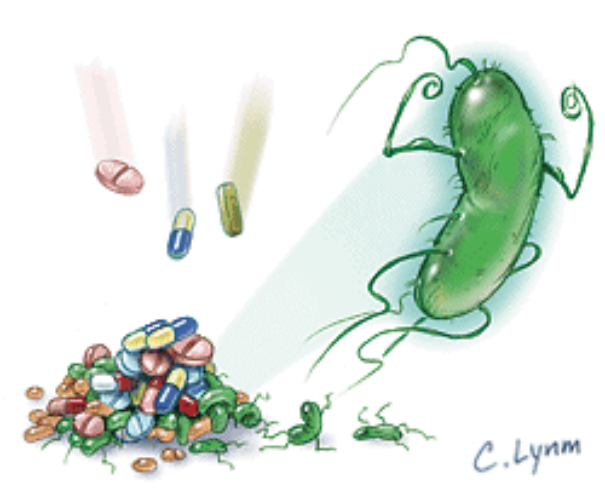
ANTIBACTERIAL DRUGS



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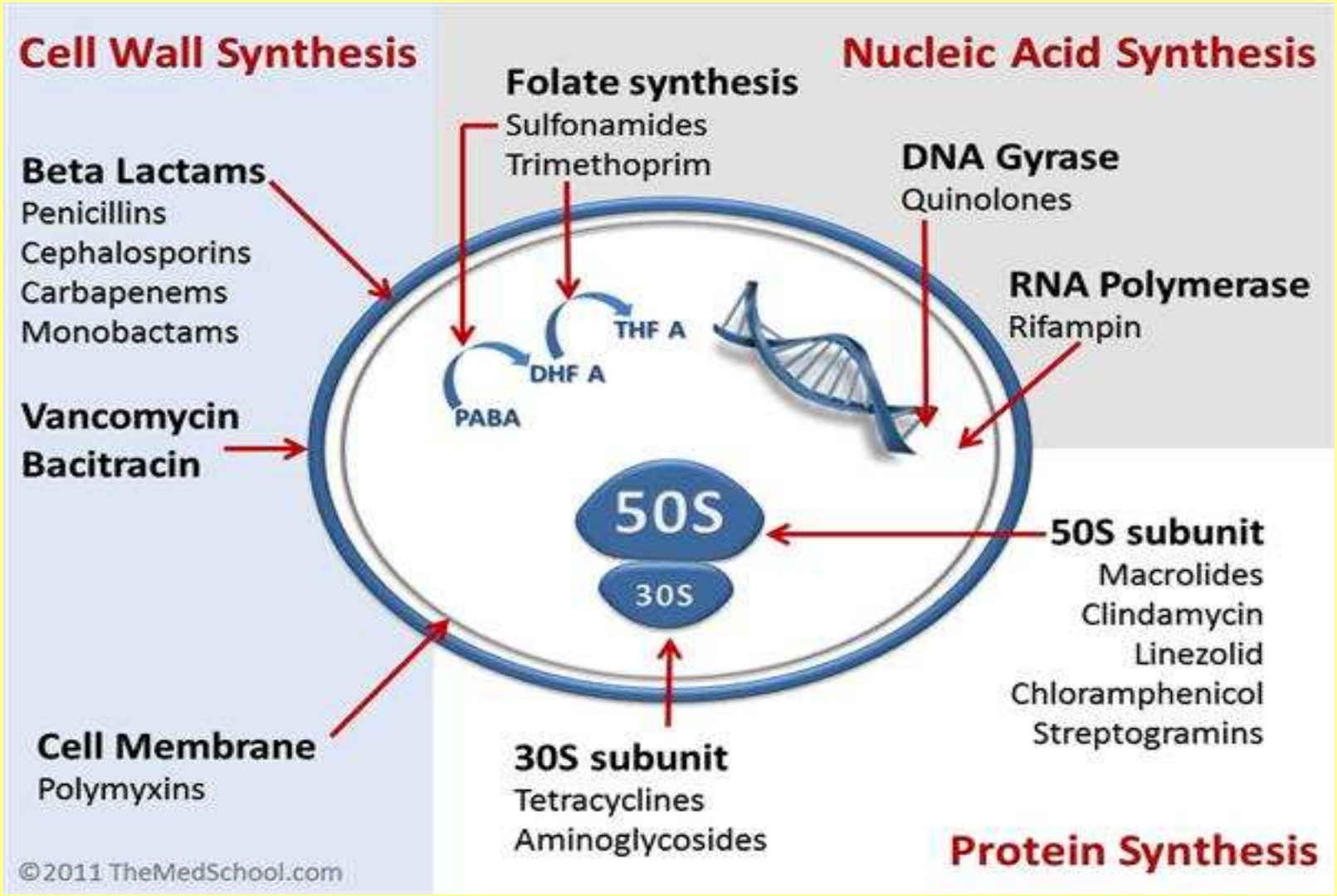
The antibacterial drugs destroy or slow down the growth of bacteria. They are widely used in medicine and dentistry. They are administered generally and locally, in prophylaxis and treatment.

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

Colloquially – all antibacterial agents are named antibiotics

Antibiotics classification and mechanism of action



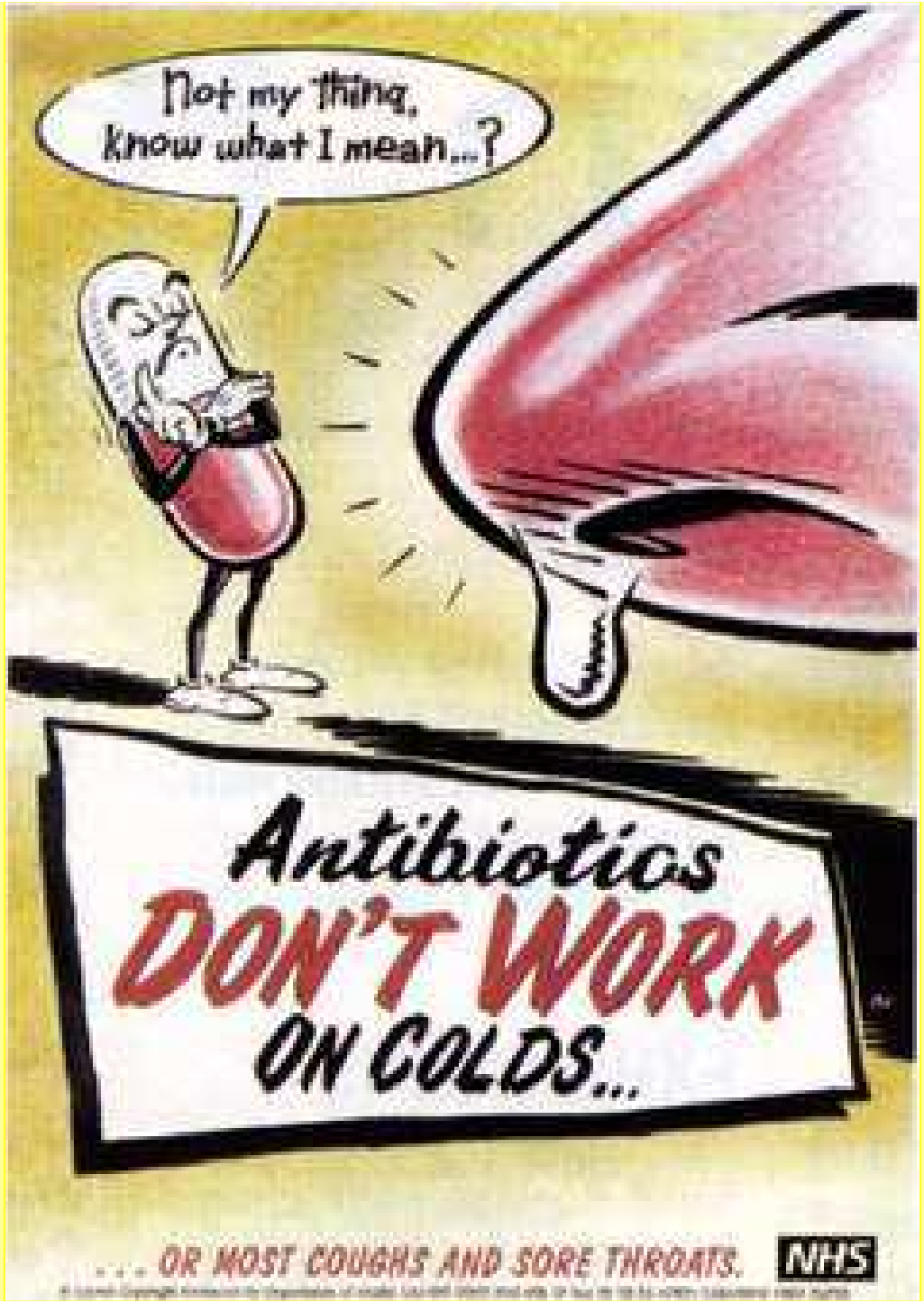
Antibiotics classification

- 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.

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

Improper administration of antibiotics

- viral infections
- treatment of fever of unknown origin
- fever due to drugs administration
- antibiotics administration on the basis of „doctor's experience"
- wrong dosage - underdosing

The causes of failure of therapy

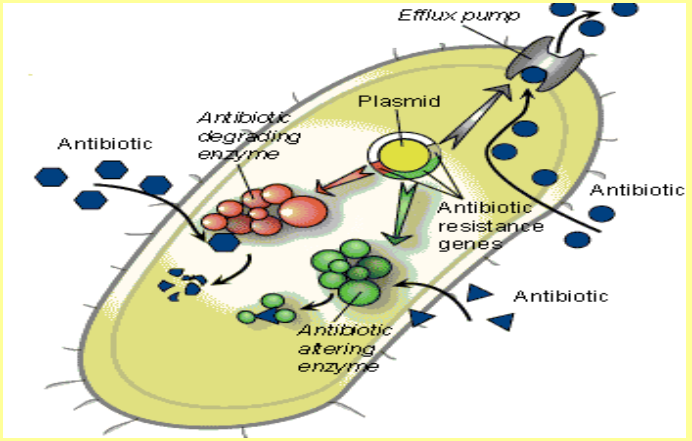
- weakened of immune response
- superinfection (*C. albicans*, *E. coli*)
- resistance of pathogens
- poor penetration of drug
- bad cooperation with patients

Three main problems of modern antibiotic therapy

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

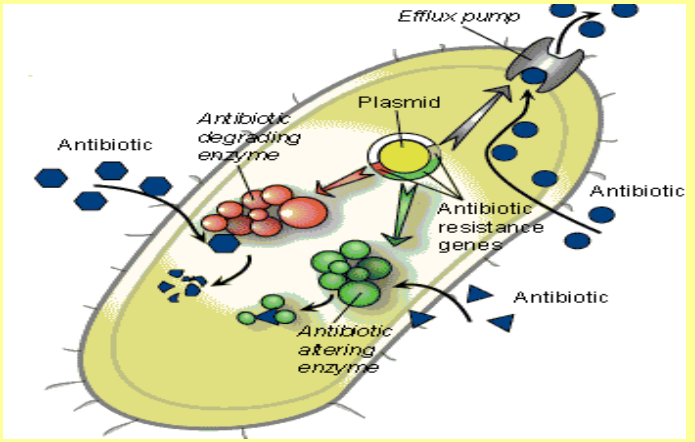

THAT WHICH DOES NOT KILL ME, MAKES ME STRONGER..
HI, I'M MRSA

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

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

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

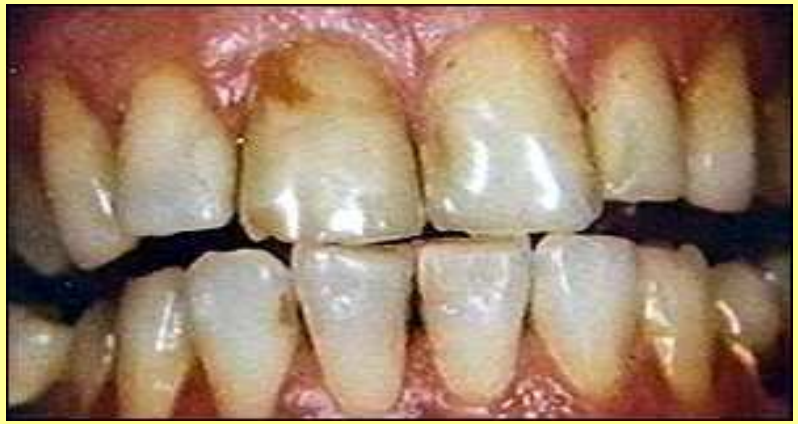
Hoigné Syndrome

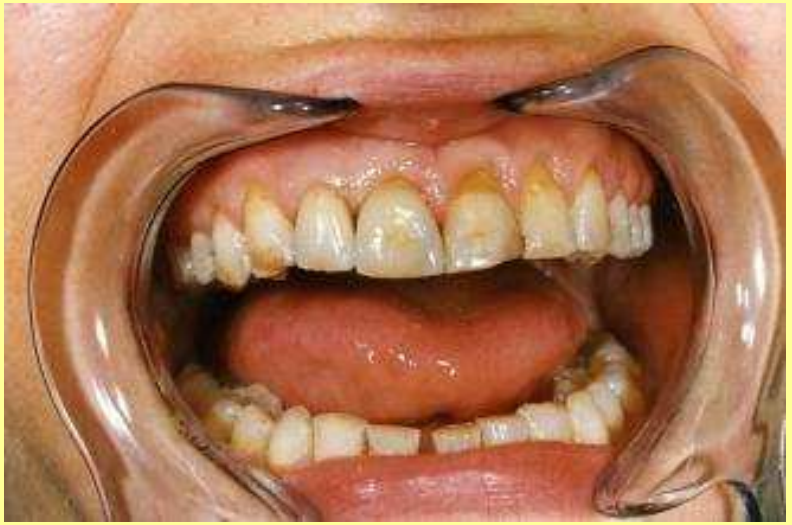
- pseudoallergic reaction
- neurological problems associated with a procaine penicilin injection into the muscle
- embolic toxic reactions possibly due to vascular occlusion by large crystals of the penicillin salts

Hoigné Syndrome

- **symptoms:**
  - ✓ severe agitation
  - ✓ confusion
  - ✓ visual hallucinations
  - ✓ auditory hallucinations
  - ✓ vertigo
  - ✓ sense of fear
  - ✓ sense of panic
  - ✓ seizures
- **treatment:**
  - ✓ steroids iv
  - ✓ sedative drugs

- teeth discoloration after tetracyclines





Organ toxicity of antibiotics

- **Hepatotoxicity** – macrolides, lincosamids, tetracyclines
- **Neurotoxicity** – penicillins
- **Myelotoxicity** – chloramphenicol
- **Nephrotoxicity** – aminoglycosides, vancomycin
- **Ototoxicity** – aminoglycosides, vancomycin

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

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
- with complete repair with prosthetic material whether placed by surgery or by percutaneous technique, up to 6 months after the procedure
- when a residual defects persist at the site of implantation of a prosthetic material or device by cardiac surgery or percutaneous technique

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. 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. single dose 30-60 minutes before procedure

Lack of progress in new antibiotics researches

- Only two completely new antibiotics (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.

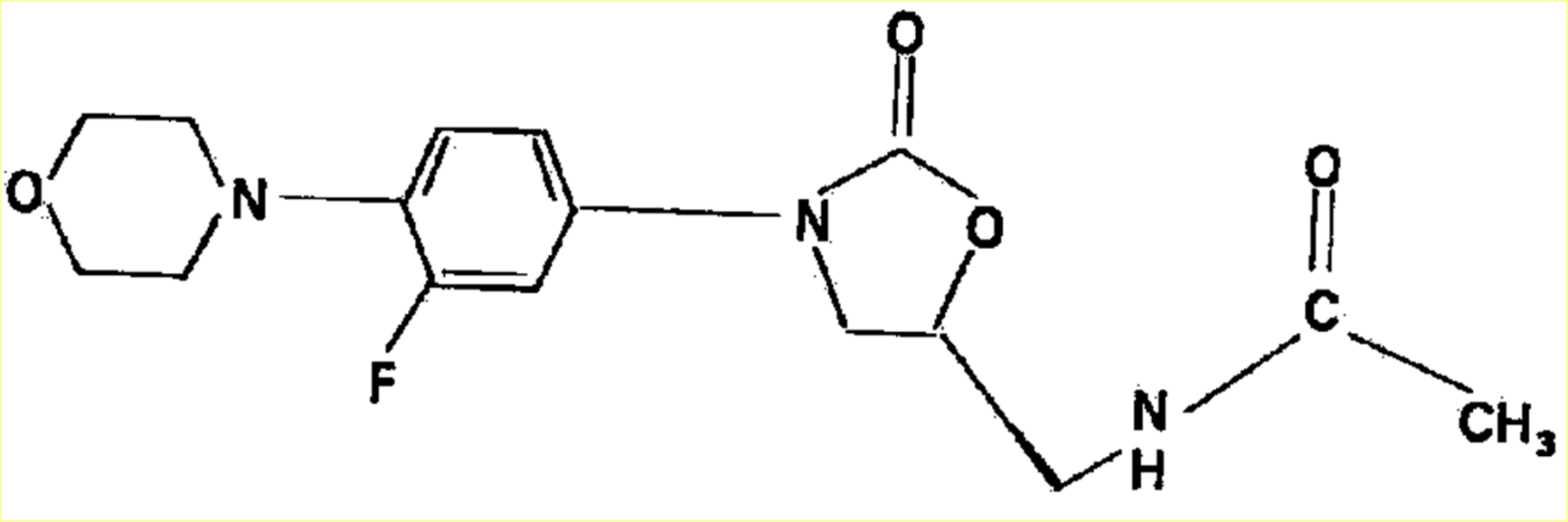
Methicillin resistance S.aureus (MRSA) - PBP2 protein

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 tRNA, mRNA) – <u>destabilisation of tRNA connecting position</u>

LINEZOLID

- lack of cross resistance of inhibiting protein synthesis antibiotics (chloramphenicol, lincosamides, 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.

Daptomycin

- antibiotic of new class of cyclic lipopeptides, registered in 2003
- registered to treatment of cutis and soft tissues infections – pes diabetic
- Endocarditis? Pneumonia - no!
- *in vitro* efficacy dependent on Ca ions

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


THE END