# Antimicrobial drugs

## Disinfectants and Antiseptics
## Antibacterial chemotherapeutic drugs

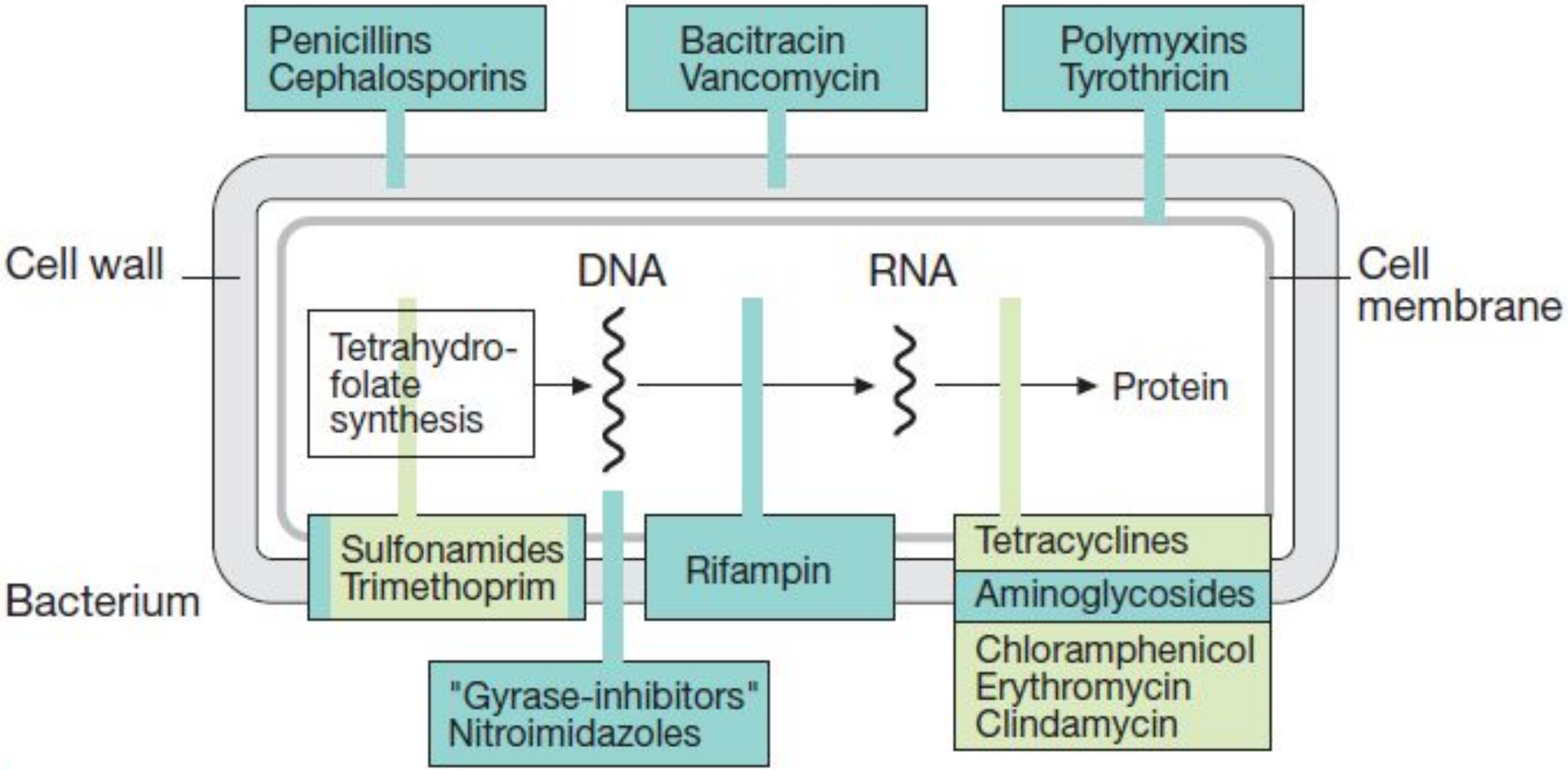
Antimicrobial drugs have antimicrobial properties. They are divided into 2 groups:

- Disinfectants and Antiseptics (drugs are used locally)
- Antibacterial chemotherapeutic drugs are applied resorptively.

Type of action:

A. Bacteriostatic: drugs delay the growth and reproduction of bacterial cells.

B. Bactericidal: drugs cause cell death.


Penicillins
Cephalosporins
Bacitracin
Vancomycin
Polymyxins
Tyrothricin
Cell wall
Cell membrane
DNA
RNA
Tetrahydro-
folate
synthesis
Protein
Sulfonamides
Trimethoprim
Rifampin
Tetracyclines
Aminoglycosides
Chloramphenicol
Erythromycin
Clindamycin
"Gyrase-inhibitors"
Nitroimidazoles
Bacterium

2.

# Disinfectants and Antiseptics

- **Disinfection denotes the inactivation or** killing of pathogens (protozoa, bacteria, fungi, viruses) in the human environment (instruments, equipment, premises, dishes, patients' excrements). They provide a rapidly developing effect. They are applied at bactericidal concentration and aimed at the prevention of the spread of infection.

Phenol was the first antiseptics.

Phenol coefficient (the ratio between the concentration of phenol and the antiseptic under test, in which both substances provide equal antimicrobial effect) is a common measure of antiseptic activity.

**Antisepsis** refers to the *reduction by chemical* agents of germ numbers on skin and mucosal surfaces.

Agents for chemical disinfection ideally should cause *rapid, complete,* and *persistent inactivation of all germs,* but at the same time exhibit low toxicity (systemic toxicity, tissue irritancy, antigenicity) and be non-deleterious to inanimate materials. But anticeptics are highly toxic and can cause side effects: local irritant and cauterizing effect.

At higher concentrations they are disinfectants.

- **Disinfectants come from various** chemical classes, including oxidants, halogens or halogen-releasing agents, alcohols, aldehydes, organic acids, phenols, cationic surfactants (detergents) and formerly also heavy metals. The **basic mechanisms of action involve denaturation** of proteins, inhibition of enzymes, or a dehydration. Effects are dependent on concentration and contact time.
- **Activity spectrum. Disinfectants** inactivate bacteria (gram-positive > gram-negative > mycobacteria), less effectively their sporal forms, and a few (e.g., formaldehyde) are virucidal.

# Applications

- Skin “disinfection.” (Reduction of germs before injections or surgical procedures). Useful agents include: alcohols (ethanol) 70–90%; iodine-releasing agents like povidone, cationic surfactants, and mixtures of these. Minimal contact times should be at least 15 s on skin .
- Mucosal disinfection: Germ counts can be reduced by PVP iodine or chlorhexidine (contact time 2 min), although not as effectively as on skin.

## Disinfection of mucous membranes

Chlor-hexidine

## Wound disinfection

Chlor-hexidine

$KMnO_4$

$H_2O_2$

## Skin disinfection

Regular — e.g., hands

Alcohols

Phenols

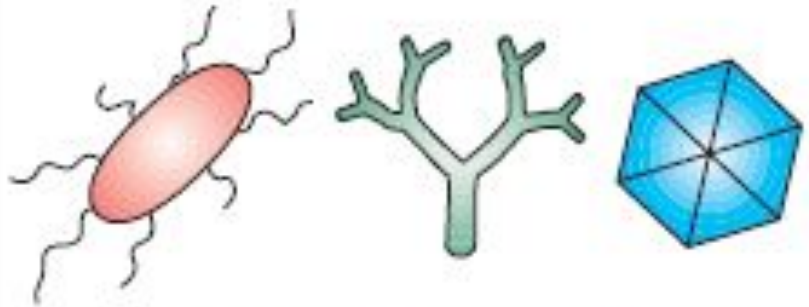
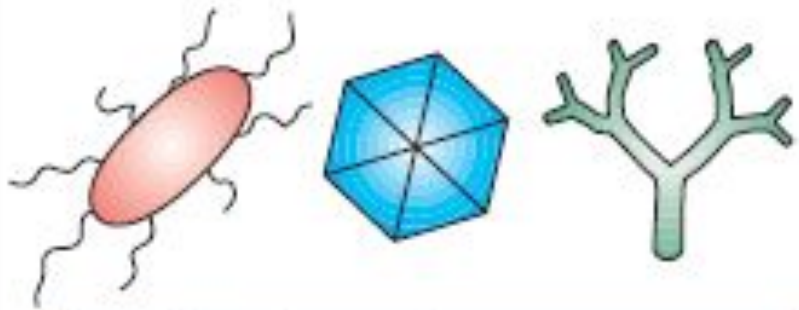
Cationic surfactants

Acute,
e.g., before local procedures

Iodine tincture

Chlor-hexidine

- ***Wound disinfection*** can be achieved with hydrogen peroxide or with potassium permanganate, as well as PVP iodine, chlorhexidine, and biguanidines.
- ***Hygienic and surgical hand disinfection:*** is required after a suspected contamination, before surgical procedures. Alcohols, mixtures of alcohols and phenols, cationic surfactants, or acids are available for this purpose.
- Admixture of other agents prolongs duration of action and reduces inflammation

| Application sites | Examples |
| --- | --- |
|  Inanimate material: durable against chemical + physical measures | Disinfection of floors or excrement<br>Phenols<br>NaOCl<br>Cationic surfactants |
|  Inanimate matter: sensitive to heat, acids, oxidation etc. | Disinfection of instruments<br>Cationic surfactants<br>Aldehydes |

- ***Disinfection of instruments:*** *Instruments* that cannot be heat- or steam sterilized can be precleaned and then disinfected with aldehydes and detergents.
- ***Surface (floor) disinfection*** *employs* aldehydes combined with cationic surfactants and oxidants or, more rarely, acidic or alkalizing agents.

Chemotherapeutic drugs inhibit/kill the infecting organism and have no/minimal effect on the recipient. They can be divided:

- *Antibiotics are produced by* microorganisms.
- *Synthetic drugs*.

❑ These drugs influence specific microorganism and have wide therapeutic window. They suppress the growth of or kill other microorganisms at very low concentrations. They are used for the treatment and prevention of diseases, for the treatment of infection carries.

# Basic principles of chemotherapy

- Early start of treatment.
- Determination of the causative agent, its sensitivity to the drug.
- The use of optimum doses.
- Accounting pharmacokinetics of the drug: the degree of absorption, distribution, features of excretion, duration of action.
- Accounting for toxicity of drugs.
- Carrying out a full course of treatment (5-10 days).
- If necessary – the possibility of combining drugs.

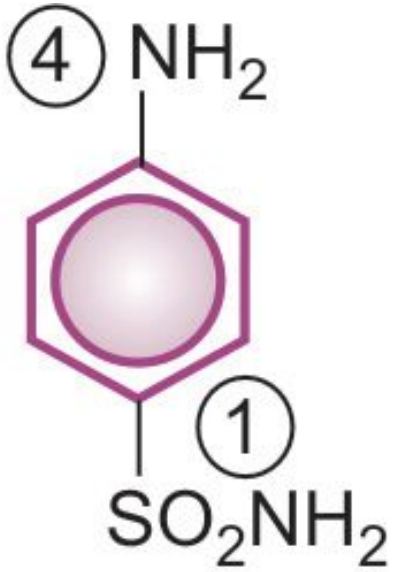
# SULFONAMIDES

Sulfonamides were the first antimicrobial agents (AMAs) effective against pyogenic bacterial infections.

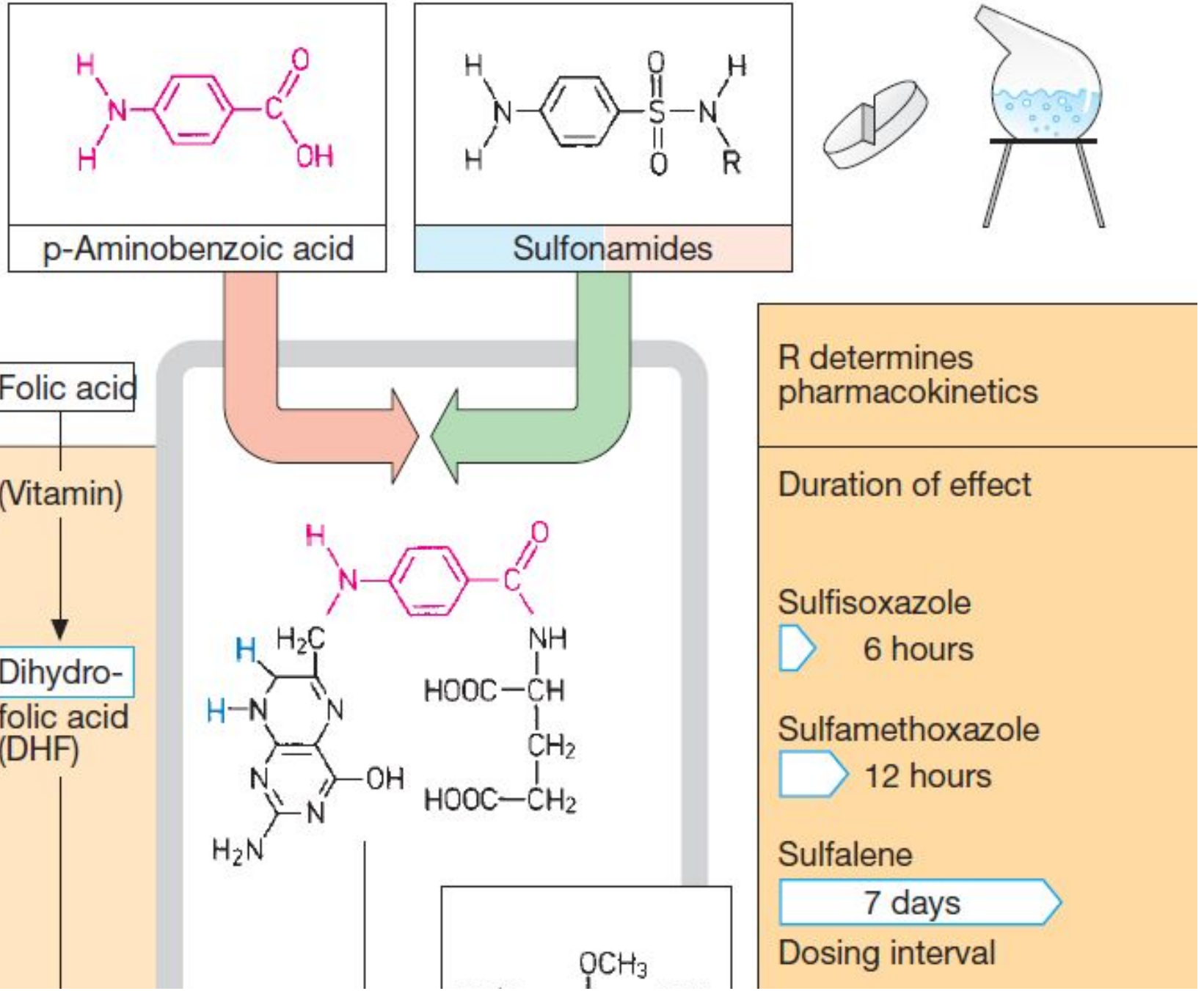
All sulfonamides are derivatives of sulfanilamide.

Individual members differ in the nature of N1 substitution, which governs solubility, potency and pharmacokinetic property.

A free amino group in the para-position (N4) is required for antibacterial activity.




SULFANILAMIDE


p-Aminobenzoic acid
Sulfonamides
Folic acid
(Vitamin)
Dihydro-
folic acid
(DHF)
R determines
pharmacokinetics
Duration of effect
Sulfisoxazole
6 hours
Sulfamethoxazole
12 hours
Sulfalene
7 days
Dosing interval

- Sulfonamides are primarily bacteriostatic against many gram-positive and gram-negative bacteria. However, bactericidal concentrations may be attained in urine. Sensitivity patterns among microorganisms have changed from time-to-time and place-to-place.
- Those still sensitive are: Streptoc. pyogenes, Haemophilus Influenzae, Vibrio cholerae, Staph. aureus, gonococci, meningococci, pneumococci, Escherichia coli, Shigella, Chlamydiae, Actinomyces, Nocardia and Toxoplasma.
- Anaerobic bacteria are not susceptible now.

## 1. Preparations used for their systemic action:

- Short acting (4–8 hr): Sulfadiazine, sulfadimidine
- Intermediate acting (8–12 hr): Sulfamethoxazole
- Long acting (12-24 days): Sulfamethoxypyrazine, sulfadimethoxine
- With a very long-term action (more 7 days): Sulfadoxine, sulfalene

**2. D. acting in the intestinal lumen:** phthalylsulphathiazole

**3. D. for topical use:** sulfacetamide sodium, silver sulfadiazine

- The mechanism is connected with their competitive antagonism with para-aminobenzoic acid (PABA). Sulfonamides block dihydropteroate synthetase also. They inhibit the union of PABA with pteridine residue to form dihydropteroic acid which conjugates with glutamic acid to produce dihydrofolic acid. They inhibit bacterial folate synthase → FA is not formed and a number of essential metabolic reactions suffer.
- Human cells also require FA, but they utilize preformed FA supplied in diet and are unaffected by sulfonamides.

- Sulfonamides are rapidly and nearly completely absorbed from G.I.T. Extent of plasma protein binding differs considerably (10–95%) among different members. The highly protein bound members are longer acting. Sulfonamides are widely distributed in the body—enter serous cavities easily. The free form of sulfadiazine attains the same concentration in CSF as in plasma. They cross placenta freely.
- The primary pathway of metabolism of sulfonamides is acetylation primarily in liver.
- The acetylated derivative is inactive, but can contribute to the adverse effects. It is generally less soluble in acidic urine than the parent drug—may precipitate and cause crystalluria.

- Sulfonamides are excreted mainly by the kidney through glomerular filtration. Both renal tubular secretion and reabsorption occur. The more lipid-soluble members are highly reabsorbed in the tubule, therefore are longer acting.

- Phthalylsulphathiazole is not absorbed from GIT and acts there. So it can be used for the treatment of intestinal infections.

## Side effects:

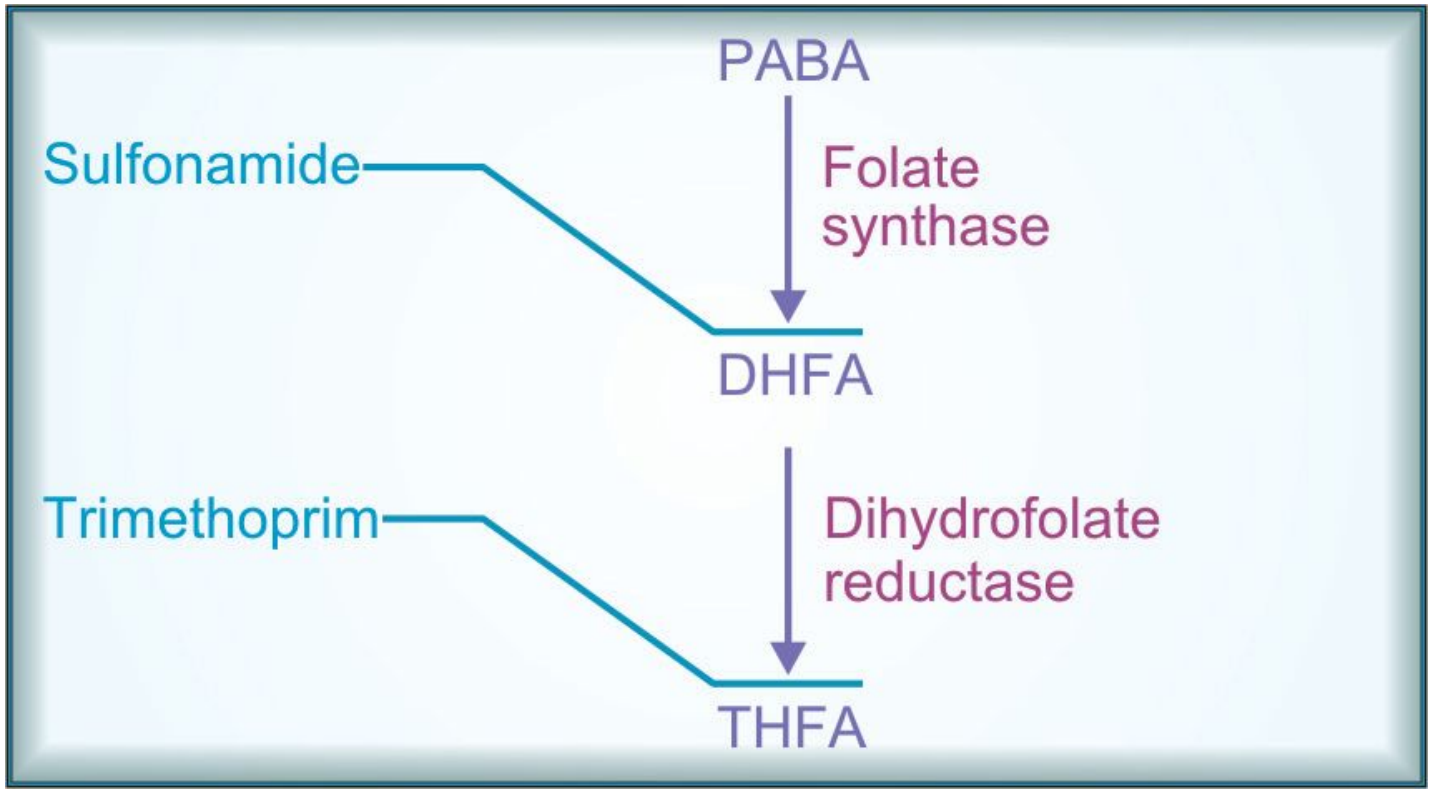
- Nausea, vomiting and epigastric pain.
- Crystalluria . Precipitation in urine can be minimized by taking plenty of fluids and by alkalinizing the urine in which sulfonamides and their acetylated derivatives are more soluble.
- Hypersensitivity reactions (rashes, urticaria and drug fever).
- Photosensitization.
- Hepatitis, unrelated to dose.
- Haemolysis can occur in G-6-PD deficient individuals with high doses of sulfonamides.

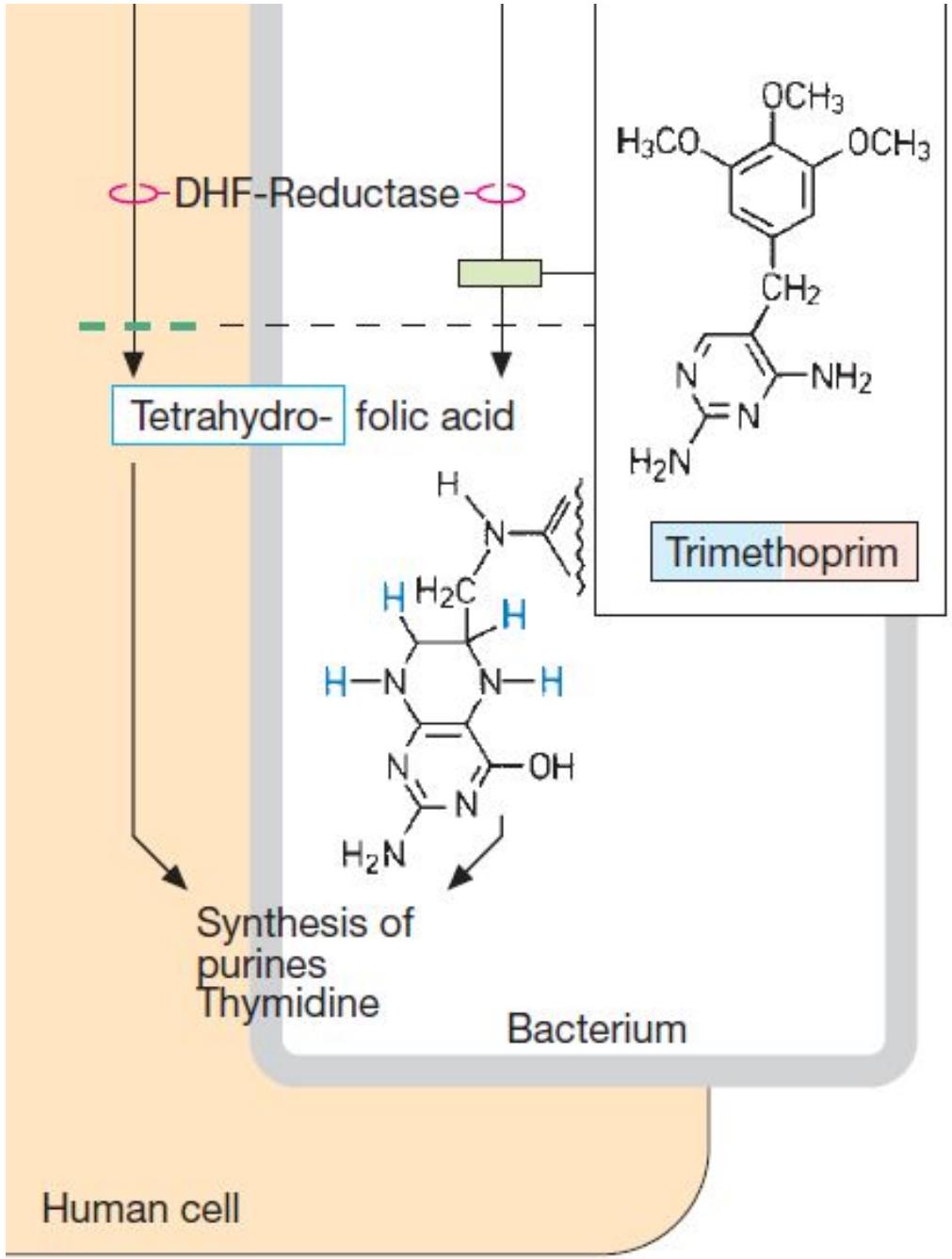
**USES**:

- suppressive therapy of chronic urinary tract infection;
- ear, throat, nose infections;
- gum infection;
- malaria and toxoplasmosis.
- **Ocular sulfacetamide sod. (10–30%)** is a cheap alternative in trachoma and conjunctivitis,
- Topical **silver sulfadiazine** is used for preventing infection on burn surfaces.

The fixed dose combination of **trimethoprim** and **sulfamethoxazole** is called **cotrimoxazole**.

Trimethoprim selectively inhibits bacterial dihydrofolate reductase (DHFRase).






7 days

Dosing interval

Co-trimoxazole =

**Co**mbination of **Trim**ethoprim and Sulfameth**oxazole**

Sulfasalazine (not absorbable)

Cleavage by intestinal bacteria

Mesalamine (absorbable)

Sulfapyridine

Individually, both sulfonamide and trimethoprim are bacteriostatic, but the combination becomes bacteriocidal against many organisms.

- **Spectrum of action of** trimethoprim and sulfonamides overlap considerably. Additional organisms covered by the combination are—*Salmonella typhi, Serratia, Klebsiella, Enterobacter, Yersinia enterocolitica, Pneumocystis and many* sulfonamide-resistant strains of *Staph. aureus, Strep. pyogenes, Shigella, enteropathogenic E. coli, H.influenzae, gonococci and meningococci.*

# Uses

- Urinary tract infections (acute cystitis, prostatitis);
- Respiratory tract infection caused by gram positive cocci and H. influenzae;
- Bacterial diarrhoeas and dysentery caused by E. coli, Shigella, nontyphoid Salmonella, and Y. enterocolitica;
- Pneumonia in neutropenic and AIDS patients caused by Pneumocystis jiroveci;
- Chancroid.

## Side effects of cotrimoxazole

- Nausea, vomiting, stomatitis, headache and
- Folate deficiency (megaloblastic anaemia).
- Cotrimoxazole should not be given during pregnancy. Trimethoprim is an antifolate, there is theoretical teratogenic risk.
- Neonatal haemolysis and methaemoglobinaemia can occur if it is given near term.

# QUINOLONES

**1.Quinolones (without F)**

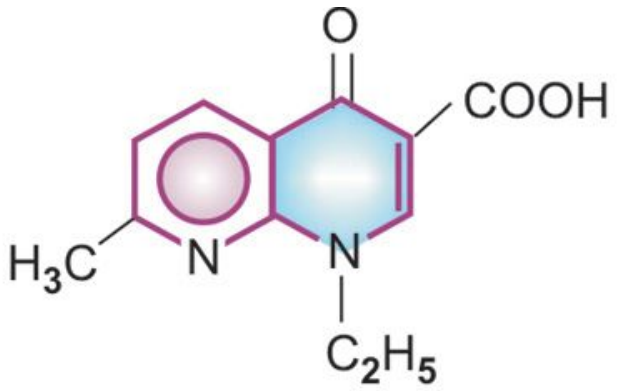
Nalidixic acid

**2.First generation fluoroquinolones**

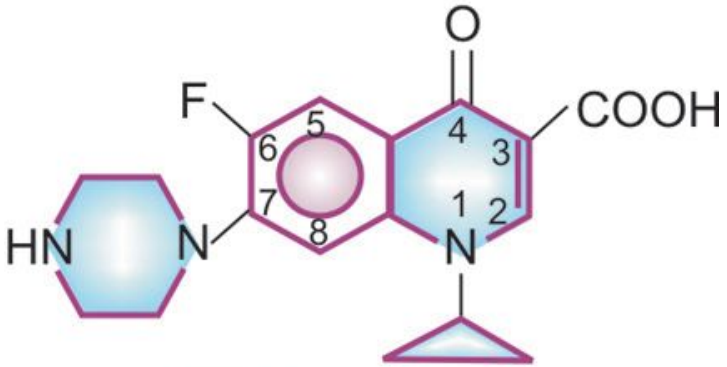
- Norfloxacin, Ofloxacin, Ciprofloxacin, Pefloxacin

**3. Second generation fluoroquinolones**

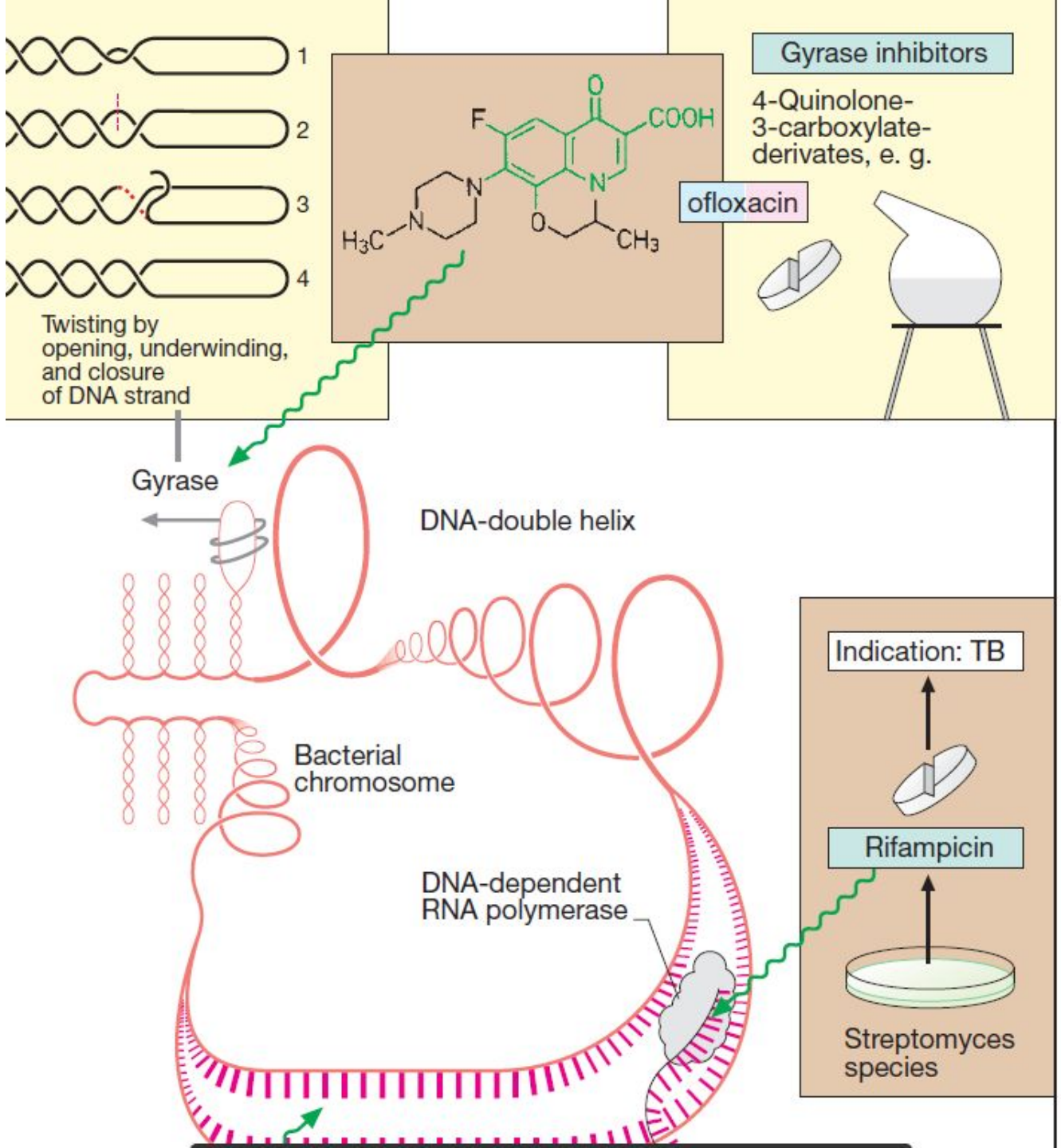
- Levofloxacin, Lomefloxacin, Prulifloxacin, Moxifloxacin




NALIDIXIC ACID




CIPROFLOXACIN


1
2
3
4
Twisting by opening, underwinding, and closure of DNA strand
F
COOH
O
N
N
$H_3C$
O
$CH_3$
Gyrase inhibitors
4-Quinolone-3-carboxylate-derivates, e. g.
ofloxacin
Gyrase
DNA-double helix
Bacterial chromosome
DNA-dependent RNA polymerase
Indication: TB
Rifampicin
Streptomyces species

# Nalidixic acid

- It is active against gram-negative bacteria ( *E. coli, Proteus, Klebsiella, Enterobacter, Shigella but not Pseudomonas).*
- It acts by inhibiting bacterial DNA gyrase and is bactericidal. Resistance to nalidixic acid develops rather rapidly.
- Nalidixic acid is absorbed orally, highly plasma protein bound and partly metabolized in liver: one of the metabolites is active. It is excreted in urine . T½ ~8 hrs.

- Nalidixic acid is primarily used as a urinary antiseptic. It has also been employed in diarrhoea caused by *Proteus, E. coli, Shigella or Salmonella.*
- *Adverse effects:* g.i. upset and rashes; headache, drowsiness, vertigo, visual disturbances, occasionally seizures (especially in children); phototoxicity; haemolysis.

# FLUOROQUINOLONES

These preparations exhibit a bactericidal effect. Mechanism of action is associated with the inhibition of bacterial enzymes – topoisomerases II (DNA- gyrase) and IV. This impairs DNA replication and RNA formation. All this interferes with bacterial growth and division.

## The spectrum of action of First generation fluoroquinolones

- **Highly susceptible**: Neisseria gonorrhoeae; N. meningitidis; E. coli; K. pneumoniae; Enterobacter; H. influenzae; Salmonellas; Campylobacter; Shigella; Yersinia enterocolitica; Proteus; Vibrio cholerae
- **Moderately susceptible:** Pseudomonas aeruginosa; Legionella; Staph. Aureus (including few MRSA); Brucella; Listeria; Bacillus anthracis; Mycobact. tuberculosis
- **Organisms which have shown low/variable susceptibility are:** Streptococci, Mycoplasma, Chlamydia.
- **Notable resistant bacteria are:** Bacteroides fragilis, Clostridia, anaerobic cocci.

The spectrum of action  of 2 generation fluoroquinolones

They are more active against gram-positive bacteria. They suppress Streptococci, Staphylococci, listeria, Corinebacteria, Enterococci, Pneumococci, Chlamydia, Mycoplasma, Ureaplasma, anaerobic microorganism.

Their bactericidal activity against gram-negative bacteria is also maintained.

# Pharmacokinetics:

- Drugs are absorbed from the gastrointestinal tract at 60-100%,
- They bind to proteins of blood.
- They penetrate the tissues and body fluids, in the cells very well.
- They can pass through the BBB.
- They are excreted in the active form by the kidneys.
- They are prescribed 1-2 times a day.
- There are drugs for intravenous and topical use.

## Uses

- Urinary tract infections;
- Gonorrhoea;
- Chancroid;
- Bacterial gastroenteritis: dysentery, salmonellosis, cholera;
- Typhoid;
- Bone (osteomyelitis, joint infections), soft tissue, gynecological and wound infections;

- Respiratory infections (2nd generation FQs is better);
- Tuberculosis;
- Septicaemias;
- Conjunctivitis;
- Meningitis


NDC 25021-130-20
LEVOFLOXACIN
INJECTION
500 mg per 20 mL
(25 mg per mL)


100 ml
CIPROFLOXACIN
INJECTION U.S.P.
(With Sodium Chloride 0.9%w/v)
FOR INTRAVENOUS
INFUSION ONLY
Ciprofloxacin Injection USP


PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
Moxifloxacin™
moxifloxacin
400 mg
5 Tablet
Moxifloxacin is a registered trade mark of Sabaa International Company for Pharmaceutical And Chemical Industries S.A.E
Sabaa


LANSIER
Lanciprox®
CIPROFLOXACINO 0,3%
Solución Oftálmica
Estéril x 5 mL

# Side effects

- Dyspeptic disorders (nausea, vomiting, anorexia, diarrhea);
- Allergic reactions (rash, itching), photosensitization;
- Dizziness, headache, insomnia, mood changes, convulsions;
- Anemia, thrombocytopenia;
- Tendovaginitis, myalgia, arthralgia;
- Dysbacteriosis;
- Impaired liver and kidney function.

**Contraindications:** to pregnant women and children under 2 years of age due to the risk of damage to cartilaginous tissue.

**Derivative of 8-hydroxyquinoline – Nitroxoline**

**Mechanism:** reducing the activity of enzymes due to the formation of complexes with metals.

**Type:** bacteriostatic or bactericidal depending on the dose;

**Spectrum:** enterobacteria (Escherichia, Shigella, Klebsiella, some Proteus strains), protozoa (amoeba, Giardia), the fungus Candida.

# Pharmacokinetics.

- Nitroxoline is administered orally 4 times a day.
- It is well absorbed from the digestive tract.
- It penetrates into the tissue badly, is excreted in the urine unchanged, staining it in yellow

**Indications:** urinary tract infections

**Side effects:** dyspepsia, allergies, neuritis

# Nitrofuran derivatives

**Nitrofural** : antiseptic

**Furazolidon**: intestinal infections, giardiasis, Trichomonas colpitis

**Nifuroxazide:** intestinal infections.

**Nitrofurantoin (Furadonin), Furazidin (Furagin):** uroinfection.

**Spectrum:**

Gram-negative bacteria: Escherichia coli, Shigella, Salmonella, Klebsiella

Cocci (entero-, staphylo-,strepto-, meningo-, gonorrhea)

Vibrio cholerae, Giardia, Trichomonas

## Mechanism:

- The restoration of the nitro group to the amino group under the influence of reductase microbial cells.
- The formation of complexes with nucleic acids,
- Disruption of the respiratory mechanisms of microorganisms.
- Increase in the body's resistance to infections.
- The decline in the production of toxins.

Type of action: bacteriostatic or bactericidal

# Pharmacokinetics

- ✔They are absorbed from the digestive tract at 30 (furazolidon) – 50 %.
- ✔They penetrate the lymph, bile. They accumulate in the bile.
- ✔They go through the placenta, they go through the BBB badly.
- ✔They are excreted by the kidneys in different forms.
- ✔They are used 3-4 times a day.

# Side effects

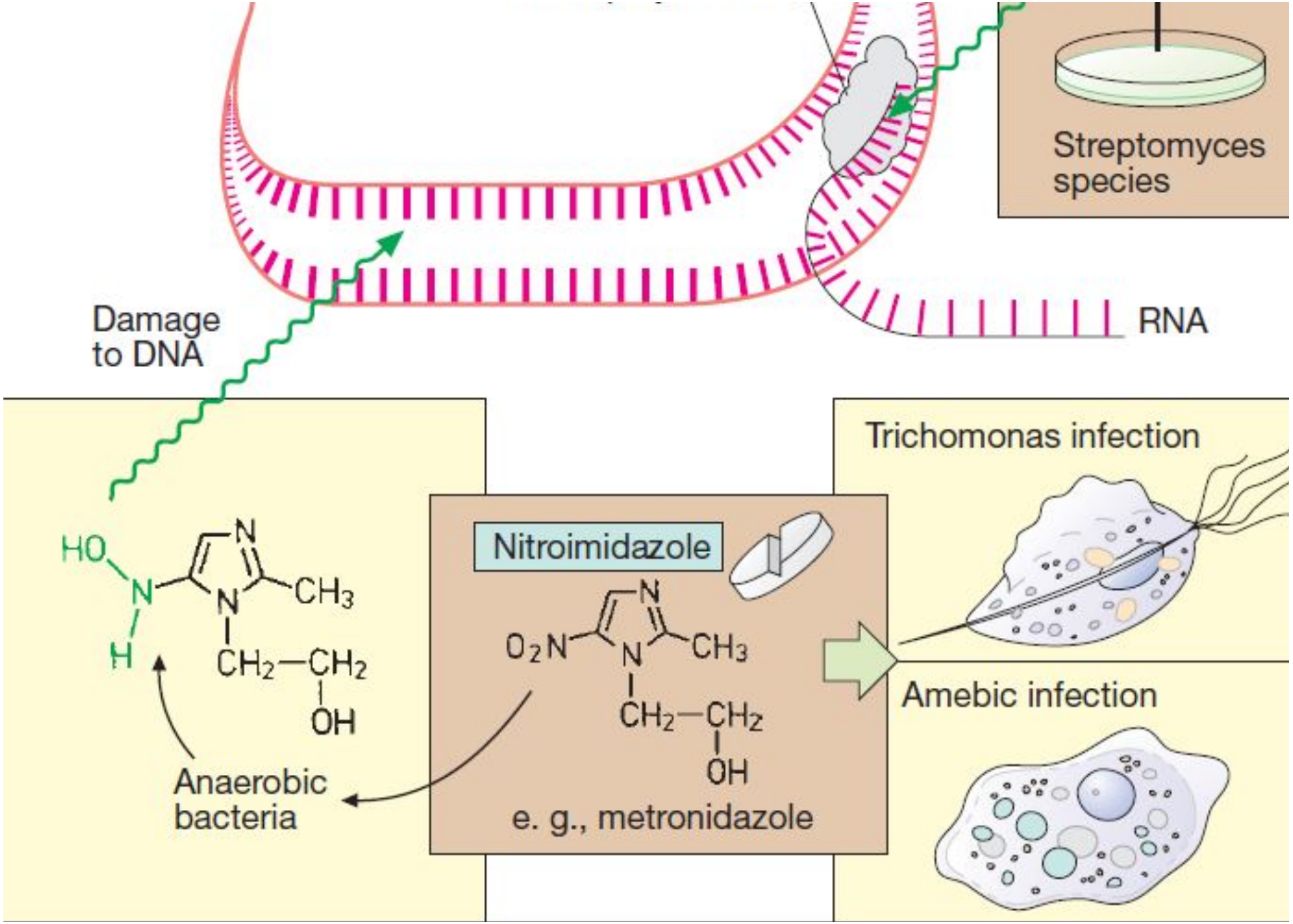
- Dyspeptic disorders: nausea, vomiting, diarrhea;
- Cholestasis; disorders of liver function;
- Allergic reaction;
- Headache, dizziness;
- Hemolytic anemia, methemoglobinemia in children up to a year;
- Arterial hypertension;

# Nitroimidazoles

## Metronidazole, Tinidazole, Ornidazole

**Spectrum:**

- Entamoeba histolytica, Trichomonas vaginalis, lamblia,
- Bact. fragilis, Fusobacterium, Clostridium perfringens, Cl. difficile,
- Helicobacter pylori,
- Campylobacter, peptococci,
- spirochetes and anaerobic Streptococci
- enterobacteria in the presence of Bac.fragilis.


Streptomyces species
RNA
Damage to DNA
Trichomonas infection
Nitroimidazole
Amebic infection
Anaerobic bacteria
e. g., metronidazole

# Mechanism of action

Metronidazole is selectively toxic to anaerobic and microaerophilic microorganisms. After entering the cell by diffusion, its nitro group is reduced by certain redox proteins to a highly reactive nitro radical which exerts cytotoxicity. The nitro radical of metronidazole acts as an electron sink which competes with the biological electron acceptors of the anaerobic organism for the electrons generated by the pyruvate (pyruvate oxidation). The energy metabolism of anaerobes that have no mitochondria is disrupted. Aerobic environment attenuates cytotoxicity of metronidazole by inhibiting its reductive activation.

- They are almost completely absorbed from the small intestines; little unabsorbed drug reaches the colon. They are widely distributed in the body, attaining therapeutic concentration in vaginal secretion, semen, saliva and CSF. Metabolism occurs in liver primarily by oxidation and glucuronide conjugation followed by renal excretion.
- Plasma t½ of **Metronidazole** is 8 hrs;
- Plasma t½ of **Tinidazole** 12 hr;
- Plasma t½ of **Ornidazole** 12–14 hr.

## Indications for uses

- *Amoebiasis*
- *Giardiasis*
- *Trichomonas vaginitis*
- *Anaerobic bacterial infections (*after colorectal or pelvic surgery, appendicectomy, brain abscesses and endocarditis)
- *Pseudomembranous enterocolitis (Cl. Difficile)*
- *Acute necrotizing ulcerative gingivitis (*fusobacteria, spirochetes and bacteroides)
- *Helicobacter pylori gastritis/peptic ulcer*
- *Guinea worm infestation*

## Side effects

- Anorexia, nausea, metallic taste and abdominal cramps are the most common.
- Less frequent side effects are—headache, glossitis, dryness of mouth and dizziness.
- Allergic reactions (urticaria, flushing, heat, itching, rashes)
- Prolonged administration may cause peripheral neuropathy and CNS effects. Seizures have followed very high doses.
- Leucopenia is likely with repeated courses.
- Thrombophlebitis of the injected vein occurs if the solution is not well diluted.
- *They are contraindicated* in neurological disease, first trimester of pregnancy

# OXAZOLIDINONE - Linezolid

- It is active against Staphylococcus aureus, penicillin-resistant *Streptococci, M. tuberculosis, Corynebacterium, Listeria, Clostridia* and *Bact. fragilis.*
- *It is primarily bacteriostatic,* but can exert cidal action against some streptococci, pneumococci and *B. fragilis.*
- *Gram-negative* bacteria are not affected.

- Linezolid inhibits bacterial protein synthesis by acting at an early step.
- Linezolid is rapidly and completely absorbed orally, partly metabolized nonenzymatically and excreted in urine.
- Linezolid given orally or i.v. is used for uncomplicated and complicated skin and soft tissue infections, pneumonias, bacteraemias and other drug-resistant gram-positive infections
- Side effects: dyspepsia, diarrhea, constipation, insomnia, dizziness, rash.

## Quinoxaline derivatives – quinoxidine and dioxidine

- Spectrum: Proteus, Pseudomonas aeruginosa, intestinal bacteria, cocci, Clostridium, bacteroids.
- Application: orally, IV and locally in the case of the inefficiency of other drugs in severe pleurisy, lung abscesses, peritonitis, pyelonephritis.
- Complications: dyspepsia, headache, dizziness, allergic reactions, chills, intestinal candidiasis, convulsions, carcinogenesis, teratogenicity.

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