Antibacterial drugs

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The antibacterial drugs destroy or slow down the growth of bacteria

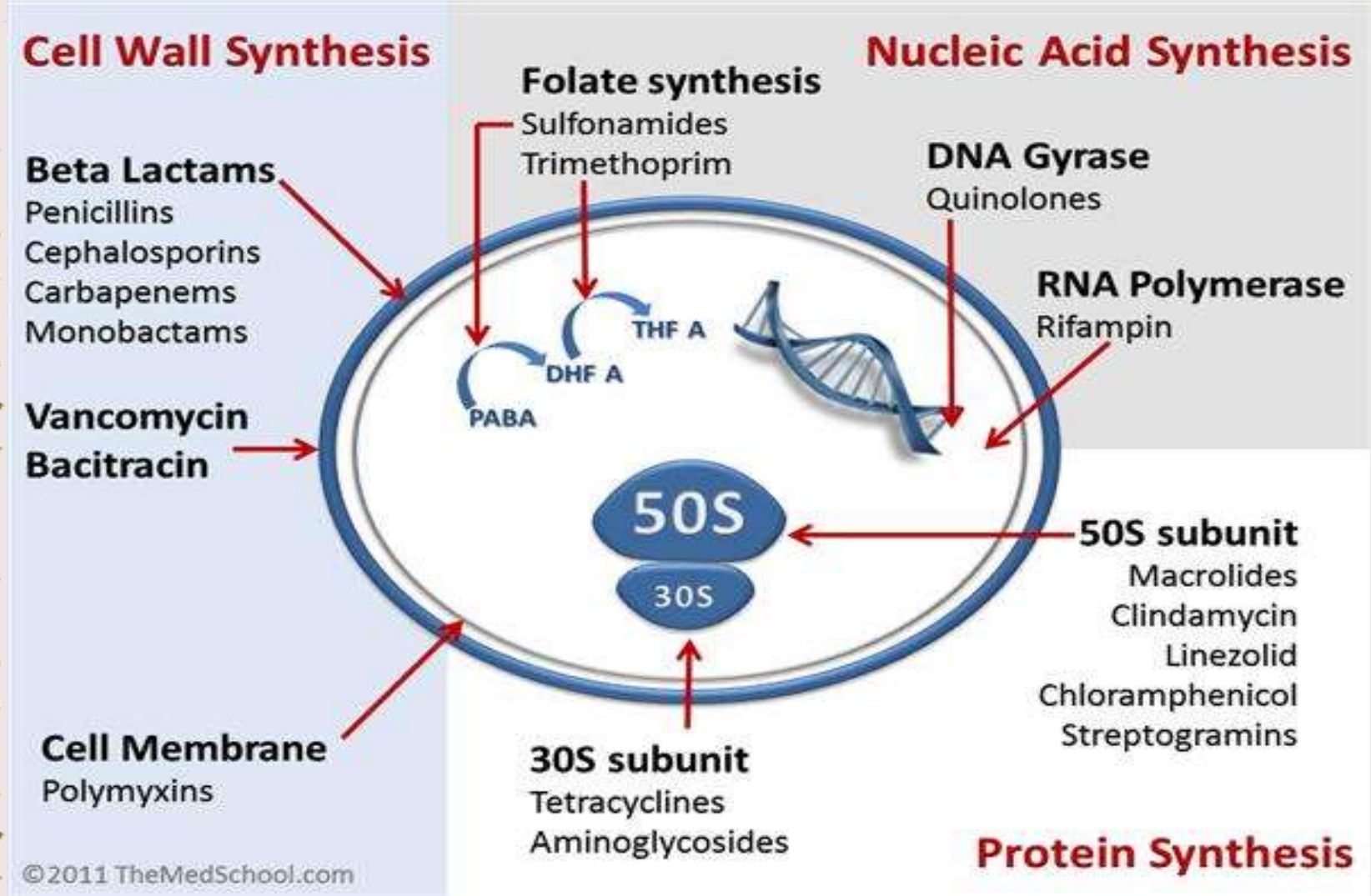
They are widely used in medicine and dentistry.

They are administered generally and locally, in prophylaxis and treatment.

- **ANTIBIOTICS**
  - ✓ antimicrobial agents produced by microorganisms
  - ✓ synthetic drugs designed based upon the structure of molecules produced in nature by microorganisms
- **CHEMOTHERAPEUTIC AGENTS**
  - ✓ antimicrobial agents synthesized in the laboratory

Colloquially – all antibacterial agents are named antibiotics

Antibiotics classification and mechanism of action



Antibiotics classification

- **bacteriostatic – slow growth or reproduction of bacteria (macrolides, lincosamides, tetracyclines, sulfonamides and chloramphenicol)**
- **bactericidal - kill bacteria (β-lactams, vancomycin, daptomycin, fluoroquinolones, metronidazole, co-trimoxazole)**

The classification is in part arbitrary because most bacteriostatic drugs are bactericidal at high concentrations, under certain incubation conditions in vitro, and against some bacteria.

B - lactams

- inhibit bacterial growth by interfering with bacterial cell wall synthesis - bactericidal
- this group of antibiotic include some groups such as penicillins, cephalosporins, monobactams, carbapenems, and β – lactamase inhibitors

Penicillins - classification

The penicillin group include:

- **prototype: penicillin G, penicillin V**
- **penicillinase – resistant: nafcillin, methilcillin, oxacillin, cloxacillin, dicloxacillin**
- **<u>extendend – spectrum:</u> ampicillin, amoxicillin, ampicillin/sulbactam, amoxicillin/clavulanic acid**
- **antipseudomonal: carbenicillin, ticarcillin, ticarcillin/clavulanic acid, mezlocillin, piperacillin**

Cephalosporins

First - generation cephalosporins:

- **include cefalotin, cefapirin, cefalexin, cefadine, cefazolin, cefadroxil**
- **good activity against most gram – positive organism and some gram – negative**
- **used mainly for urinary tract infections caused by *E. coli, Klebsiella,* upper respiratory tract, skin, soft tissue, bones infections and prophylactically in various surgical procedures**

Cephalosporins

Second - generation cephalosporins:

- **include cefamandole, cefoxitin, cefaclor, cefuroxime, cefonicid, cefmetazole, ceforanide**
- **extend the spectrum of the first generation to include *H. influenzae* and indole – positive *Proteus;* they are less effective against gram - positive bacteria than first generation agents**
- **used primarily in the management of lower respiratory tract, urinary tract, bone and soft - tissue infections and prophylactically in various surgical procedures**

Cephalosporins

Third - generation cephalosporins:

- **include cefotaxime, ceftizoxime, ceftazidime, cefixime, ceftriaxone, cefotetan, cefoperazone**
- **good activity against gram – negative organism and moderate activity against anaerobes**
- **used primarily for serious hospital – acquired gram – negative infections, alone or in combination with an aminoglycosides**

Monobactams

- **good activity against gram - negative organism but it lacks activity against anaerobes and gram – positive organism (similar to aminoglycosides)**
- **useful for various types of infections caused by *E. coli, Klebsiella pneumoniae, H. influenzae, P. aeruginosa, Enterobacter* species, *Citrobacter* species and *Proteus mirabilis***
- **demonstrate no cross – reactivity with penicillins or cephalosporins for hypersensitivity reactions**
- **Aztreonam is the representative of this group**

Carbapenems

- very broad spectrum of antibacterial activity (against gram – positive and negative, aerobes and anaerobes organisms)
- useful for infections caused by penicillinase – producing *S. aureus, E. coli, Klebsiella, Enterobacter* and *H. influenzae* among others
- patient allergic to penicillin may also have a hypersensitivity to carbapenems
- imipenem and meropenem are the representative of this group

Aminoglycosides

The representatives of this group of antibiotics are:

- **Streptomycin**
- **Gentamycin**
- **Tobramycin**
- **Netilmycin**
- **Amikacin**
- **Neomycin**
- **Kanamycin**
- **Spectinomycin**

Aminoglycosides

- **inhibit bacterial protein synthesis by interacting with receptor protein on the 30S ribosomal subunit thus block the initation complex and leads to a buildup of monosomes; it also causes translation errors - bacteriostatic**
- **in high concentration cause damage of cell membrane - bactericidal**

Aminoglycosides

- active against most gram – negative aerobic bacteria
- use of these agents is decreasing as a result of the development of broader – spectrum penicillins and cephalosporins and other antibiotics that are less toxic

Tetracyclines

The representatives are:

- **Tetracycline**
- **Demecyclocycline**
- **Doxycycline – most often used agent of this group**
- **Methacycline**
- **Minocycline**
- **Oxytetracycline**

Tetracyclines – mechanism of action

- bind to the 30S subunit of bacterial ribosomes
- prevent the binding of aminoacyl tRNA to the acceptor site on the mRNA – ribosome complex, inhibiting bacterial protein synthesis
- bacteriostatic

Tetracyclines

- active against both gram – positive and gram – negative organisms, but the use of these agents is declining because of increased resistance and the development of safer drugs
- used predominantly for the treatment of rickettsial infections, including Rocky Mountain spotted fever, cholera, Lyme disease, and infections caused by *Chlamydia* and *Mycoplasma pneumoniae*
- may be useful for the treatment of inflammatory acne vulgaris

Tetracyclines – adverse effects

- gastrointestinal upset, including nausea, vomiting and diarrhea
- at high doses can cause hepatic damage, particularly in pregnant women
- form complex with calcium in bone:
  - can cause teeth discoloration in children age 6 months to 5 years
  - can retard bone growth in neonates

Macrolides

The representatives are:

- **Erythromycin**
- **Clarithromycin**
- **Azithromycin**

Macrolides – mechanism of action

Inhibit protein synthesis by binding irreversibly to the bacterial 50S ribosomal subunit to terminate protein synthesis.

Macrolides

- **active against gram – positive organism**
- **useful as a penicillin substitute in penicillin – hypersensitive patients**
- **the most effective drugs for Legionnaires' disease (*Legionella pneumophila*)**
- **also useful for the treatment of syphilis, *Mycoplasma pneumoniae*, corynebacterial infections (e.g. diphtheria) and *Bordetella pertussis* diseases (whooping cough)**

Clindamycin – mechanism of action

- derivative of lincomycin
- inhibits protein synthesis by binding irreversibly to the bacterial 50S ribosomal subunit to terminate protein synthesis

Clindamycin

- active against gram-positive and gram-negative anaerobic organisms and gram-positive aerobic
- the most important indication is the treatment of severe anaerobic infection caused by *Bacteroides* and other anaerobes that often participate in mixed infections: respiratory tracts, skin and soft tissue, bone infections, endocarditis, sepsis
- recommended for prophylaxis of endocarditis in patients with valvular heart disease who are undergoing certain dental procedures

Clindamycin

- in combination with aminoglycosides or cephalosporins used to treat:
  - ✓ penetrating wounds of the abdomen and the intestine
  - ✓ infections originating in the female genital tract, e.g. septic abortion and pelvic abscesses
  - ✓ aspiration pneumonia
- in combination with pyrimethamine used for AIDS-related toxoplasmosis of the brain

Vancomycin

- tricyclic glycopeptide
- binds to the terminal end of growing peptidoglycan to prevent further elongation and cross – linking - inhibits cell wall biosynthesis
- also reduces the permeability of the cell wall and the synthesis of ribonucleic acid

Vancomycin

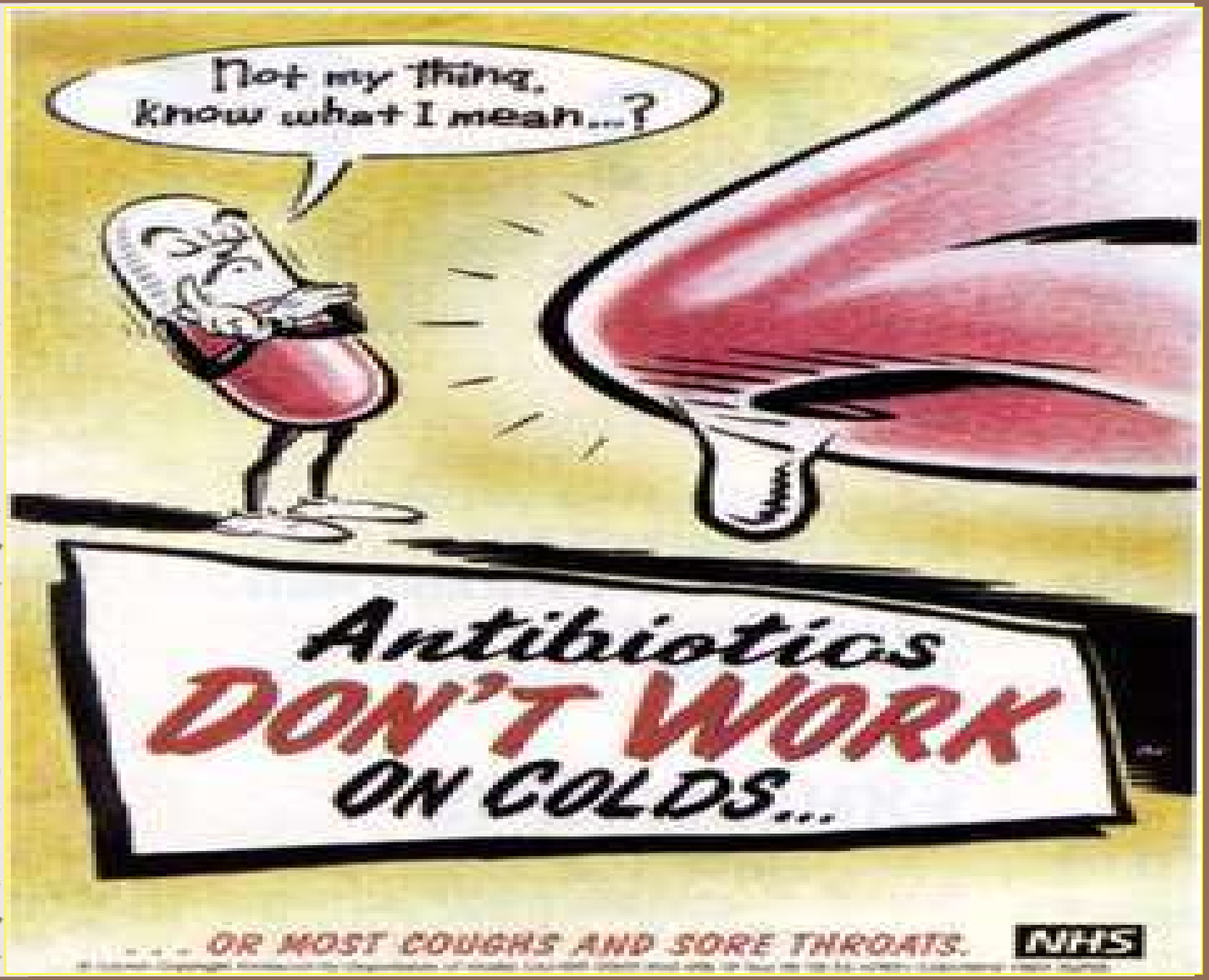
- active against gram – positive organisms
- used in serious staphylococcal, enetrococcal and streptococcal infections (sepsis, endocarditis, CNS, lower respiratory tract, skin and soft tissue infections), in patients allergic to penicillins and cephalosporins
- treatment of MRSA infections
- treatment antibiotic associated enterocolitis - orally

Metronidazole

- synthetic antibacterial drug
- blocks of DNA biosynthesis after transformation of the drug to its active form in the cell of anaerobic bacteria - bactericidal
- used to treatment anaerobic bacterial infections – sepsis, aspiration pneumonia, abscess of the liver, brain, abdomen and pelvic infections
- dentistry - acute periodontal infections, acute ulcerative gingivitis

Principles of rational antibiotic therapy

- presence of substantiated indications for prescription of an antibiotic
- choosing of the most effective and the least toxic drug
  - ✓ empiric antibiotic therapy
  - ✓ targeted antibiotic therapy
- choosing of the optimal way of introduction
- introduction of optimal doses with optimal frequency, taking into consideration complexity of the disease
- assignation of contraindication and interaction with other administered drugs
- estimation of duration of treatment
- monitoring and prophylaxis of negative side effects
- decision on expediency of combined antibiotic therapy


Not my thing, know what I mean...?
Antibiotics DON'T WORK ON COLDS...
... OR MOST COUGHS AND SORE THROATS.
NHS

Adverse effects of antibiotics

- disturbances of biological balance
- allergic reactions
- organ toxicity

- gastrointestinal disturbances

Disturbances of biological balance

- diarrhea
- overgrowth of pathogenic fungi in oral cavity and vulvo-vaginal area
- may be alleviated by ingesting probiotics during a course of antibiotics

Disturbances of biological balance

- **antibiotic-associated enterocolitis with severe diarrhea after administration of clindamycin or other antibiotics is caused by toxigenic *C. difficile***
- **potentially fatal complication**

Disturbances of biological balance

- must be recognized promptly
- treatment:
  - ✓ metronidazole 500 mg orally or intravenously three times a day (the preferred therapy)
  - ✓ or vancomycin 125 mg orally four times a day

Allergic reactions

- anaphylactic shock (very rare-0.0001% of recipients)
- serum sickness type reactions (urticaria, fever, joint swelling, angioneurotic edema, intense pruritus, and respiratory embarrassment occurring 7-12 days after exposure)
- variety of skin rashes
- treatment: epinephrine, antihistamine agents, corticosteroides

Stevens–Johnson syndrome

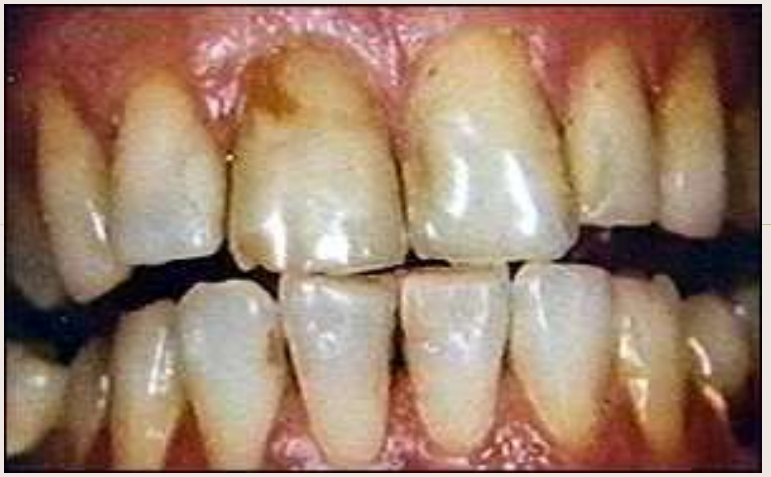
- life-threatening condition - a milder form of toxic epidermal necrolysis
- caused by hypersensivity complex affecting the skin and the mucous membranes
- usually idopathic, may be caused by medications (especially antibiotics)

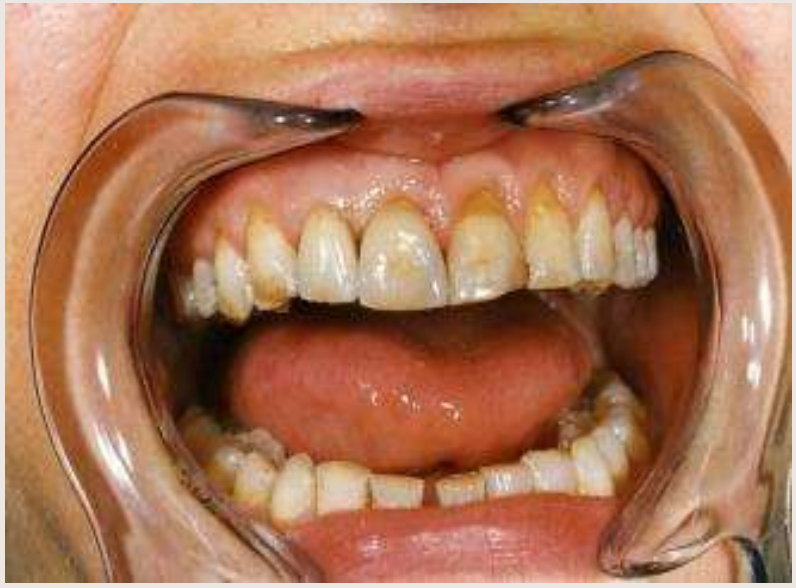
Stevens–Johnson syndrome

- **symptoms:**
  - ✓ **fever, sore throat, fatigue,**
  - ✓ **ulcers and other lesions in the mucous membranes, almost always in the mouth and lips but also in the genital and anal regions;**
    - **usually extremely painful (oral cavity) and reduce the patient's ability to eat or drink**
  - ✓ **a rash on the face, trunk, arms and legs, and soles of the feet, but usually not the scalp**
  - ✓ **conjunctivitis**

Stevens–Johnson syndrome

- **treatment:**
  - ✓ **all medications should be discontinued**
  - ✓ **supportive and symptomatic treatment**
    - **intravenous fluids**
    - **nasogastric or parenteral feeding**
    - **analgesic (intravenously and mouth rinse for mouth ulcer)**
  - ✓ **administration of corticosteroids, cyclophosphamide, cyclosporine and intravenous immunoglobulin is controversial**





- **teeth discoloration after tetracyclines**

Organ toxicity of antibiotics

- **hepatotoxicity – macrolides, tetracyclines, lincosamides**
- **neurotoxicity – penicillins**
- **myelotoxicity – chloramphenicol**
- **nephrotoxicity – aminoglycosides, vancomycin**
- **ototoxicity – aminoglycosides, vancomycin**

Indication to local antibiotic therapy in dentistry

- acute and sharpen pulpitis
- acute and sharpen periodontitis
- treatment of profound, complicated decay

Indication to general antibiotic therapy in dentistry

- subperiosteous, submucous and periodontal abscesses
- posttraumatic and postoperative complications (injury, fracture, extraction, craniofacial operation)
- salivary gland, sinus and mucosa of oral cavity infection
- fistula (complication of inflammation)
- specific and unspecific inflammation

Combined therapy - indications

- severe infections
- infections due to bacteria weakly sensitive to many antibiotics or quickly developing antibiotic resistance
- infections due to a few bacteria – difficulty establish the pathogenic organism
- infections in patients with impaired defense mechanisms

General principle of combined therapy

- **bactericidal + bactericidal**

  often synergism, hardly ever antagonism
- **bactericidal + bacteriostatic**

  sometimes synergism, more often antagonism
- **bacteriostatic + bacteriostatic**

  hardly ever synergism, often antagonism

Synergism – combination has a greater effect than the sum of the two individual drug effects

Antagonism – combination has less activity than that of individual drug alone

Prophylaxis of endocarditis

Prophylaxis should only be considering for patients at highest risk of IE

(patients with the highest incidence of IE and/or highest risk of adverse outcome from IE).

Prophylaxis of endocarditis

1) prosthetic valve or a prosthetic material used for cardiac valve repair
2) previous IE

Prophylaxis of endocarditis

3) congenital heart disease

- cyanotic, without surgical repair, or with residual defects, palliative shunts or conduits
- when a residual defects persist at the site of implantation of a prosthetic material or device by cardiac surgery or percutaneous technique
- with complete repair with prosthetic material whether placed by surgery or by percutaneous technique, up to 6 months after the procedure

Prophylaxis of endocarditis

Antibiotic should only be considered for dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa

Prophylaxis of endocarditis

Antibiotic prophylaxis is not recommended for:

- ✓ other dental procedures (local anesthetic injection, dental X-rays)
- ✓ respiratory tract procedures (bronchoscopy, intubation)
- ✓ gastrointestinal or urogenital procedures (gastroscopy, cystoscopy)
- ✓ skin and soft tissue

Prophylaxis of endocarditis

No allergy to pencillin or ampicillin

- **amoxicillin or ampicillin 2 g p.o. or i.v. in adults and 50 mg/kg p.o. or i.v. in children, single dose 30-60 minutes before procedure**
- **alternatively cephalexin, cefazolin, or ceftriaxon i.v.**

Cephalosporins should not be used in patients with anaphylaxis, angio-oedema, or urticaria after intake of penicillin and ampicillin

Prophylaxis of endocarditis

Allergy to pencillin or ampicillin:

- **clindamycin 600 mg p.o. or i.v. in adults and 20 mg/kg p.o. or i.v. in children single dose 30-60 minutes before procedure**

Antibiotics in pregnancy

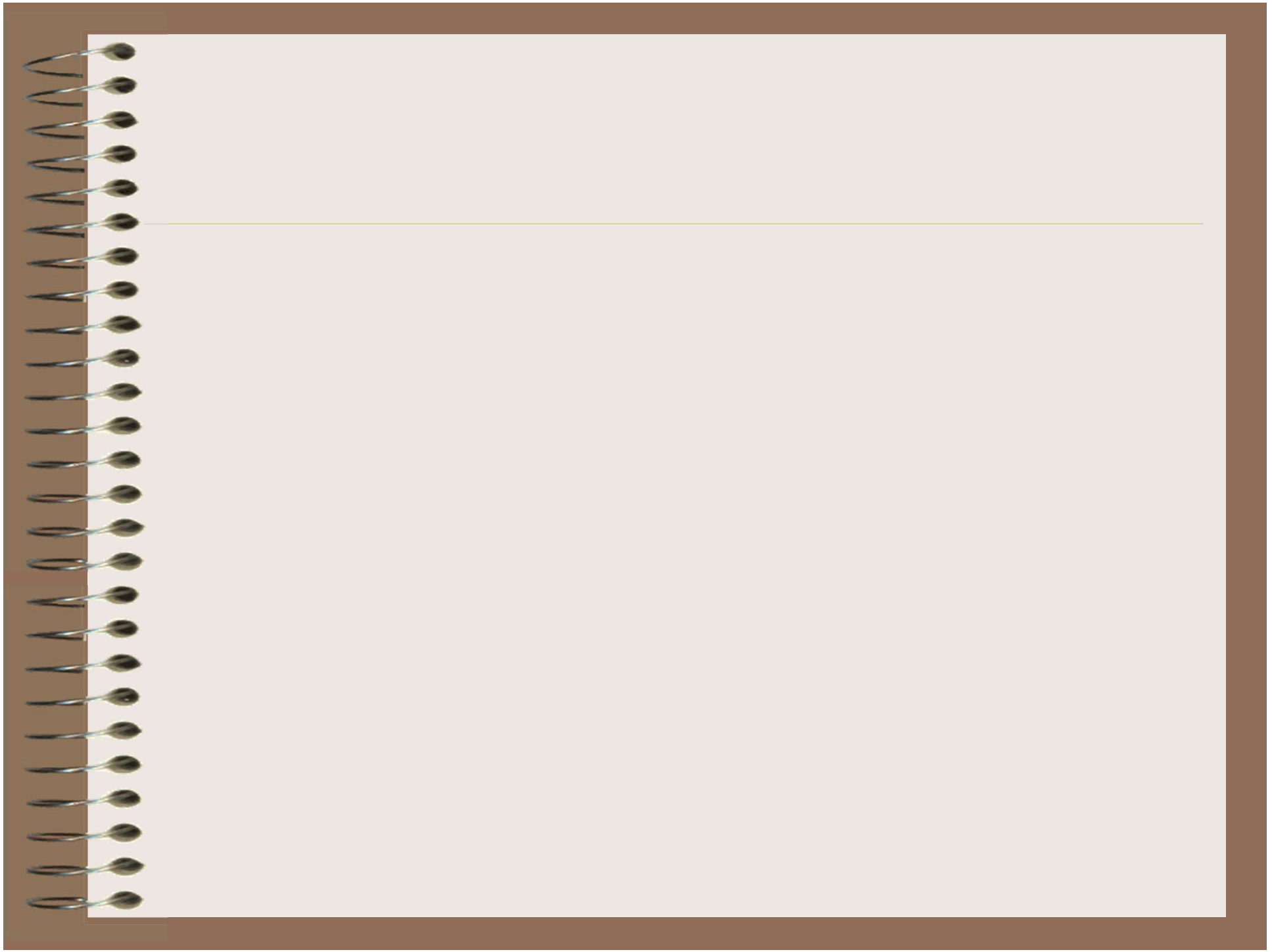
- use medications only if absolutely indicated (treatment of confirmed infection)
- if possible, avoid initiating therapy during the first trimester (the highest risk for iatrogenic teratogenicity)
- select a safe medication (often means an older drug with a proven track record in pregnancy)
- wherever possible, single-agent therapy is preferred over polypharmacy (moreover, narrow-spectrum antibiotics are preferred over those with a broad spectrum for the treatment of established infection)
- use the lowest effective dose

Antibiotics in pregnancy

- **recommended:**
  - ✓ **β – lactams**
  - ✓ **macrolides (preferred erythromycin)**
  - ✓ **lincosamids**
  - ✓ **nitrofurantoin**

Antibiotics in pregnancy

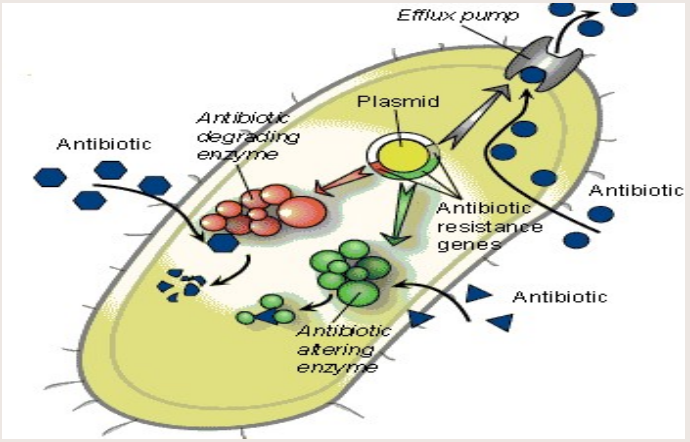
- **contraindicated:**
  - ✓ **tetracyclines**
  - ✓ **metronidazole**
  - ✓ **quinolones**
  - ✓ **aminoglycosides**
  - ✓ **glycopeptide**
  - ✓ **polypeptide**
  - ✓ **chloramphenicol**



Three main problems of modern antibiotic therapy

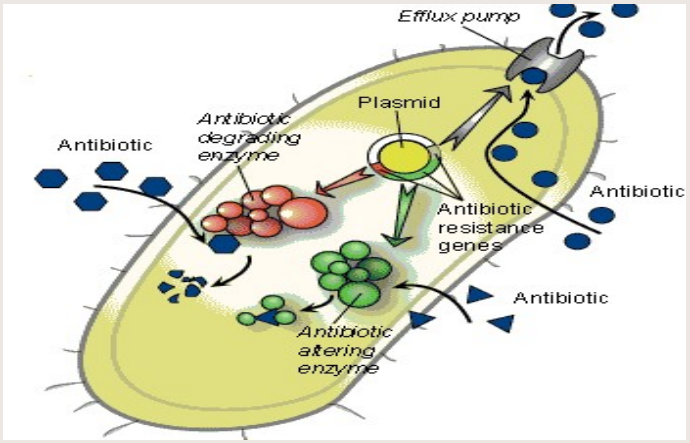
1) Resistance on antibiotics (inside and outside of hospitals)
2) Disregard of indications of antibiotics company by physicians
3) Lack of progress in new antibiotics researches i.e. drugs with different structure or mechanism of action

Mechanism of resistance against antibiotics – change/loss of therapeutic value



1) **Natural resistance**
2) **Acquired resistance**
   - **appearance of chromosomal mutation**
   - **extrachromosomal transmission of genes of resistance by means of plasmids, transposons („leaping genes”)**

The results of chromosome mutations and extrachromosomal transmission of genes



1) **Enzymatic inactivation**
2) **Reduced permeability/uptake of antibiotic**
3) **Active removal of antibiotics by bacterial strain**
4) **Diminished binding ability of antibiotic with bacterial structures**

Lack of progress in new antibiotics researches

- **Only two completely new antibiotic (linezolid, daptomycin) has been introduced into therapy for the last 30 years**

Lack of progress in new antibiotics researches

- **Other new antibiotics originated as:**
  1. **Chemical modification of well-known antibiotics**
  2. **Reactivation of old antibiotics which were no longer used**

Limitation in research of new antibiotics (non-profitability!)

- the atributes of new antibiotics must be studied (10- years clinical researches for exact therapeutic indications - high costs)
- resistance may occur after registration

Limitation in research of new antibiotics (non-profitability!)

- **delay and limitation of extent of researches by small biotechnological companies (e.g. for infection of cutis and subcutaneous tissue of patients in good general condition)**

The greatest clinical problem is unusual prevalence of MRSA (methicillin resistance *S. aureus*) strains, VRE (vancomycin resistance *Enterococci*) strains and glycopeptide resistance (including vancomycin) *Enterococus faecium*.

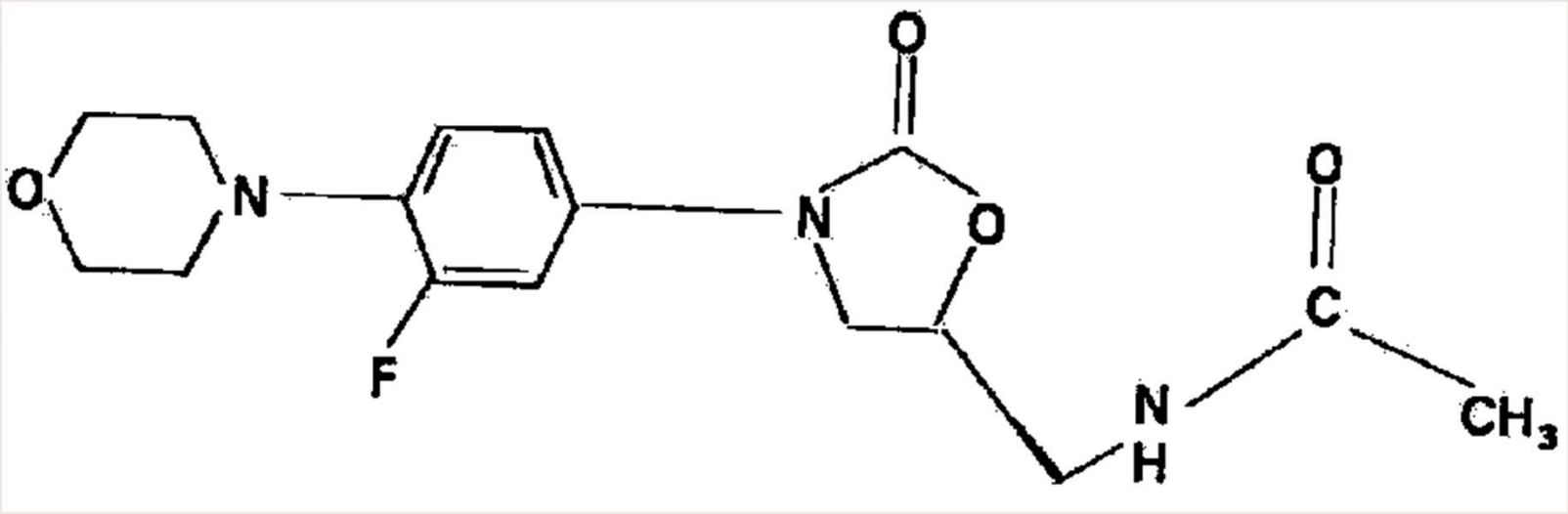
Methicillin resistance S.aureus (MRSA) – PBP2 protein

All beta- lactams are ineffective!

1) **Even „high level" beta-lactams e.g. CARBAPENEMS are ineffective!**
2) **Effective are new antibiotics: oxalizolidinones - linezolid, lipopeptides – daptomycin and vancomycin, teicoplanin**

LINEZOLID

Chemical structure



Ranbezolid – new derivative, tested actually

LINEZOLID

- member of the oxazolidinones, a new class of synthetic antimicrobials, registered in 2000
- active against gram-positive organisms including *Staphylococci* (MRSA), *Streptococci*, *Enterococci* (VRE), gram-positive anaerobic cocci and gram-positive rods such as *Corynebacteria* and *Listeria monocytogenes*

LINEZOLID

- ***in vitro*** **active against** ***Mycobacterium tuberculosis***
- **used to treatment of cutis and connective tissue infections, pneumonia (inside of hospitals) and sepsis**

LINEZOLID

The unique mechanism blocking protein synthesis in early stage!

- **binds to the 50S subunit of bacterial ribosomes**
- **blocks forming of initation complex (30S, 50S and t RNA, mRNA) – <u>destabilisation of tRNA connecting position</u>**

LINEZOLID

- **lack of cross resistance of inhibiting protein synthesis antibiotics (chloramphenicol, linkosamides, macrolides, tetracyclines, streptogramins)**

LINEZOLID

- **actually slight resistance**

  (*S. aureus, E. faecalis*)

  - no resistance in Poland

- **resistance make no practical and clinical problems**

LINEZOLID - pharmacokinetics

- oral bioavailability - approximately 100%
- serum protein binding – 31%
- good penetration into tissue compartments
- cleared by the kidney – 80-85%

LINEZOLID - pharmacokinetics

Tissues concentration as serum concentration	
Bones	60%
Cerebrospinal fluid	70%
Surfactant	450%
Inflammatory alveolar fluid	104%
Muscles	94%
Pancreatic fluid	109%
Dialysis peritoneal fluid	61%
Saliva	120%
Sweat	55%

LINEZOLID

1) Adverse effects
   - allergy
   - diarrhea
   - vomiting
   - headache
   - thrombocytopenia
2) Interaction
   - MAO inhibitors

Linezolid is recommended as guided and empirical therapy of pneumonias and diabetic foot if MRSA infection is confirmed or highly probable in alternative to vancomycin in USA.

Enterococci VRE

1) Frequent resistance to different antibiotics
2) Selection of *Enteroccoci* is caused by abuse of cephalosporin (natural resistance)
3) Main cause of sepsis of patients with immunodeficiencies
4) Therapy: new glycopeptides (orytavancin, dalbavancin), oxazolidinones, daptomycin


☺THANK YOU☺