hair, nails, mucosa | Dermatophytosis, Candidiasis, Malaseziasis |
| Subcutaneous | Dermis and subcutaneous tissue | Sporotrichosis |
| Systemic | Disease ≥ 1 internal organ | |
| Opportunistic | | Candiadias, Cryptococcosis, Aspergillosis, Mucormycosis |
| Nonopportunistic | | Histoplasmosis, Blastomycosis, Coccidiomycosis |

Classification of antifungal agents

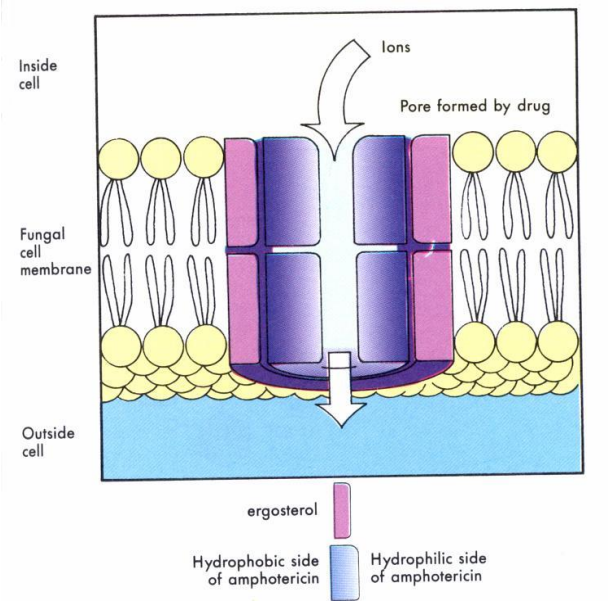
- polyene antibiotics: nystatin, natamycin, amphotericin B
- azoles: ketoconazole, fluconazole, itraconazole
- allyloamines: terbinafine, naftifine
- morpholines: amorolphine
- echinocandins: micafungin, caspofungin
- others: flucitosine, griseofulvin, ciclopirox

1.agents inhibiting mitosis: griseofulvin
2.agents which impair fungal cell membrane

- directly impairing structure of cell membrane: polyene antibiotics
- inhibitors of ergosterol synthesis: azoles, allyloamines, morpholines
- inhibitors of cell membrane synthesis: ciclopirox

3. inhibitors of nucleic acids synthesis: flucytosine
4. inhibitors of fungal cell wall synthesis: echinocandins

### AMPHOTERICIN B



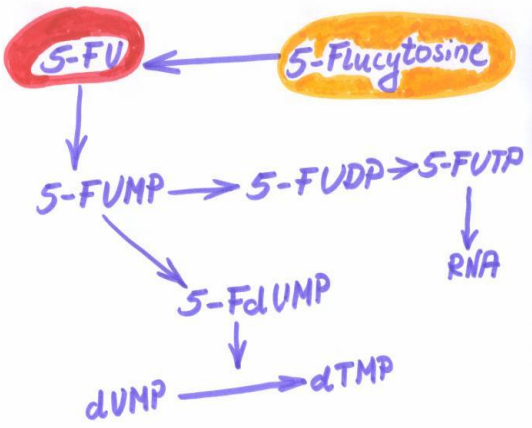

Spectrum: fungi responsible for deep mycoses
Pharmacokinetics:

- well distributed in certain tissues (liver, spleen),
- does not penetrate CNS,
- catabolism is extremly slow,
- mainly excreted into the bile.

Adverse effects:

- fever and chills, hyperpnea, respiratory stridor, hypotension
- azotemia, tubular acidosis, renal wasting of potassium and magnesium
- anemia

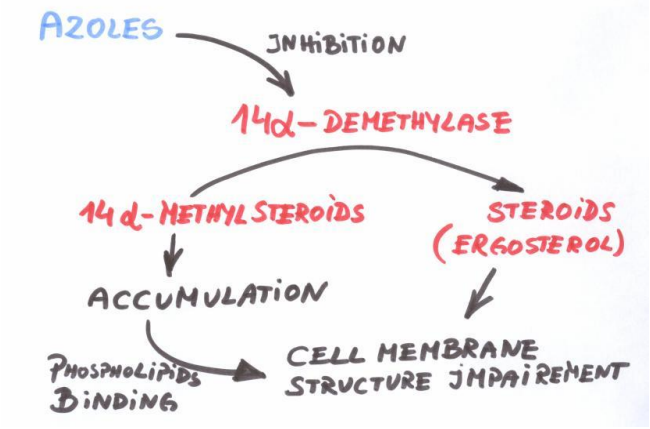
### FLUCYTOSINE




Spectrum: Candida, Cryptococcus
Pharmacokinetics: well and rapidly absorbed, volume of distribution = total body water (inc. CSF, aeqous humor),
as unchanged substance in 80% excreted in the urine,

Adverse effects: depression of the bone marrow

AZOLES




Imidazoles: clotrimazole, miconazole, ketoconazole, econazole
Triazoles: terconazole, itraconazole, fluconazole, voriconazole
Triazoles have less effect on human sterols
Spectrum: numerous fungi responsible for deep mycoses (Candida spp., Blastomyces, Histoplasma, Coccidiodes, Aspergillus, Fusarium, Sporothrix) and dermatophytes

Pharmacokinetics: preparation-dependent

| Ketoconazole | Fluconazole |
|---|---|
| Requires acidic gastric juice | - |
| Widely distributed, except CSF | Widely distributed, penetrates CSF |
| Cytochrom P450 | - |
| - | Eliminated by the kidneys |
| Inhibits steroids synthesis | - |

Adverse effects:

- gynecomastia, menstrual irregulation, azoospermia, decreased libido and potency (ketoconazole)
- hypertension and fluid retention
- hepatic damage
- blurred vision, altered colour perception (voriconazole)
- QT prolongation

ALLYLOAMINES

- inhibit squalenic epoxidase - accumulation of squalen and deficiency of ergosterol
- inhibit fungal fimbrias adhesion, germination and penetration inside tissues
- effective against dermatophytes, less effective against Candida

Terbinafine is lipophylic, bound to chylomicrones, well penetrates adipose tissue and skin, high concentrated in stratum corneous of epidermis, nails, seborrhea and hair, extensively metabolized in the liver, eliminated by the kidneys

- therapeutic level of terbinafine in nails is maintained within 2-3 month after discontinuation, in plasma - within 8 weeks

Adverse effects: GI deterioration, skin reactions, fatigue, rare: erythrema multiforme, unpleasant taste, cholestase, granulo- and trombocytopenia

ECHINOCANDINES
Inhibition of D-glucans formation in the cell aall - Caspofungin, micafungin
Spectrum: Candida sp., Aspergillus sp
Pharmacokinetics:

- Not absorbed from GI, metabolized in the liver, unactive metabolites excreted with the urine and with feces
- Well tolerated, histamine-like effects

GRISEOFULVIN
Mechanism: ihibits polimerization of microtubules
Spectrum: dermatophytes
Pharmcokinetics:

- absorbed with fatty meals,
- distribution limited to the stratum corneum of the skin, is deposited in keratin precursor cells
- excreted in urine within 5 days mostly as metabolites

Adverse effects:

- peripheral neuropathy, mental confusion, lethargy, fatigue, syncope, vertigo, blurred vision
- nausea, vomiting, diarrhea, flatulence, dry mouth, stomatitis
- leukopenia -dissapears spontaneously

- albuminuria - without renal insufficiency
- urticaria, photosensitivity, lichen planus, serum-sickness syndromes
- induction of microsomal enzymes

MORPHOLINES: amorolphine
Spectrum: dermatophytoses, yeasts, pityriasis versicolor
Mechanism: inhibits Δ14 - reductase and Δ8Δ→7 - reductase (ergosterol synthesis) and causes squalen accumulation, inhibits NADH oxidase, succinate reductase of cytochrom c

CYCLOPIROX

- used topically (varnish, cream)
- dermatophytoses, yeasts, Gram positive and negative bacteria
- inhibits amino acids transport, phosphates and potassium through cell membrane, inhibits synthesis of substances necessary to cell membrane synthesis, inhibits prostaglandins and leucotriens synthesis
- penetrates through epidermis into the dermis and hair follicles and seborrhoic glands