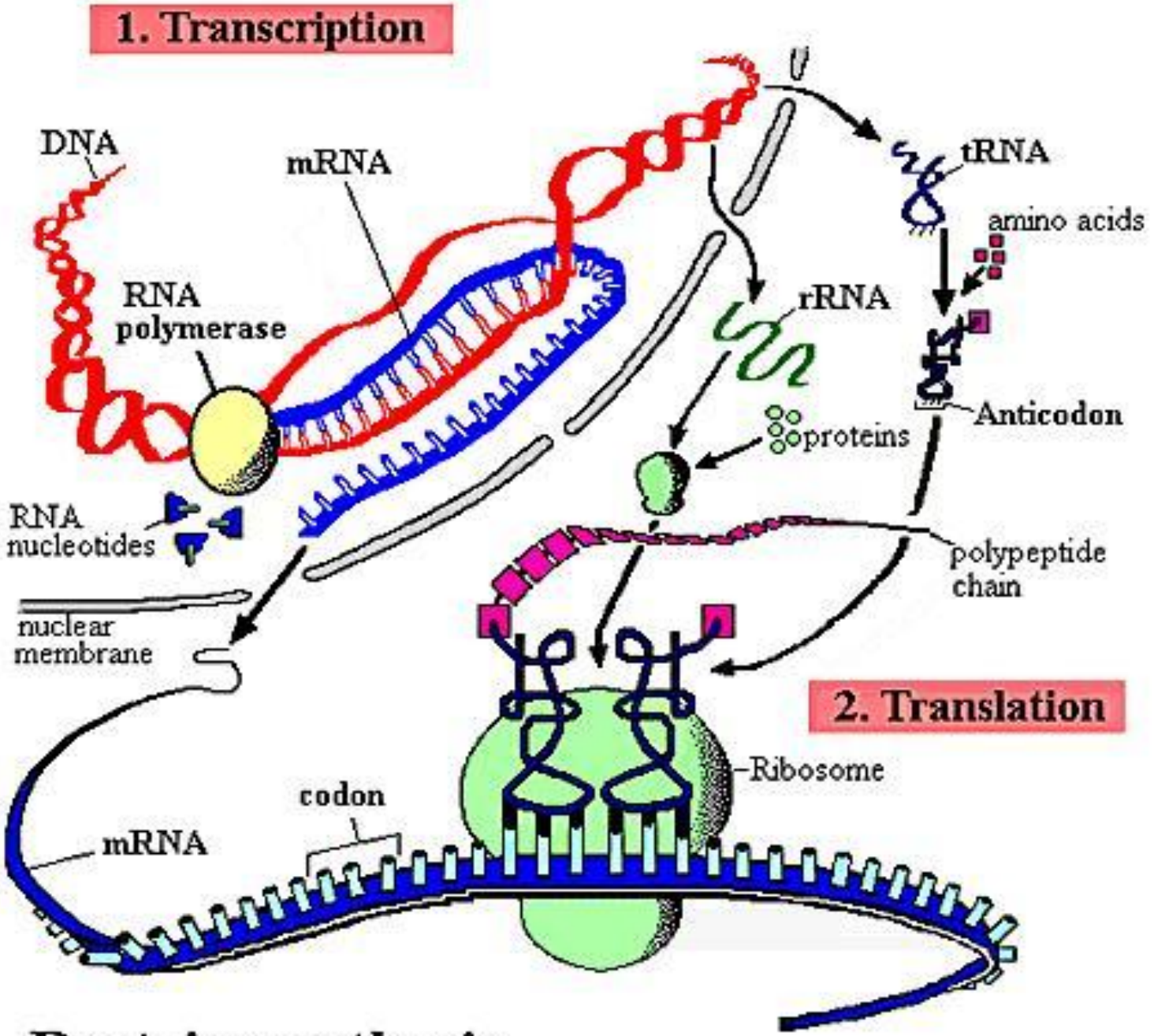
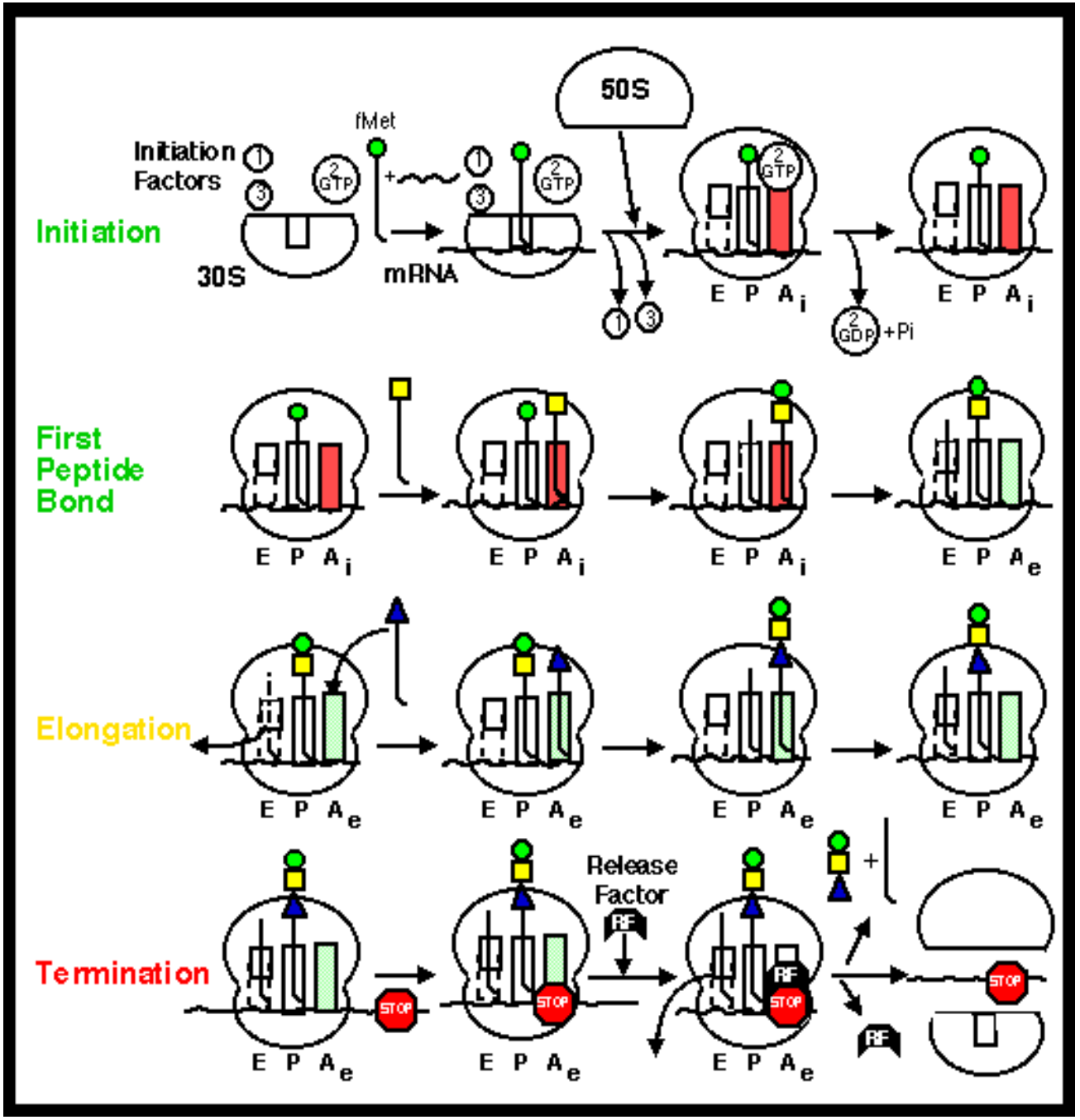
ANTIBIOTICS II.

Protein synthesis inhibitors
Inhibitors of nucleic acid synthesis



Protein synthesis



Initiation

Aminoglycosides

Elongation

Aminoglycosides

Chloramphenicol

Tetracyclines

Macrolides

Clindamycin

Protein synthesis (50S inhibitors)

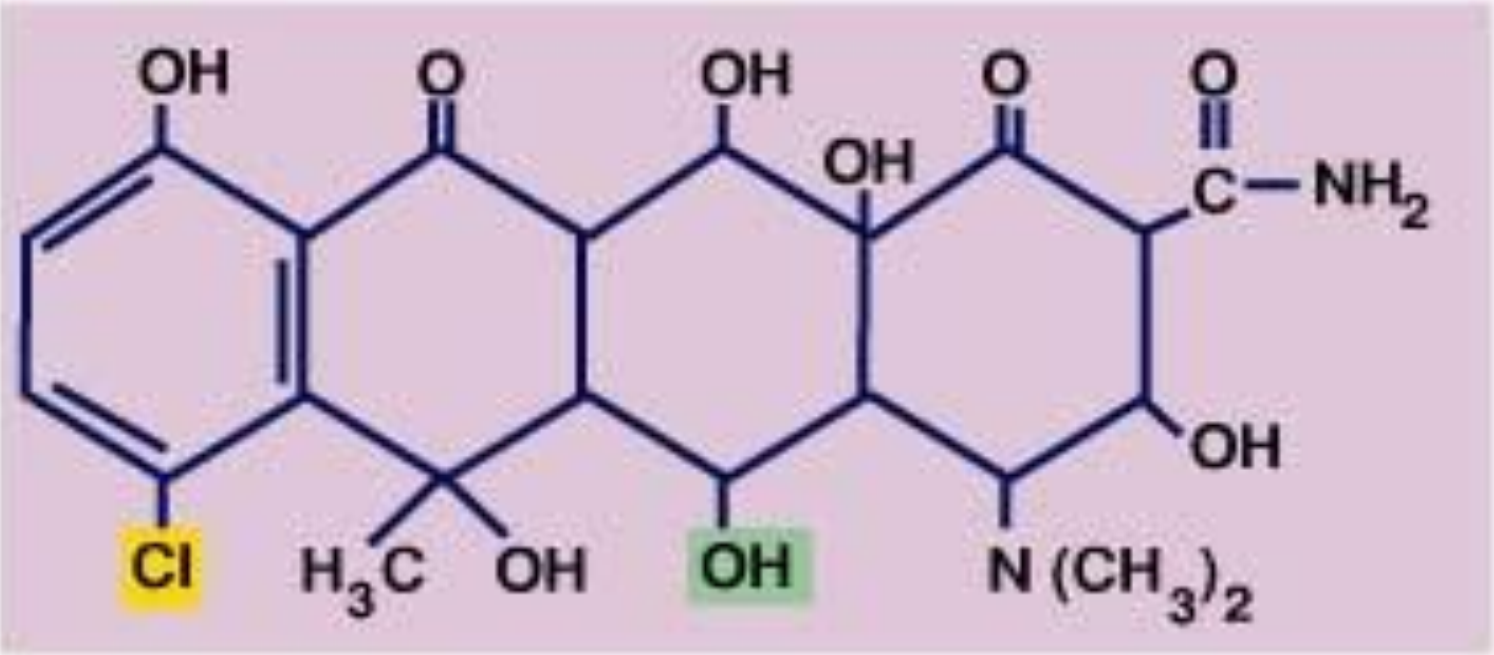
- Erythromycin (Macrolides)
- Chloramphenicol
- Clindamycin

Protein synthesis (30S Inhibitors)

- Tetracycline
- Spectinomycin
- Streptomycin
- Gentamicin, Tobramycin (aminoglycosides)
- Amikacin

Tetracyclines

Tetracyclines



Tetracyclines:

Tetracycline—lacks **Cl** and **OH**

Chlortetracycline (aureomycin)—is a tetracycline with **Cl**

Doxycycline—is a tetracycline with **OH**

Tetracyclines

- **Natural**

Tetracycline	SUMYCIN
Oxytetracycline	TERRAMYCIN
Chlortetracycline	
Demeclocycline	DECLOMYCIN

Tetracyclines

- **Semi-synthesized**
  - **Doxycycline** DEOXYMYKOIN
  - **Minocycline** MINOCIN
  - **Methacycline** RONDOMYCIN
  - **Tigecycline** TYGACIL
  - (Rolitetracycline)

Tetracyclines

Short-acting (Half-life is 6-8 hrs)

Tetracycline

Chlortetracycline

Oxytetracycline

Intermediate-acting (Half-life is ~12 hrs)

Demeclocycline

Methacycline

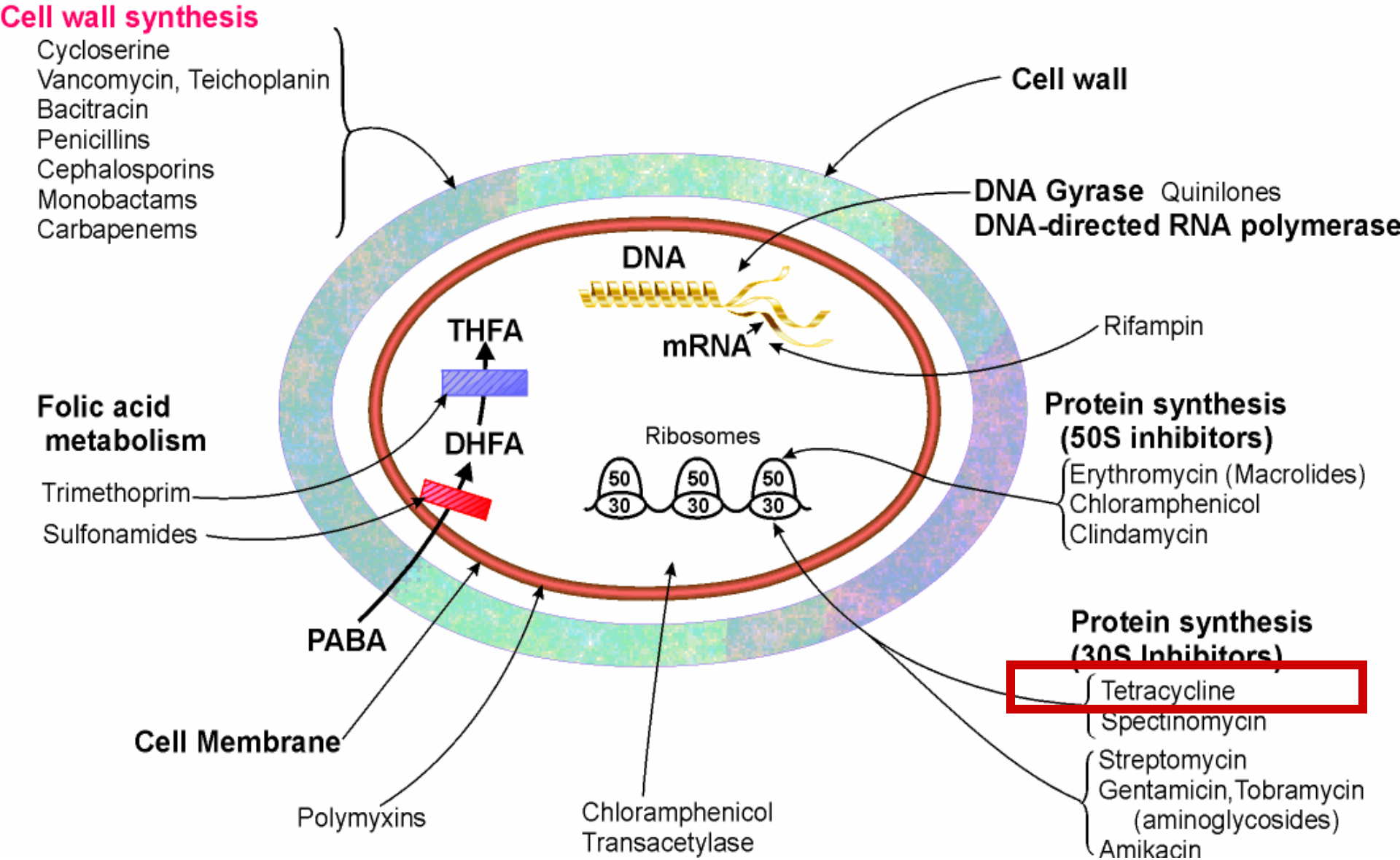
Long-acting (Half-life is 16 hrs or more)

Doxycycline

Minocycline

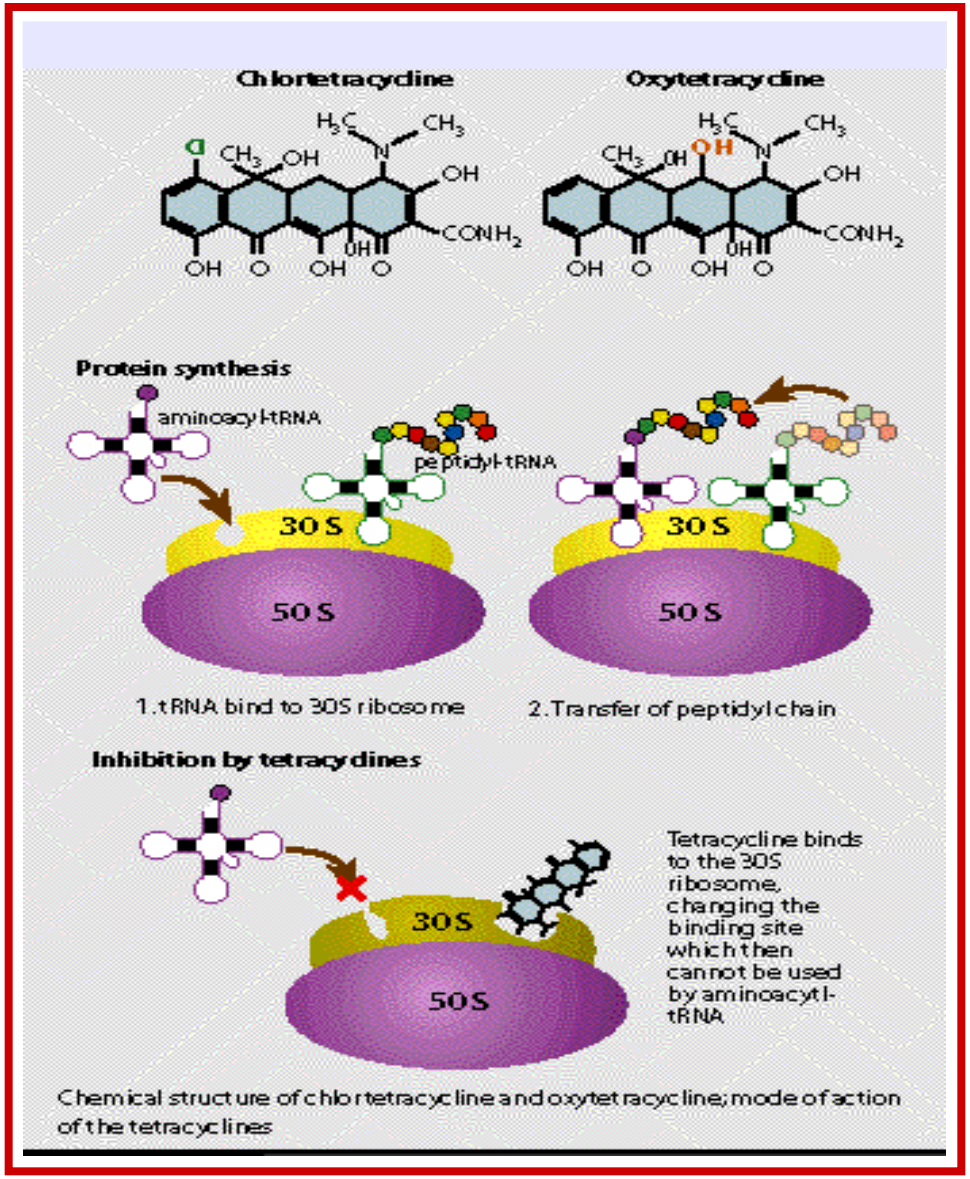
Tigecycline

Mechanism of Action



Mechanism of Action

- **bacteriostatic**
- **broad** spectrum ATB
- bind reversibly to **30S** ribosomal subunits
- block the binding of aminoacyl-tRNA to the acceptor site of mRNA-ribosome complex
- prevent the addition of AA to the growing peptide chain



Pharmacokinetics

- **Absorption**
  - 30% - 100% (doxy-, mino-)
  - is affected by **food**, divalent cations （Ca^{2+}, Mg^{2+}, Fe^{2+}, Bi^{2+} - **chelates**), dairy products, antacids (except doxy-, minocyclin)

Pharmacokinetics

Distribution

- distribute widely to tissues, body fluids - bile (except cerebrospinal fluid)
- bind and damage growing **bone** and **teeth**
  - cross **plancental** barrier
    excreted in **milk**

Elimination

- occurs mainly via liver and kidney
- some of TTC have **enterohepatic** circulation

Clinical Uses

- many G+, G-, anaerobes, rickettsiae, chlamydiae, mycoplasma, some protozoa – amebias
- drug of choice in Mycoplasma pneumoniae, Spirochetes
- respiratory, urinary tract, billiary infection, tularemia, brucellosis, shigelosis, acne vulgaris....
- in combination - ulcer disease caused by Helicobacter pylori

TTC - Adverse Effects

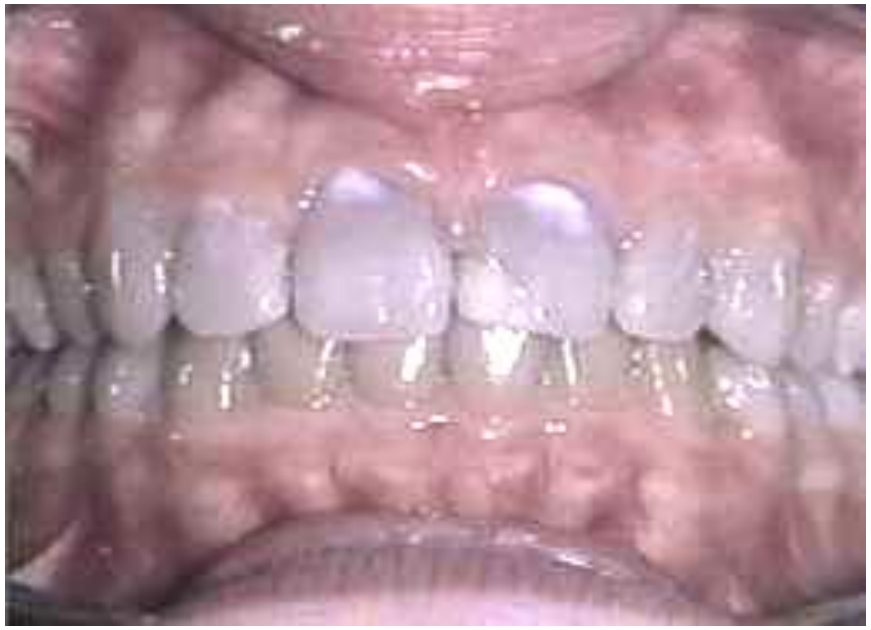
- Gastrointestinal irritation
  - nausea, vomiting and diarrhea
  - intestinal flora - superinfection
- Bony structures and teeth
  - teeth discoloration
  - bone growth inhibition
  - contraindication in young children to 12 years and during pregnancy - teratogen

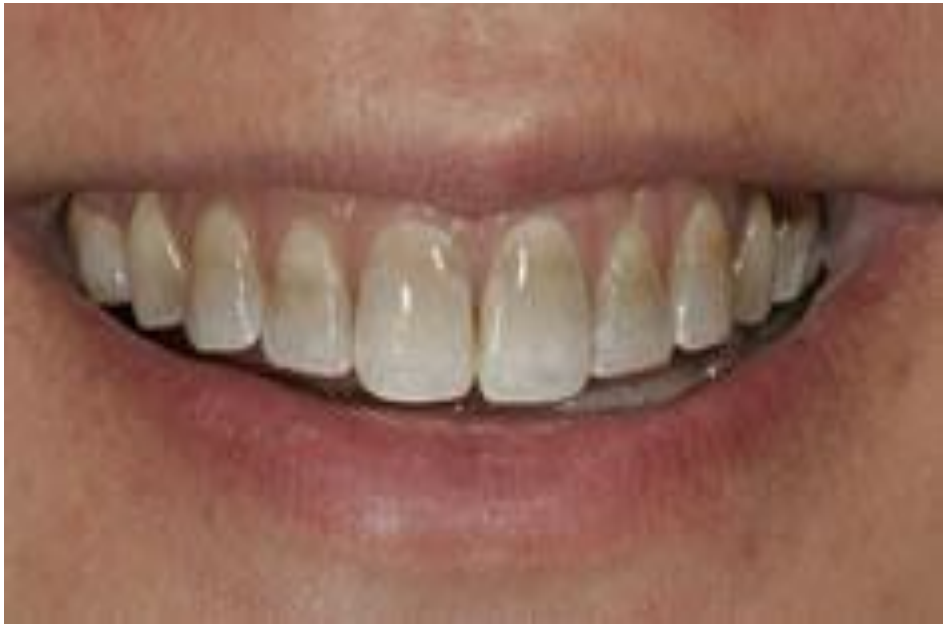
TTC - Adverse Effects

- toxicity to liver and kidney
- skin photosensitivity (!! sun, intense light)
- **Fanconi syndrom** - expired TTC
  !!!! time of expiration

  - urinary excretion of large amounts of amino acids, glucose, phosphates, uric acid bicarbonate
  - symptoms - osteomalacia, rickets, muscle weakness, cystinosis

Tetracycline teeth

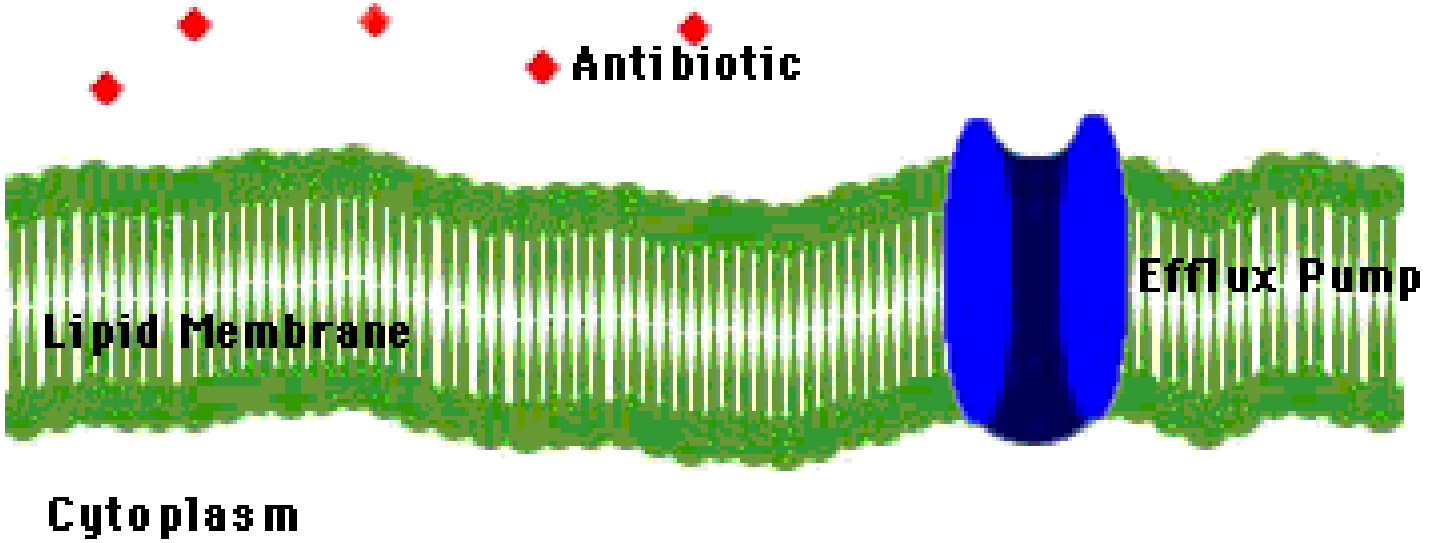




Mechanisms of Resistance

- altered expression of proteins in drug resistant organisms
  - modification of target sites
  - **decreased accumulation**
    - **efflux pump** - tetracycline resistance is a marker for resistance to multiple drugs
  - enzymatic inactivation

Efflux pump



Doxycycline

  - Capsules
  - Injection
  - Tablet
  - (Suspension)
- Dosing:
  - Adults: 100-200 mg/day in 1-2 divided doses p.o. or i.v.

- Give with meals to decrease GIT upset
- Take with water to avoid esophageal irritation, ulceration

Tigecyclin

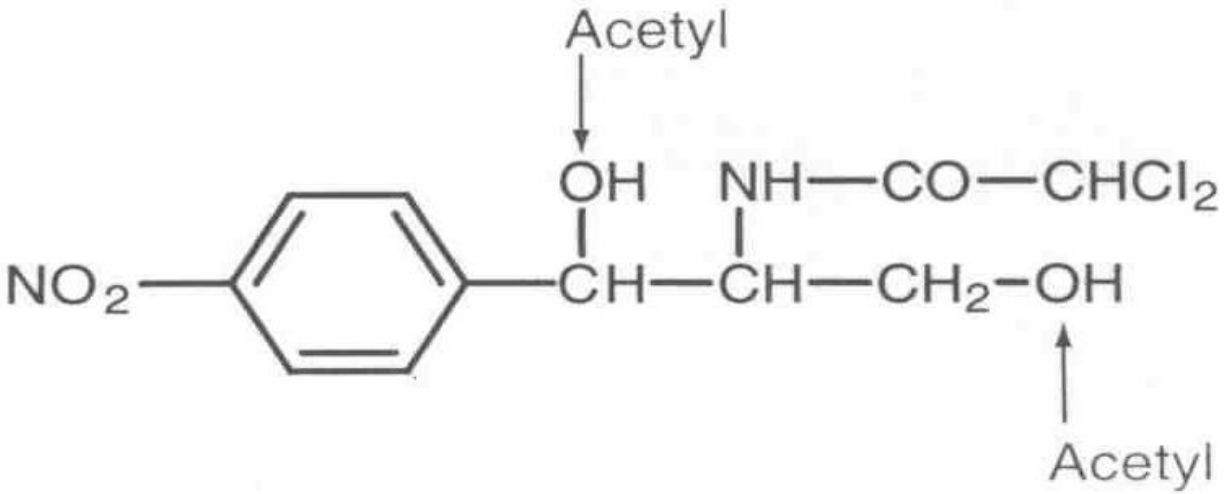
- glycylcycline antibiotic
- very broad spectrum
- not affected by specific efflux pump
- by slow i.v. infusion

- G+, G- bacteria, anaerobes, MRSA
- it has no activity against Pseudomonas, Proteus
- for the treatment of skin, soft tissue, intra-abdominal infections

Tigecycline

- **Distribution**:
  - gall bladder, colon, lung > serum
  - bone, synovial fluid < serum
- **Elimination**:
  - Mostly feces/biliary excretion (59%)
  - Some excretion in urine (33%)
- **Adverse Effects**
  - Nausea
  - Vomiting
  - Diarrhea
  - Local reaction

Chloramphenicol



CHLORAMPHENICOL inj.

CHLORAMPHENICOL cps.

BETABIOPTAL gtt. opht.

BETABIOPTAL ung. opht.

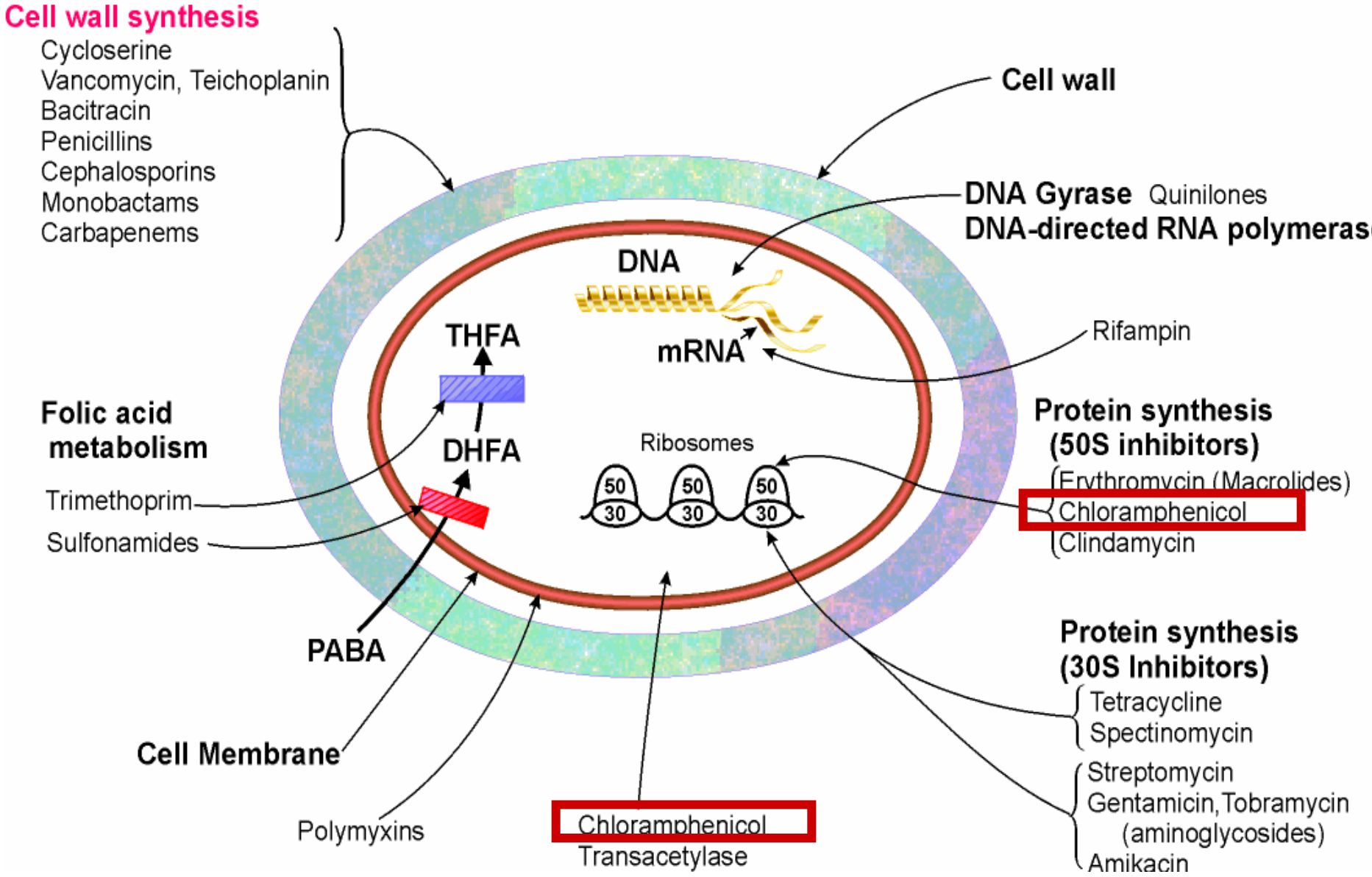
OPHTALMO-CHLORAMPHENICOL ung. opht.

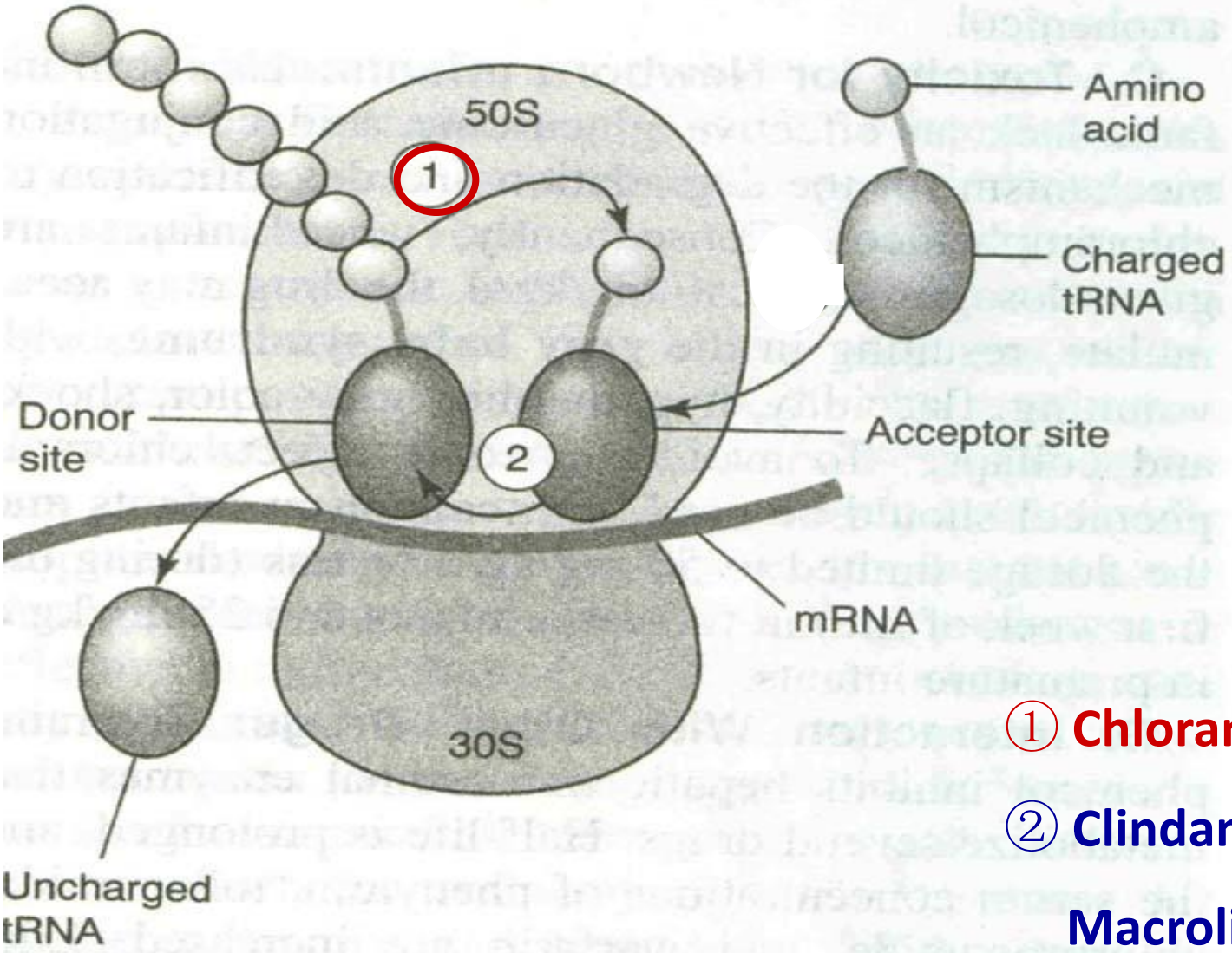
SPERSADEX gtt. opht.

Mechanism of Action

- **broad**-spectrum **bacteriostatic** ATB
- inhibitor of microbial protein synthesis
- bind reversibly to **50S** ribosomal subunits
- inhibits the peptidyl transferase step of protein synthesis

Mechanism of action





① **Chloramphenicol**

② **Clindamycin**

Macrolides

Pharmacokinetics

- absorbed rapidly, completely from GIT

  parenteral - IV

- weak protein bound (less than 30%)
- well distributed into body fluids including CNS cerebrospinal fluids, bile
- metabolized in the liver – conjugation with glucuronic acid - **!!! newborn**
- excreted in the urine

Antimicrobial activity

- G+ G- aerobic and... anaerobic organisms
- Rickettsiae, spirochetes, mycoplasma

  H. influenzae, S. typhi, E. coli,

  N. meningitidis, S. Pneumoniae

  V. cholerae, Clostridium, *B. fragilis*...

  50-100 mg/kg/d p.o. or i.v. divided into 4 doses

Clinical uses

- toxicity and resistance limits the use of chloramphenicol
- **typhoid** and **paratyphoid fever**, serious Salmonella infections, serious rickettsial infections
- **topical use** for treatment of eye infections
- **bacterial menigitis** in penicillin-resistant bacteria or penicillin-allergic patients
- anaerobic infections - *B. fragilis*

Adverse reactions

- GIT disturbances - nausea, vomiting, diarrhea
- superinfections - oral, vaginal candidosis
- **Bone marrow** disturbances - two types
  - reversible dose-related suppression of

    RBC production - interference with Fe metabolism
  - aplastic anemia - rare reaction unrelated to dose - irreversible, can be fatal

- **Irreversible idiosyncratic aplastic anemia**
  - onset may be delayed until after therapy has been discontinued
- **The reversible form** is likely to occur with:
  - High doses (> 50 mg/kg/d)
  - A prolonged course of treatment (1-2 weeks)
  - In patients with liver disease
- **Signs of the reversible form**
  - Serum iron and saturation of serum iron-binding capacity increase
  - Reticulocytes decrease
  - Vacuolization of RBC precursors
  - Anemia
  - Leukopenia
  - Thrombocytopenia

Adverse reactions

- toxicity for newborn infants

  - dose > 25 mg/kg/d

  – **Gray baby syndrom** - vomiting, shock, limp body tone, hypotension, hypothermia, gray coloration (skin, lips)

- interaction with other drugs

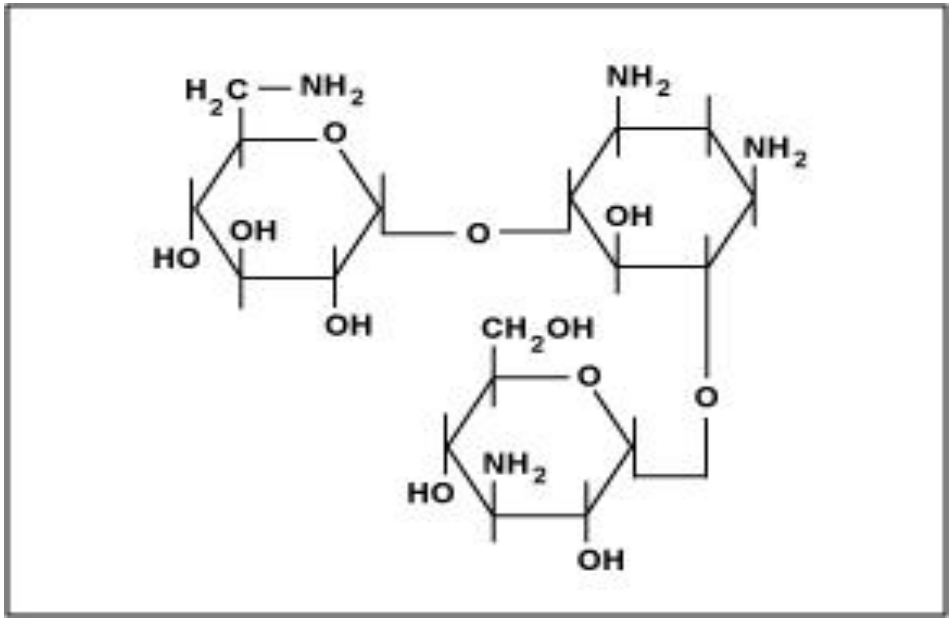
  - inhibits liver microsomal enzymes

- nausea, vomiting, and diarrhea
- hypersensitivity- uncommon, low incidence

Mechanisms of Resistance

- frequent (50%) connected to TTC resistance
- altered expression of proteins in drug resistant organisms
  - decreased accumulation
  - enzymatic inactivation

Aminoglycosides



Aminoglycosides - classification

- **mycin (Streptomyces spp.)**

- **Streptomycin**
- **Neomycin** (Framycetin, **Paromomycin**, Ribostamycin)
- Kanamycin (**Amikacin**, Arbekacin, Bekanamycin, Dibekacin, **Tobramycin**)
- Hygromycin B · **Spectinomycin**
- **Paromomycin**

- **micin (Micromonospora actinomycetes)**

- **Gentamicin** (**Netilmicin**, Sisomicin, Isepamicin)
- Verdamicin
- Astromicin

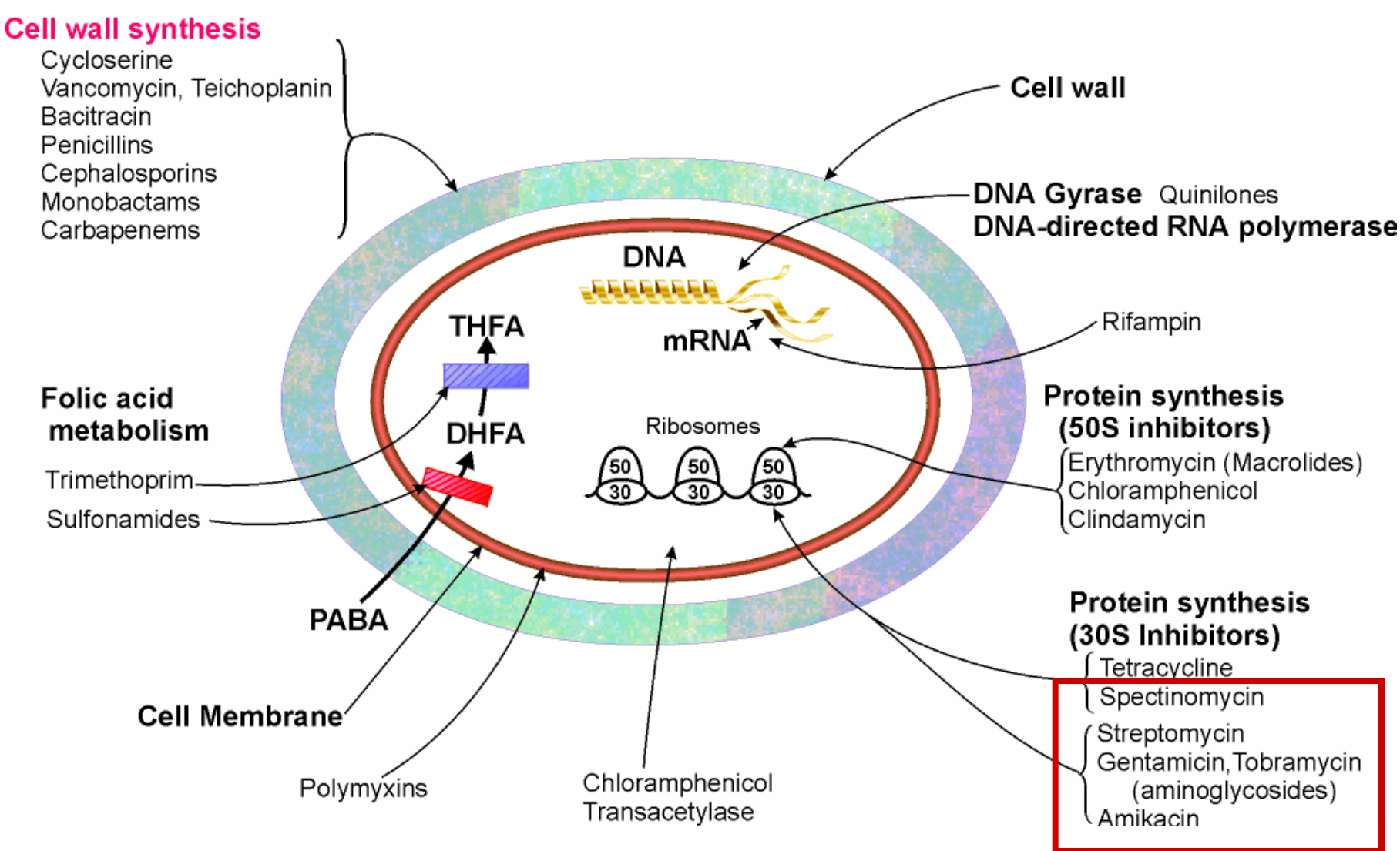
Representative Sources of Antibiotics

Microorganism	Antibiotic
Gram-Positive Rods	
Bacillus subtilis	Bacitracin
Bacillus polymyxa	Polymyxin
Actinomycetes	
Streptomyces nodosus	Amphotericin B
Streptomyces venezuelae	Chloramphenicol
Streptomyces aureofaciens	Chlortetracycline and tetracycline
Streptomyces erythraeus	Erythromycin
Streptomyces fradiae	Neomycin
Streptomyces griseus	Streptomycin
Micromonospora purpureae	Gentamicin
Fungi	
Cephalosporium spp.	Cephalothin
Penicillium griseofulvum	Griseofulvin
Penicillium notatum	Penicillin

Aminoglycosides

- Streptomycin STREPTOMYCIN inj.
- Gentamicin GARAMYCIN, GARASONE inj, loc
- Tobramycin NEBCIN, TOBREX inj, loc
- Amikacin AMIKIN, MIACIN inj
- Netilmicin NETROMYCIN inj, loc
- Kanamycin KANTREX inj, po, loc
- Neomycin MYCIFRADIN, PAMYCON po, loc
- Paromomycin HUMATIN po

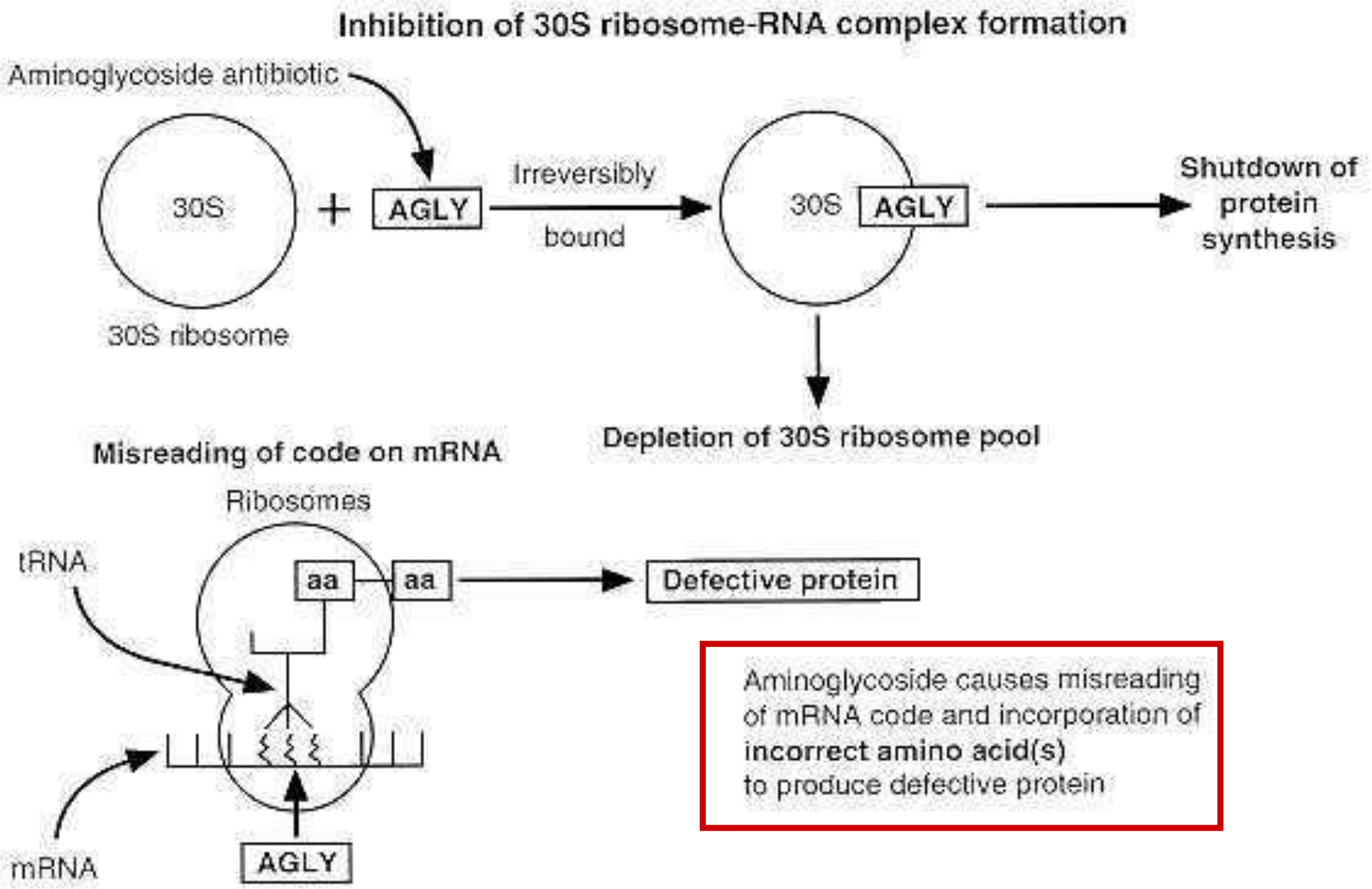
Bacterial Targets for AG



AG - Mechanism of Action

- They interfere with the „initiation complex“ of peptide formation
- They induce misreading of mRNA which causes an incorporation of incorrect amino acids into peptide resulting in a non-functional or toxic protein
- They cause a breakup of polysomes into non-functional monosomes

AG - Mechanism of Action



AG - Pharmacokinetics

- poor oral absorption
  - oral administration only for intestinal infection – GIT decontamination
  - parenteral administration – i.m., i.v.
  - topical - tobramycin in a nebulized form
- minimally protein bound (10%)
  - do not penetrate into the CNS, eye, milk
  - may cross the placenta

AG - Pharmacokinetics

- high concentrations kidney, cochlea, vestibul.app.
- strong tissue binding at the injection site
  - elimination T1/2 from tissues - much longer than from plasma
- **postantibiotic effect** (2 - 8 hrs)
- are not metabolized
- 90% eliminated by kidney
  - renal dysfunction - ↓ dose, ↑ time interval,

AG - Antibacterial Spectrum

- most bacterial species are sensitive
- **intracellular** concentration - dependent up on a oxygen transport system in the cell membrane - absent in anaerobes
- only clinically useful against organisms growing in **aerobic** conditions
- much stronger than the protein synthesis inhib.
- aerobic G-, Pseudomonas,Proteus, Klebsiella, Serratia, *E. coli*, mycobacteria

Therapeutic Uses of Aminoglycosides

Streptomycin

- Tularemia, brucellosis, plague
- G- bacillary infections of the urinary tract
- The use of streptomycin in the management of tuberculosis has declined

Gentamicin

- wide range of activity - *Enterobacter, Serratia*, *Staphylococcus aureus*
- combination with penicillins - bacterial endocarditis
- *Pseudomonas* - effective with gentamicin, carbenicillin or ticarcillin
- initial treatment of bacteremia

Other Aminoglycosides

- amikacin, netilmicin, tobramycin

  - used as gentamicin

- tobramycin - more active against *Pseudomonas aeruginosa*

- tobramycin, netilmicin - less ototoxic and nephrotoxic

AG - Adverse Effects

- dangerous factors:
  - using continuously more than 5 days
  - high dose
  - elderly and children
  - renal insufficiency
  - concurrent use with loop diuretics or other nephrotoxic drugs

AG - Adverse Effects

- **Dose related !!!!**
- **Concentration x Time** dependence
  - proximal tubular cell damage
  - destruction of sensory cells in cochlea
  - destruction of sensory cells in vestibular apparatus
  - neuromuscular paralysis

AG - Adverse Effects

- **Ototoxicity** – irreversible damage
  - auditory - tinnitus, hearing loss
  - vestibular - vertigo, ataxia, loss of balance
  - audiometric testing for early detection
- **Nephrotoxicity -** retention of AG in kidney up to necrosis
- **Suppression of neuromuscular transmission**
- **Allergic reaction** – after local administr.

Spectinomycin TROBICIN

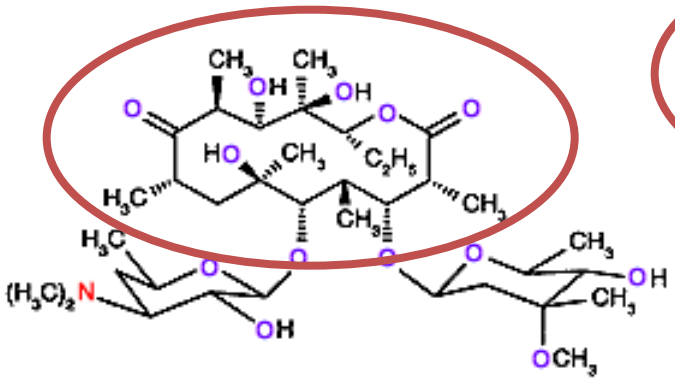
- aminocyclitol - similar to AG
- interaction with 30S – inhibition of protein synthesis
- as one i.m. dose for gonorrhea treatment caused by penicillinase-producing *Neisseria gonorrhea*
- or in patients allergic to PNC

Adverse effects - hypersensitive reactions

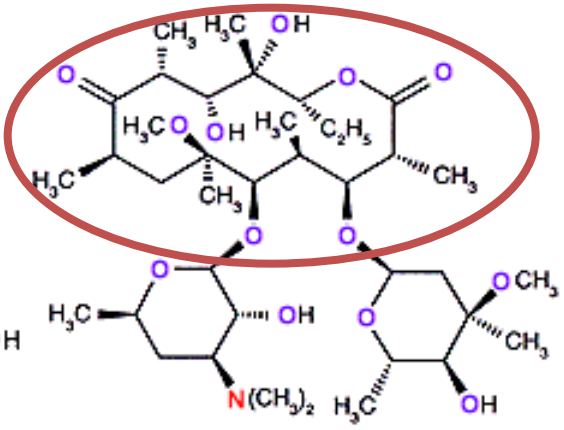
Macrolides

Macrolides

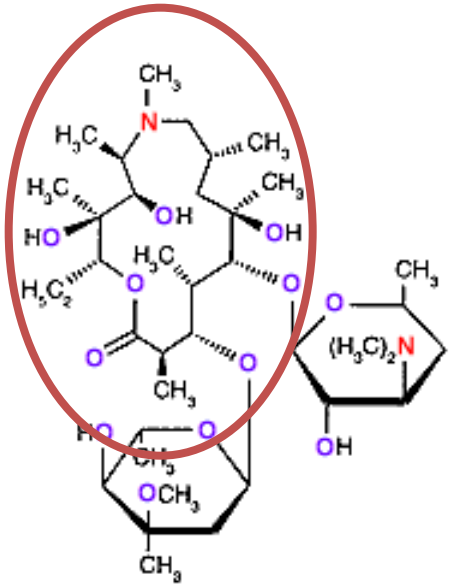
Macrocyclic lactone ring



Erythromycin



Clarithromycin



Azithromycin

History

- **1952 Erythromycin**
- **1970s Acetylspiramycin**
  Medecamycin, josamycin

- **1980s Clarithromycin**
  Roxithromycin
  Azithromycin

New macrolides antibiotics

- **Advantage**
  - broader spectrum, higher activity (G-)
  - improved tolerability
  - less toxicity
  - improved PK properties
    - orally effective
    - better bioavailability
    - better tissue penetration
    - high blood concentration
    - prolonged half-lives

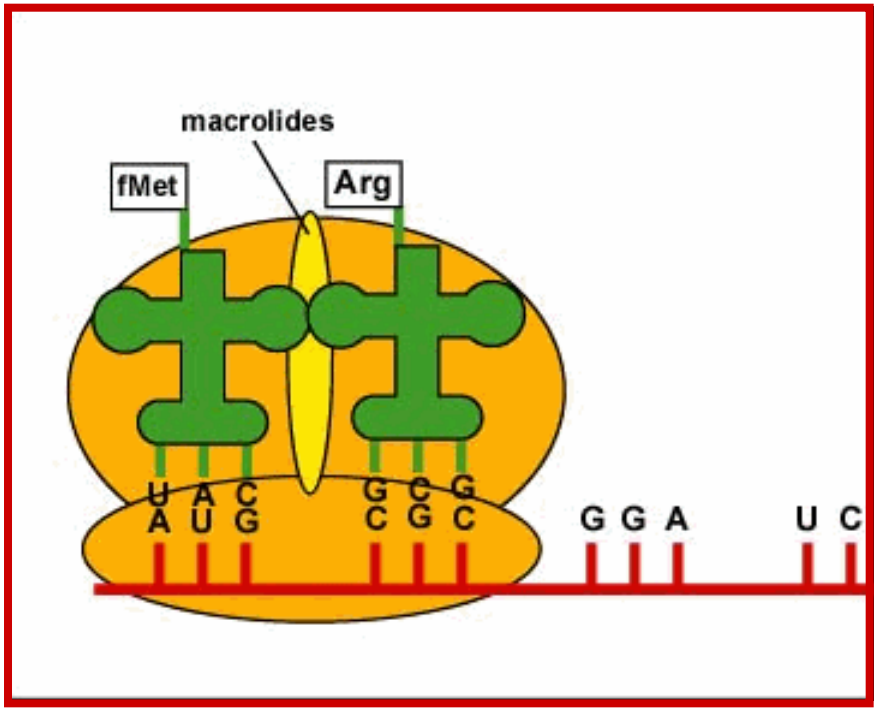
Macrolides

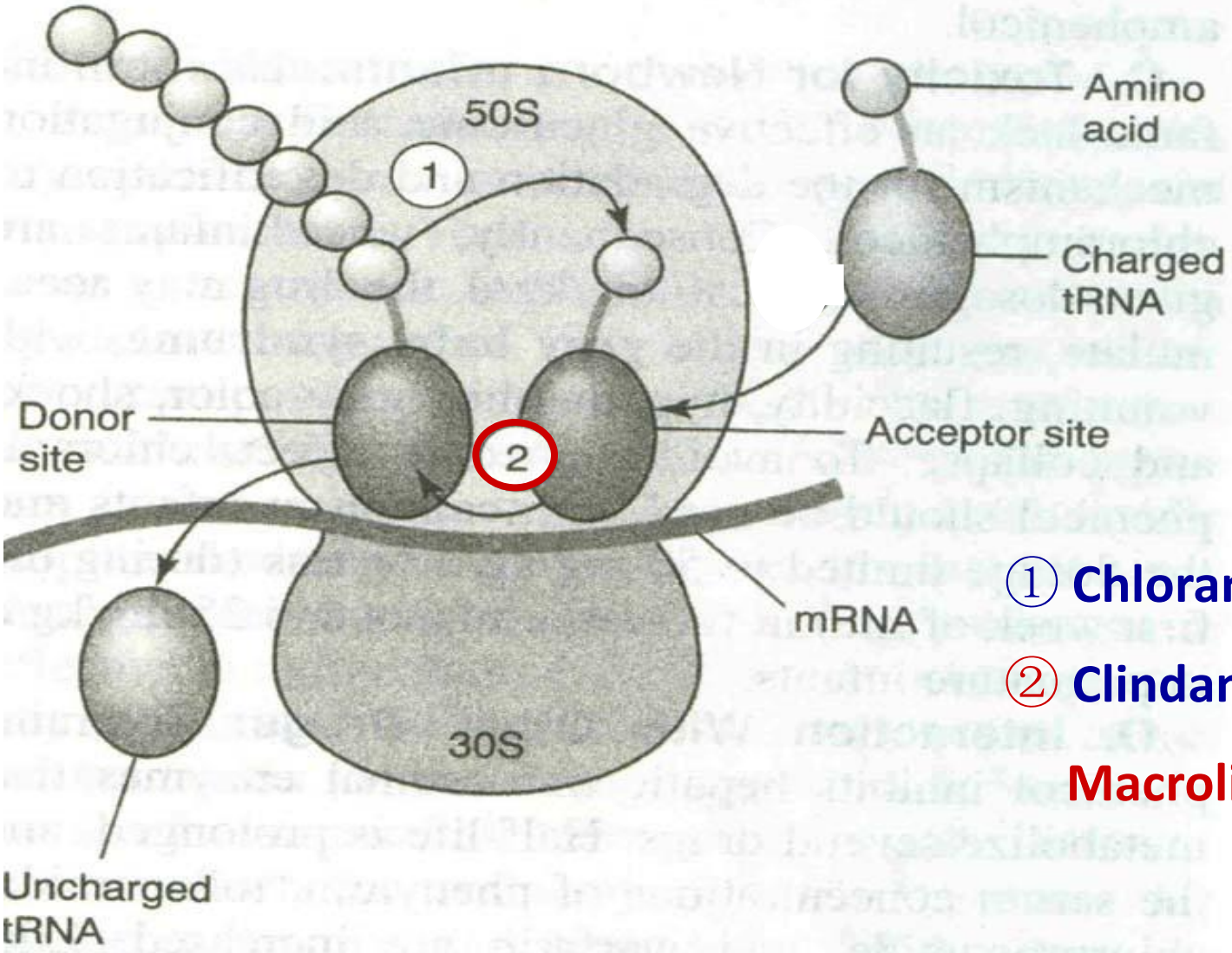
- **Erythromycin** generic, ERYTHROCIN
- **Josamycin** WILPRAFEN
- **Spiramycin** ROVAMYCINE
- **Roxithromycin** RULID, SURLID, ROXID
- **Azithromycin** SUMAMED, AZITROX, ZITHROMAX
- **Clarithromycin** FROMILID, KLACID, KLABAX, BIAXIN

- Dirithromycin DYNABAC

Mechanism of Action

- Bind reversibly to the **50S** subunit
- Inhibit elongation of the protein by the peptidyltransferas
- Suppression of RNA-dependent protein synthesis





① **Chloramphenicol**

② **Clindamycin**

Macrolides

Cross-resistance occurs among all macrolides

Macrolides

- **bacteriostatic** activity

bactericidal - at high concentrations against very susceptible organisms

- time-dependent activity
- extra-, intracellular activity
- **postantibiotic effect** (3 – 7 hrs)

Macrolide Spectrum

G-Aerobes

- *H. influenzae* (not erythro), *M. catarrhalis, Neisseria sp.*
- Do NOT have activity against any *Enterobacteriaceae*

Gram-Positive Aerobes

Methicillin-susceptible *Staphylococcus aureus*

- *Streptococcus pneumoniae* – resistance
- Group and viridans streptococci
- *Bacillus sp., Corynebacterium sp.*

Anaerobes – activity against upper airway anaerobes

Atypical Bacteria –excellent activity:

- *Legionella pneumophila*
- *Chlamydia sp.*
- *Mycoplasma sp.*
- *Ureaplasma urealyticum*

Other Bacteria – *Mycobacterium avium, Treponema pallidum Campylobacter, Borrelia, Bordetella, Brucella. Pasteurella*

Pharmacokinetics

absorption

- erythromycin base - destroyed in stomach
  - is administered with enteric coating
  - esters and ester salts: more acid stable
- clarithromycin – acid stable and well absorbed regardless of presence of food
- azithromycin – acid stable – food can decrease absorption of capsules
- i.v. risk of the trombophlebitis
- i.m. - painful

Pharmacokinetics

distribution

- extensive tissue and cellular distribution
- clarithromycin and azithromycin
  - extensive penetration

- into body fluids (except brain, CSF)
  - into prostatic fluids, also
- special ability - to accumulate in the macrophages
- inflammation - ↑ penetration into tissue

Pharmacokinetics

metabolism

- metabolized, concentrated in the liver
- erythromycin and clarithromycin
  - inhibit cytochrom P-450
  - drug interactions !!!!!

(theophylline, anticoagulants, astemizol, terfenadine, carbamazepine, statines, antiarrhytmic drugs I. class)

Pharmacokinetics

excretion

- excreted in bile in the active form - all

  - clarithromycin - partially - by the kidney

- partially reabsorbed

  – enterohepatic circulation

Erythromycin

- a naturally- occurring macrolide *Str. erythreus*
- problems - acid lability,
  - narrow spectrum,
  - poor GI intolerance,
  - short elimination half-life
- used - as PNC substitute in PNC-allergic or resistant patients with infections caused by Staphyl., Strept., Pneumoc.
  - pertussis, diphtheriae
  - Legionella, *Mycoplasma pneumonia*
  - *H. pylori* infection

p.o. 0.25-0.5 g every 6 h, i.v. 0.5-1 g every 6 h
Children – 40 mg/kg/d

Clarithromycin

- structural derivative
  - include broader spectrum of activity
- strongest activity on G+, *L. pneumophila, Ch. pneumoniae and H.pylori*
- good pharmacokinetic property
- low toxicity
- p.o. 0.25-0.5 g every 12 h or 1 g once daily

Azithromycin

- **azalid**
- the strongest activity against Hemophilus, *M. pneumoniae*, Neisseria, *H. pylori*, Campylobacter, atypical mycobacteria
- more effective on G-
- does not inhibit CYP 450
- well tolerated
- T1/2 - 35~48h - once daily, 3 days only
- mainly in respiratory infection
- Daily dose 500 mg

Roxithromycin

- The highest blood concentration
- Bioavailability 72%~85%
- Respiratory infection

  soft tissue infection
- Low adverse effects
- interval 12 hrs

Spiramycine (ROVAMYCINE)

- produced by *Streptomyces ambofaciens*
- effective against G+ aerobic pathogens, *N. gonorrhoeae*, staphylococci
- used for infections caused by bacteria and *Toxoplasma gondii*

Macrolides - Adverse Effects

- **Gastrointestinal** – up to 33 %
  - nausea, vomiting, diarrhea, dyspepsia
  - erythro, less with new agents
- Cholestatic **hepatitis** - rare
  - > 1 to 2 weeks of erythromycin estolate

Macrolides - Adverse Effects

- Thrombophlebitis – i.v. Erythro and Azithro
  - dilution of dose, slow administration
- **Other** - ototoxicity (high dose erythro,RI)
  - QTc prolongation
  - allergy
  - drug interactions

ATB RELATED TO MACROLIDES

- **STREPTOGRAMINS**
  - Quinupristin/Dalfopristin **(SYNERCID)**
- **KETOLIDES**
  - Telithromycin **(KETECK)**
- **OXAZOLIDINONES**
  - Linezolid **(LIZOLID, ZYVOX)**

Quinupristin/dalfopristin

- Quinupristin – streptogramin A
- Dalfopristin – streptogramin B
- Binds 50S ribosome - each agents at different place - synergic inhibition of the protein synthesis
- Bactericidal, long postantibiotic effect
- High activity against MRSA and VISA
- Synergy with β-lactams,
  Additive with vancomycin

Quinupristin/dalfopristin

- Interavenously; 7.5 mg/kg every 8-12 h
- Penetration into macrophages and PMNL
  – important (VRE are intracellulary)
- Low level in the CSF
- Both metabolized
  (less active metabolit - quinuprostin
  similar active – dalfopristin)
- Eliminated by bile, feaces

Adverse effects:

- Arthralgias, myalgias
- Hyperbilirubinemia

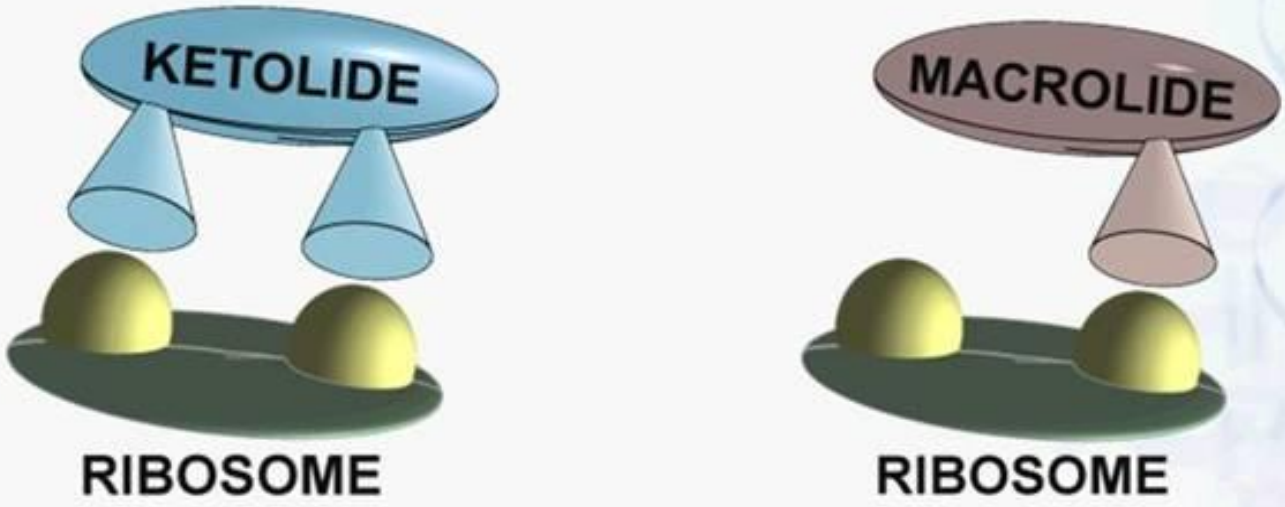
Telithromycin (KETEK)

Mechanism of action

- binds to the subunit 50S of ribosome, blocks growing polypeptide chain
- 10 x higher affinity to 50S than Eryth
- strongly binds to two domains 50S – older agents bind strongly only to one domain
- can also inhibit the formation of ribosomal subunits 50S and 30S

Ketolides: Mechanism of Action

Ketolides tightly bind to <u>two</u> sites on ribosomal RNA



- Ketolides block bacterial protein synthesis

Telithromycin

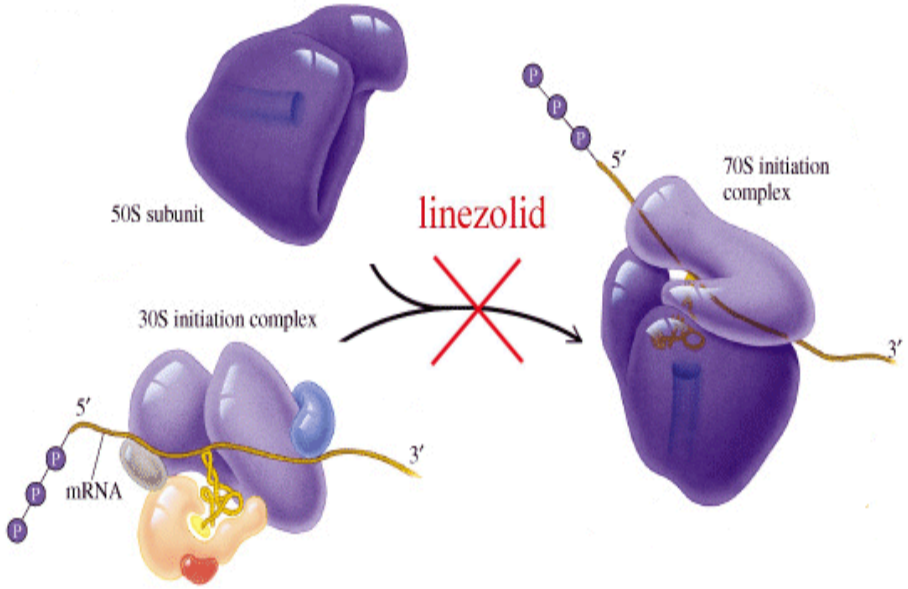
- acid-stable – orally tbl. with or without food
  rapidly absorbed (800 mg/d)
- diffused into most tissues and phagocytes
  - transported to the site of infection
- during phagocytosis - large concentrations of telithromycin is released
  - concentration in the tissues is much higher than in plasma
- **Metabolism**
- metabolized mainly in the liver
- elimination - the bile
- half-life is approximately 10 hours

Telithromycin

Adverse effects

- GIT - diarrhea, nausea, abdominal pain vomitus
- headache, disturbances in taste
- blurred vision, rashes
- rare but severe side effects - liver damage
- palpitations, prolongation QT interval
- can cause myasthenia gravis
- safety - controversies
- used - treatment of community acquir. pneumonia
  (mild to moderate severity)

Linezolid

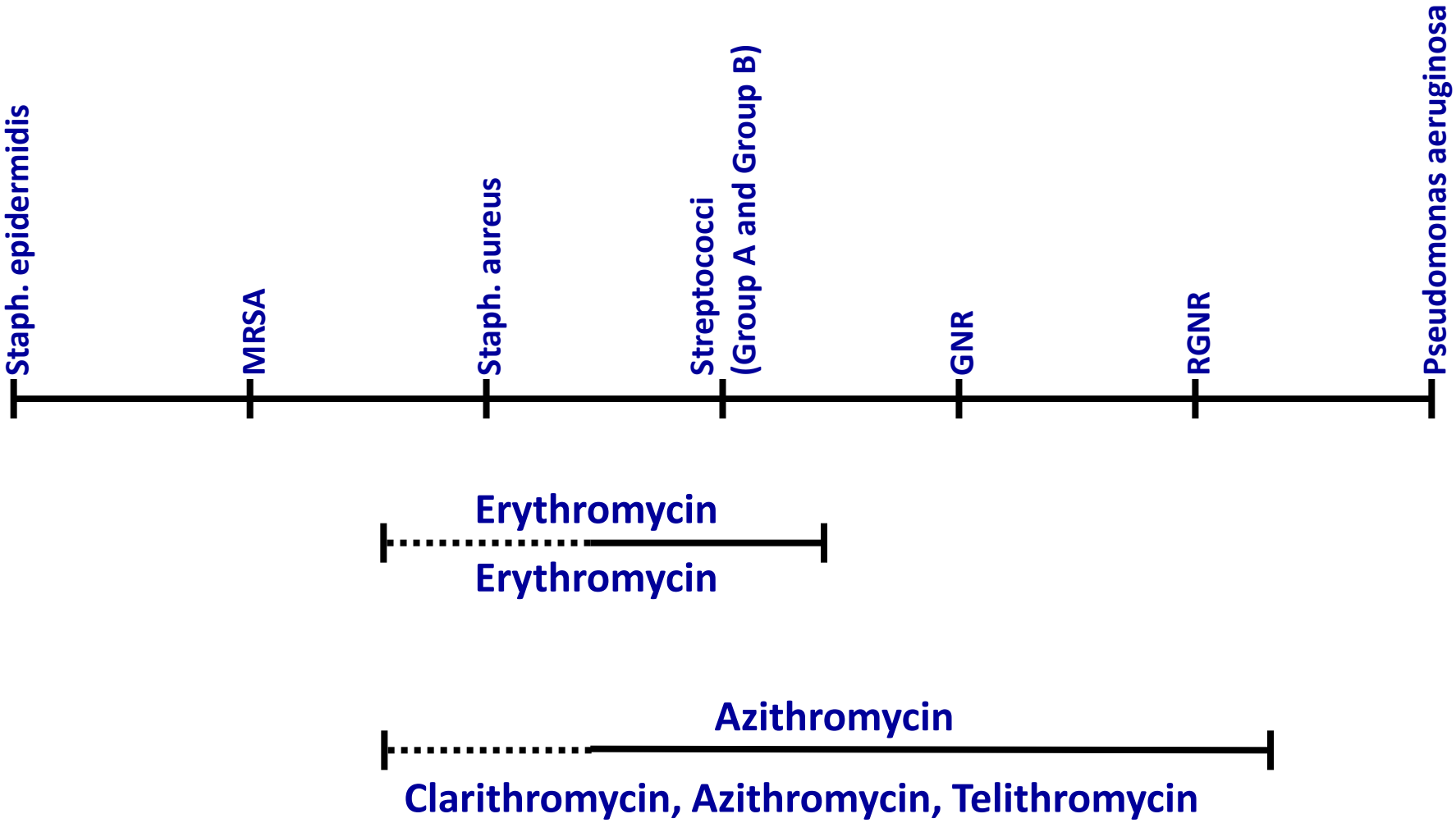


- oxazolidinone – i.v., p.o.
- high bioavailability
- inhibits the protein synthesis
  by preventing formation of 70S
- spectrum – G+
- lack cross-resistance – other mode of action
- P.o. or i.v. administration 600 mg every 12 h

Adverse effects

  - myelosuppresion
  - thrombocytopenia

Macrolides, Azalides and Ketolides



Inhibitors of Nucleic Acid Synthesis

Quinolones

Classification

- **Quinolones – non-fluorated**

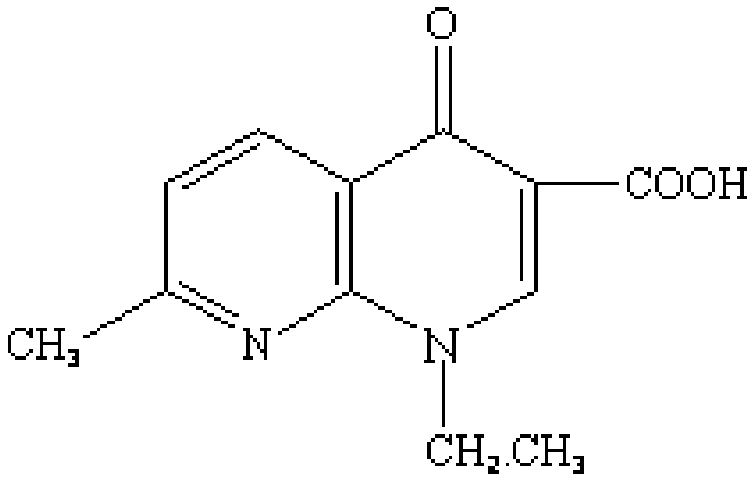
  (1st generation)

- **Fluoroquinolones**

  (2nd, 3rd, 4th generation)

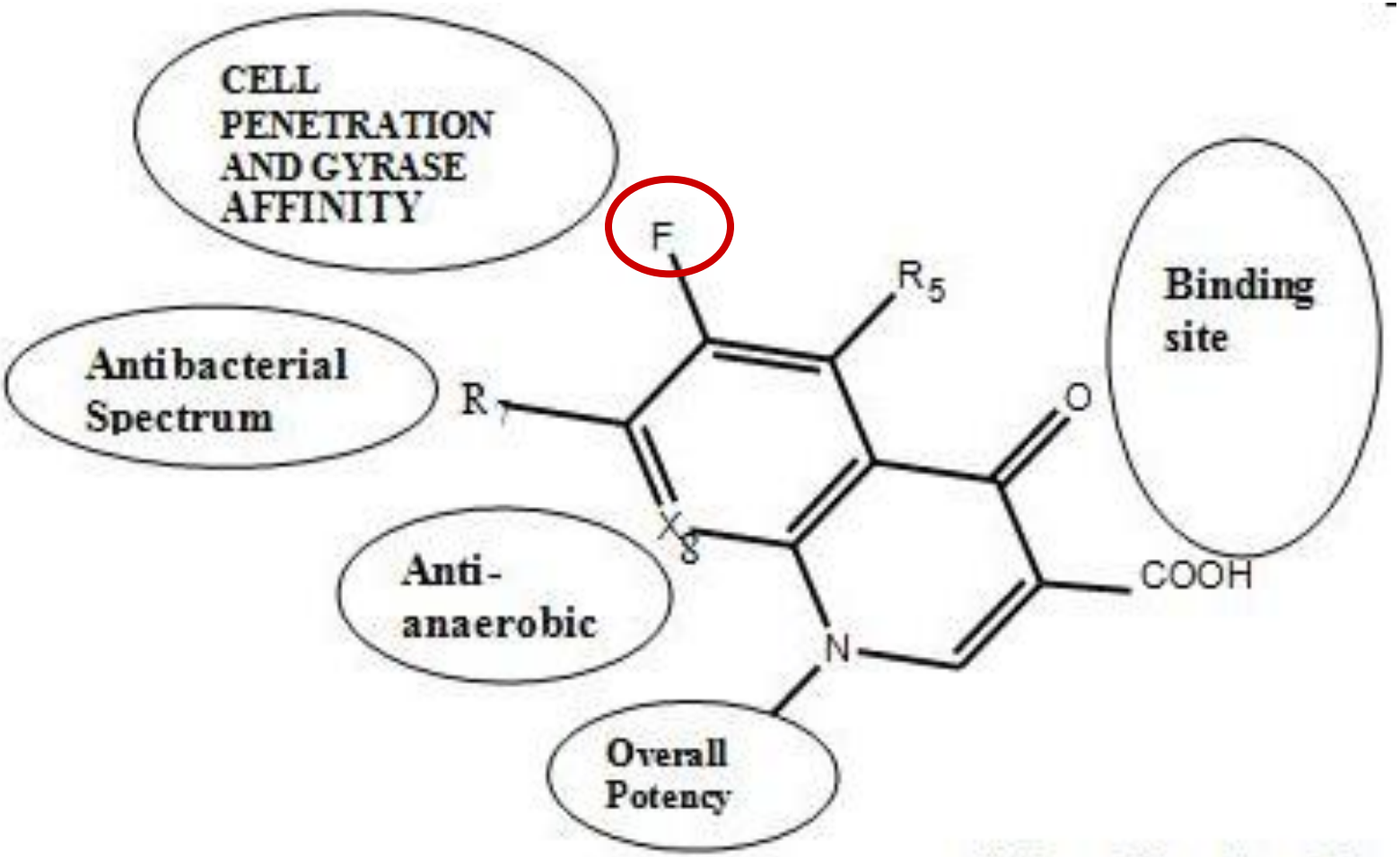
Quinolones

- parent drug: nalidixic acid



Quinolones (1st generation)

- Non-fluorated
- Narrow spectrum
- Low antimicrobial activity
- Low bioavailability
- High metabolism
- Adverse effect and resistance
- Low concentration - serum, tissue
- Mostly used in UTIs



Where X = C or N

Structural Sites Determining Antibacterial Activity Of Fluroquinolones

Fluoroquinolones
(2^{nd}, 3^{rd}, 4^{th} generation)

- Modified 1^{st} generation quinolones
- Fluorine atom C-6 or C-7 position
- Better pharmacokinetics
- Bactericidal
- Broad spectrum
- High antimicrobial activity
- Intracellullar patogens, too
- Post-antibiotic effect
- Wide distribution to urine and other tissues
  limited CSF penetration

Quinolones

- bactericidal agents - broad spectrum
- both concentration dependent effect
- act intracellullary

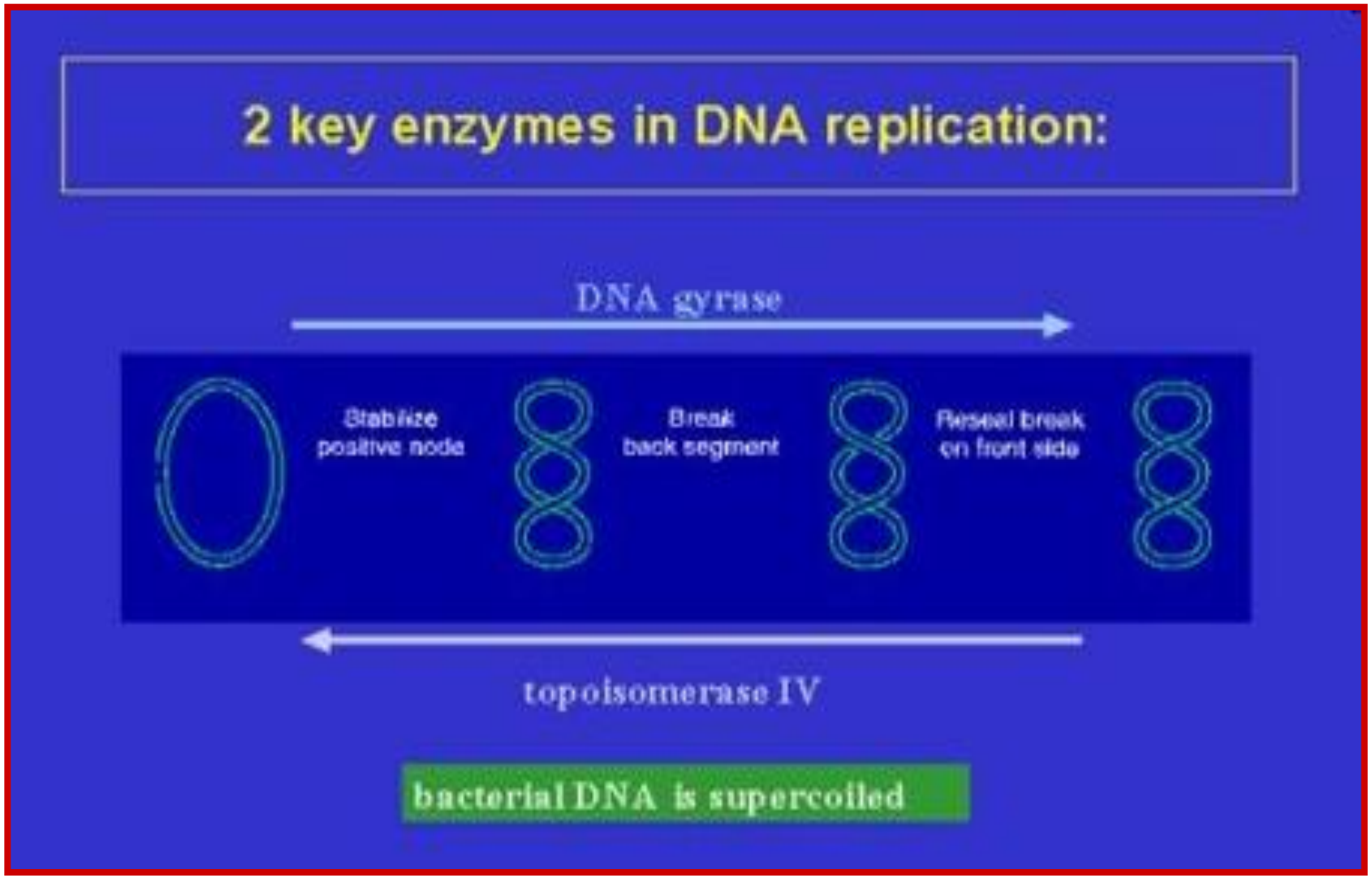
  (*Legionella pneumophila*,

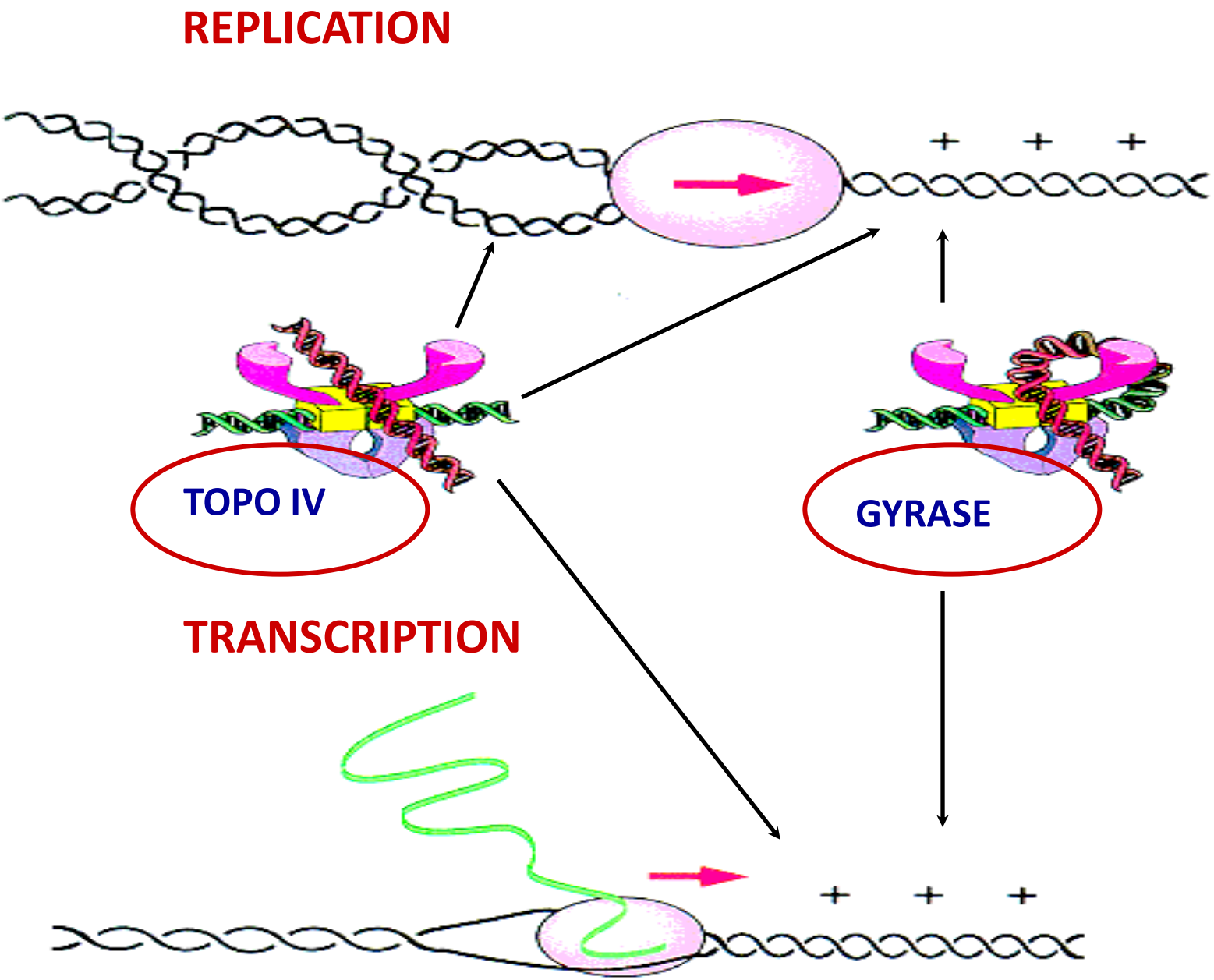
  Mycoplasma pneumoniae)
- **Post-antibiotic effect** - 1 to 2 hours

  - ↑ with increasing concentration

Generation	Drug Names	Spectrum
1st	nalidixic acid (NEGRAM) cinoxacin	G- but not Pseudomonas sp
2nd	norfloxacin (NOROXIN) ciprofloxacin* (CIPRO) enoxacin (PENETREX) ofloxacin (FLOXIN,TARIVID) lomefloxacin (MAXAQUIN)	G- (Pseudomonas species), some G+ (S. aureus) and some atypicals * intracellullary
3rd	levofloxacin * (LEVAQUIN) sparfloxacin (ZAGAM) moxifloxacin (AVELOX) gatifloxacin (TEQUIN) pefloxacin (ABACTAL)	Same as 2nd generation with extended G+ and atypical * intracellullary
4th	trovafloxacin (TROVAN) (hepatotoxicity) gemifloxacin (FACTIVE)	Same as 3rd generation with broad anaerobic

Mechanism of action




REPLICATION
+ + +
TOPO IV
GYRASE
TRANSCRIPTION
+ + +

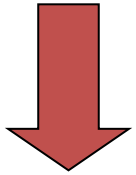
Mechanism of Action

1. Inhibition of bacterial DNA Gyrase (Topoisomerase II)

2. Inhibition of bacterial Topoisomerase IV

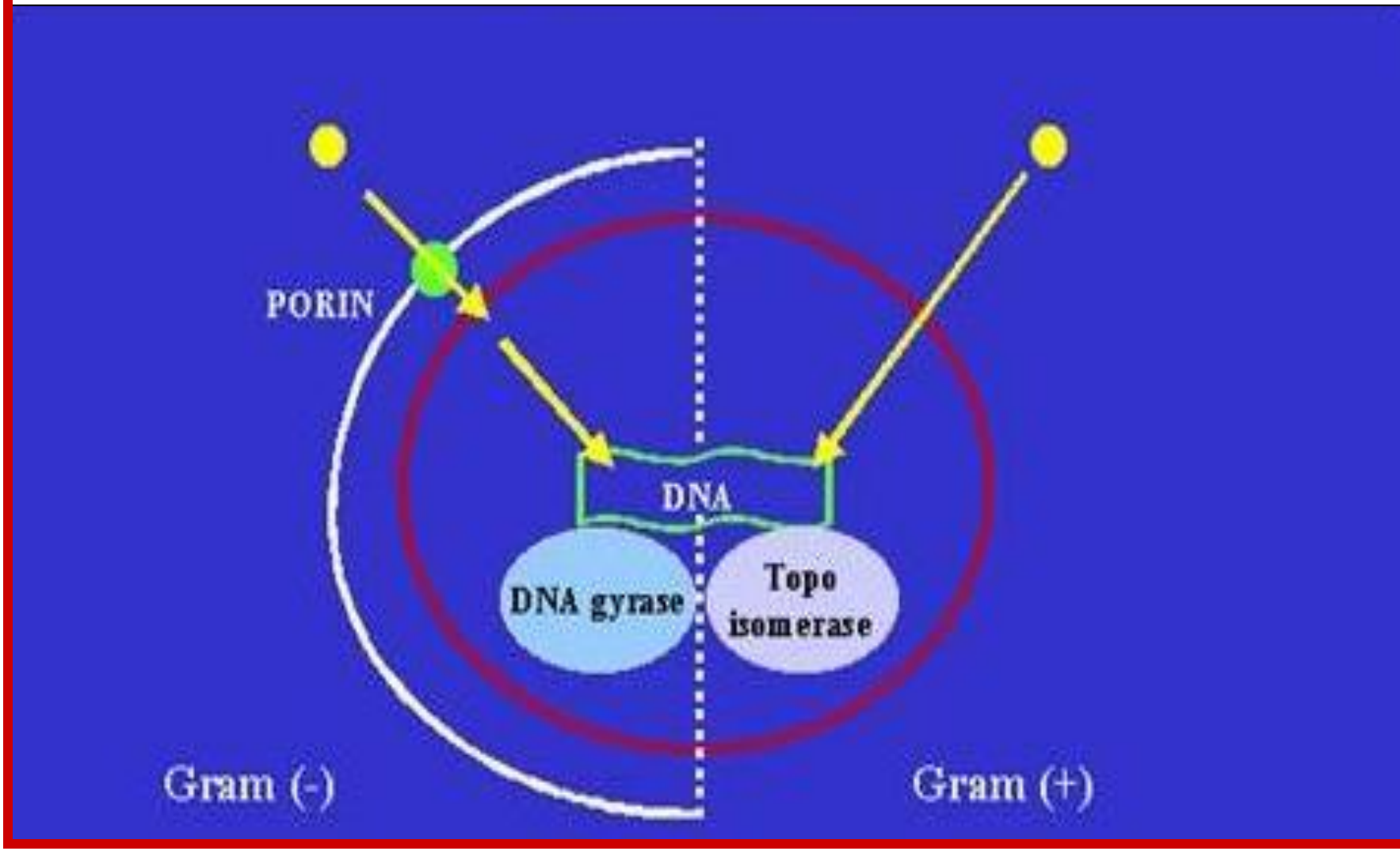
– they prevent bacterial DNA from unwinding and duplicating

– inhibiting DNA synthesis, replication and transcription

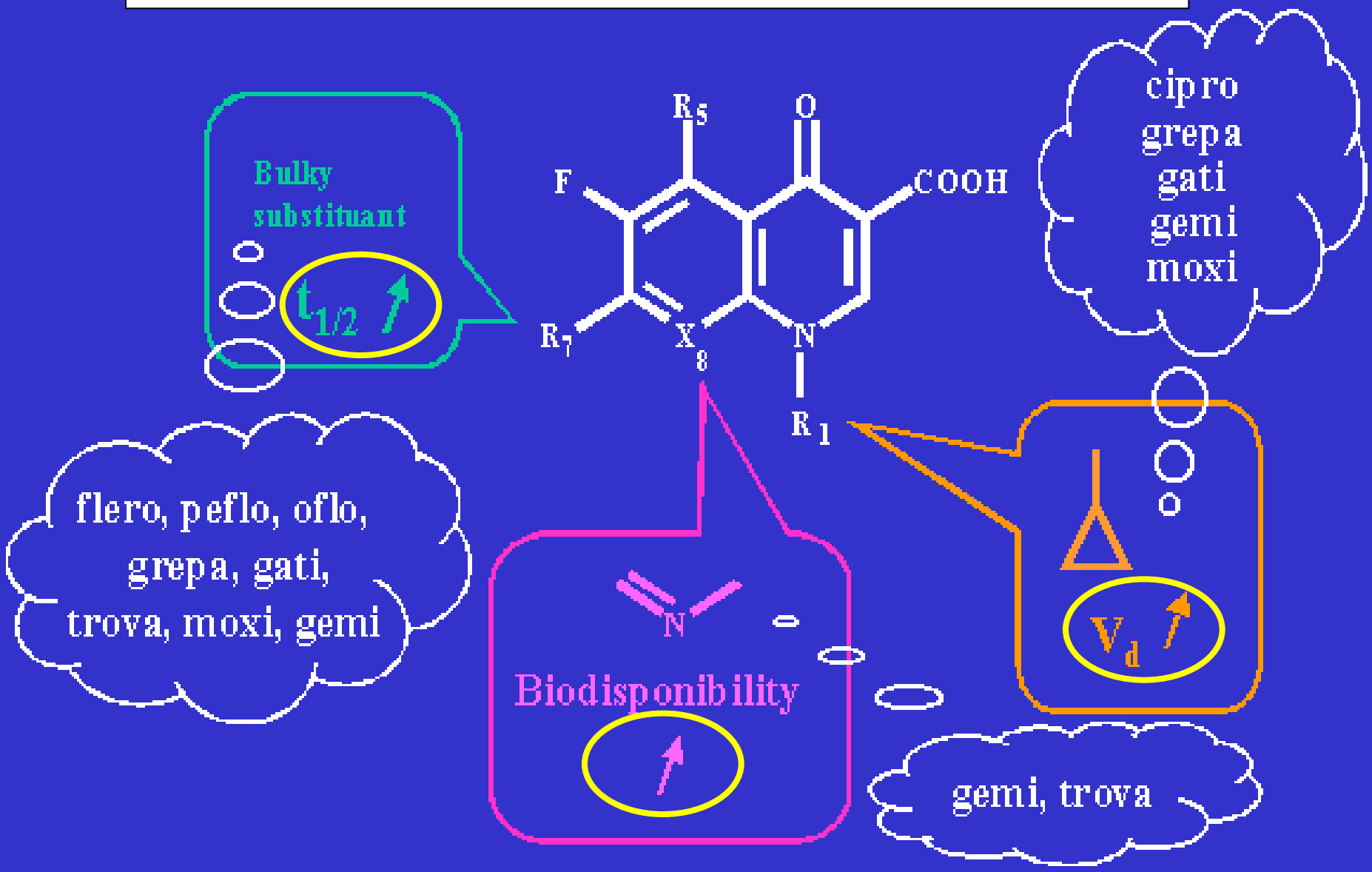


– rapid cell death

Mechanism of Action



Pharmacokinetics



Drug by brand name	Orally absorbe	Cmax (Mg/dl)	T ½ (hrs)	Regards to food	Protien bound	Elimination path	Dosage forms
Norfloxacin	30-40%	1.5	3.5	Empty stomach	10-15%	Billiary and renal	Oral
Ciprofloxacin	70%	2.4	4.0	Empty stomach	20-40%	Renal 66% Hepatic 33%	Oral, IV
Ofloxacin	98%	2.9	4.5	Not studied	32%	Renal	Oral, IV, Opthalmic
Lomefloxacin	>95%	-	8.0	Empty stomach	10%	Renal, 65% unchanged in urine	Oral
Levofloxacin	99%	5.7	6-8	No effect	24-38%	Renal, 87% unchanged in urine	Oral, IV
Sparfloxacin	-	-	16-30	No effect	45%	Hepatic glucuronidation	Oral
Moxifloxacin	90%	4.5	12	No effect	50%	Renal, 45% unchanged in urine, Hepatic conjugation	Oral
Gatifloxacin	96%	3.8	7.8	No effect	20%	Renal, 70% unchanged in urine	Oral, IV
Trovafloxacin	88%	2.1	9.6	No effect	76%	Conjugation, 43% unchanged in faeces	Oral, IV

Pharmacokinetics

- absorption
  - significantly ↓ with Al+, Mg+, Ca+, Fe+,Zn+
  - chelation complex
  - administer 4 h before or 2 h after agent
- longer half life in newer agent - 1 x or 2 x daily
- eliminated by kidneys - !! renal function
- urine concentration of Cipro and Floxin are 25 x higher than serum
- Moxifloxacin - excreted by liver, low urinary conc.
  - do not use in UTIs

Quinolones

- **Conc > serum**
  - Prostate tissue
  - Stool
  - Bile
  - Lung
  - Neutrophils
  - Macrophages
  - Kidneys
- **Conc < serum**
  - Prostatic tissue fluid
  - Bone
  - CSF

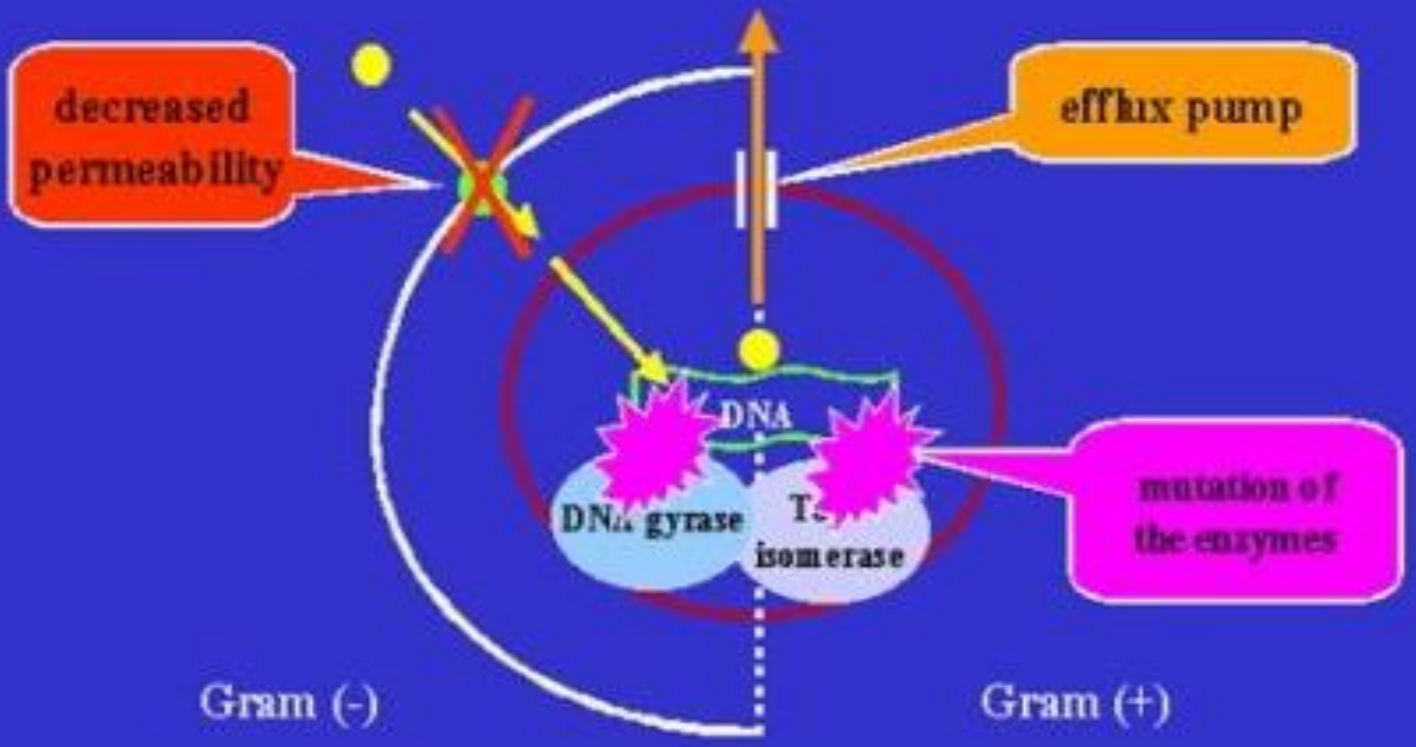
Quinolones - adverse effects

- GIT - nausea, vomiting
- CNS - headache, dizziness, confusion, insomnia, seizure (rare)
- Cardiovascular - torsades de pointes (rare)
  - arrhythmias
- Musculoskeletal - rupture of tendon (rare)
  arthropatogenic effect
  (!! contraindicated to 18 years)

Quinolones - adverse effects

- Neurologic - polyneuropathy (rare)
- Photosensitivity
- Blood picture
- Liver function
- Blood glucose disturbances in DM patients
- Dysmicrobia – enterocolitis
- Resistance
- !!! pregnancy, lactation

Resistance to fluoroquinolones



Quinolones - adverse effects

- **Drug interactions**
  - ↓ absorption - Al^{3+}, Mg^{2+}, Ca^{2+}, Bi^{2+}
  - antacids
  - H_2 antihistaminics

↓ of Fch bioavailability

Quinolones - adverse effects

- **Drug interactions**

CYP 450 inhibition – ciprofloxacin

warfarin, coumarin, ranitidine,

theophyline, cyclosporine, caffeine,

opioids, rifampicin, glibenclamide

Therapeutic Use

- Urinary tract infection (complicated also)
- Skin, Soft Tissue Infections
- Urethral, Cervical gonococcal infections
- Prostatitis
- Sexual, Chlamydia, gonococcal infections
- Bone, joint Infections (G-)
- Infectious diarrhea
- Thyphoid fever, salmonelosis, shigelosis
- Nosocomial pneumonia, CF
- Acute sinusitis, otitis