ANTIBIOTIC GROUPS AND THEIR INDICATIONS – PART 1

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- **ANTIBIOTICS**
- **ANTIMICROBIAL AGENTS**
- **CHEMOTHERAPEUTIC AGENTS**

ANTIBIOTICS

- **Natural substances produced by various species of microorganisms**
  - **bacteria**
  - **fungi**
  - **actinomycetes**
- **suppress growth / kill other microorganisms**

ANTIMICROBIAL AGENTS

- **Synthetic analogues**
- **ANTIMICROBIAL AGENTS :**
- includes **synthetic** as well as **naturally** obtained drugs that attenuate microorganisms

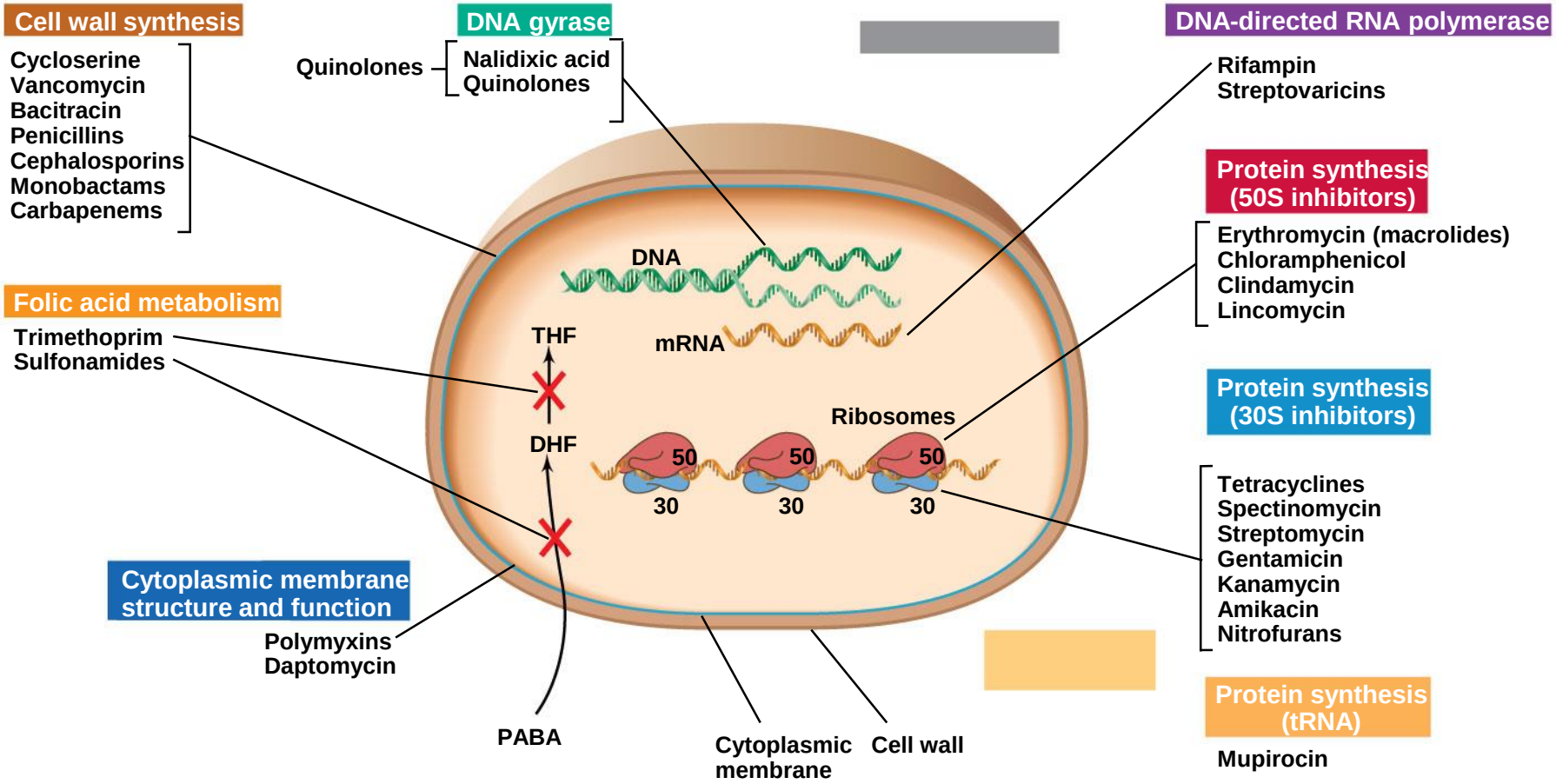
CHEMOTHERAPEUTIC AGENTS

- Drugs in this class differ from all others in that they are
- Designed to inhibit/kill the infecting organism and have **no/minimal effect on the recipient – selective toxicity**

Classification of Antimicrobials

- Inhibit cell wall synthesis
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Monobactams (aztreonam)
  - Vancomycin
- Inhibit protein synthesis
  - Chloramphenicol
  - Tetracyclines
  - Macrolides
  - Clindamycin
  - Streptogramins (quinupristin/dalfopristin)
  - Oxazolidinones (linezolid)
  - Aminoglycosides
- Alter nucleic acid metabolism
  - Rifamycins
  - Quinolones
- Inhibit folate metabolism
  - Trimethoprim
  - Sulfamethoxazole

Mechanismus of Action



Mechanism of Action

- **Agents that inhibit synthesis of bacterial cell walls**

Penicillins & cephalosporins &monobactams &carbapenems

Vancomycin

Fosfomycin

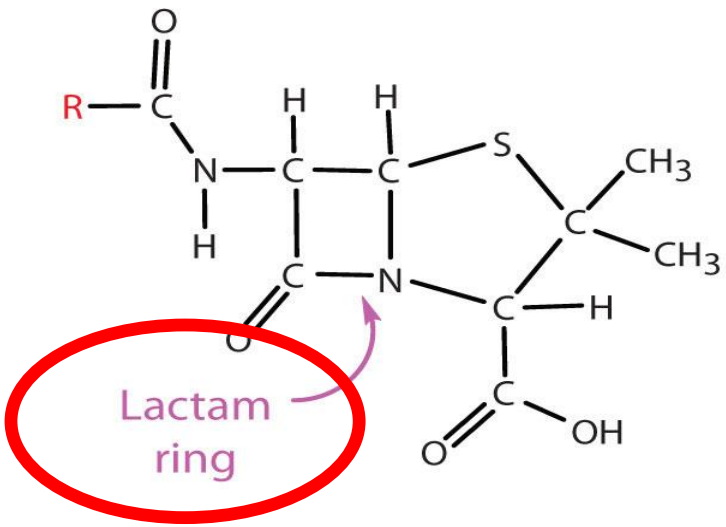
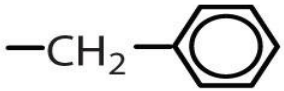
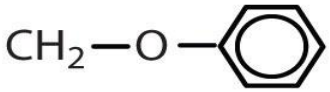
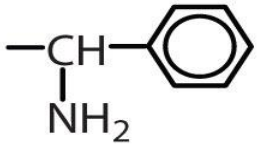
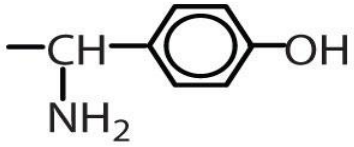
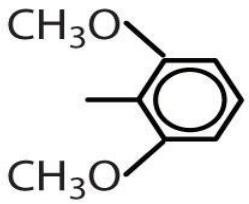
Target –cell wall synthesis

The bacterial cell wall is a cross linked polymer called peptidoglycan which allows a bacteria to maintain its shape despite the internal turgor pressure caused by osmotic pressure differences.

If the peptidoglycan fails to crosslink the cell wall will lose its strength which results in cell lysis.

All β-lactams disrupt the synthesis of the bacterial cell wall by interfering with the transpeptidase which catalyzes the cross linking process.

Penicillins

Penicillin Structure	R Group	Drug Name
		penicillin G
		penicillin V
		ampicillin
		amoxicillin
		methicillin

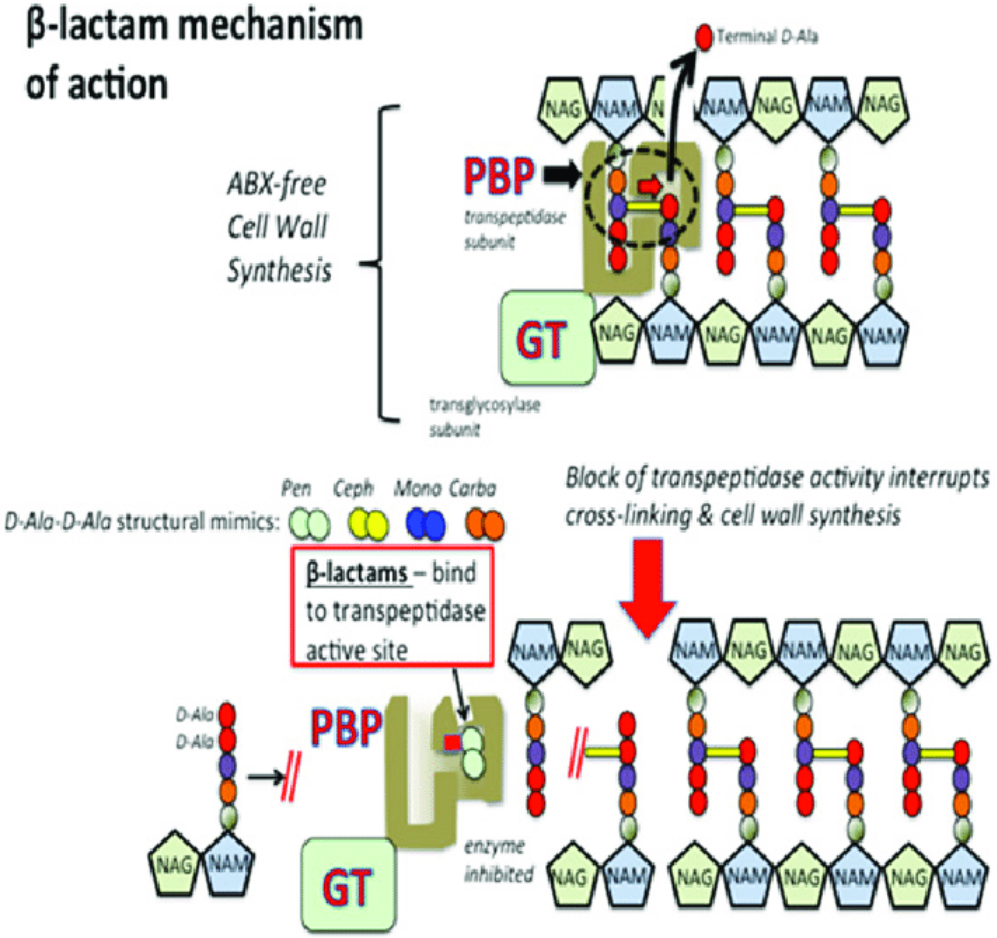
Transpeptidase- PBP

The cross linking reaction is catalyzed by a class of transpeptidases known as penicillin binding proteins

A critical part of the process is the recognition of the D-Ala-D-Ala sequence of the NAMA peptide side chain by the PBP. Interfering with this recognition disrupts the cell wall synthesis.

beta-lactams mimic the structure of the D-Ala-D-Ala link and bind to the active site of PBPs, disrupting the cross-linking process.

Betalactam mechanism of action



Penicillins

- **There are semi-synthetic forms of penicillin.**
  They are created through modifications that can be made in a laboratory.
- **Chemists can create and modify side chains.**
  This produces new forms of penicillin.
- **Natural penicillin has a very narrow spectrum. Chemically modifying penicillin broadens the spectrum.**
- **Semi-synthetic penicillins can be further modified to increase the efficiency of inhibiting bacterial growth**

Narrow – spectrum Penicillins – Clinical Uses

Benzylpenicillin (Penicillin G) is the prototype of a subclass of penicillins.

Clinical uses include therapy of infections caused

by common streptococci, meningococci, gram-positive bacilli, and spirochetes..

Many strains of pneumococci (penicillin-resistant *S. pneumoniae* [PRSP] strains). *Staphylococcus aureus* and *Neisseria gonorrhoeae* are resistant via production of beta-lactamases

Penicillin G remains the drug of choice for syphilis. Activity against enterococci is enhanced by coadministration of aminoglycosides. Penicillin V is an oral drug used mainly in oropharyngeal infections..

BENZYLPENICILLIN: MAIN INDICATIONS

- ***Strep pyogenes* infection (from sore throat to fasciitis and sepsis)**
- **Pneumococcal pneumonia, meningitis**
- **Meningococcal meningitis, sepsis**
- **Infective endocarditis (strep)**
- **Strep group B sepsis**
- **Diphtheria**
- **Syphilis**
- **Leptospirosis…**

Very-narrow-spectrum penicillinase-resistant drugs

This subclass of penicillins includes methicillin, nafcillin, and oxacillin….

They are stable to staphylococcal beta lactamase, penicillinase

Their primary use is in the treatment of known or suspected different types staphylococcal infections.

Methicillin-resistant (MR) staphylococci (*S. aureus* [MRSA] and *S. epidermidis* [MRSE]) are resistant to all penicillins and are often resistant to multiple antimicrobial drugs).

Wider-spectrum penicillinase-susceptible drugs

Ampicillin and amoxicillin—has a wider spectrum of antibacterial activity than penicillin G.

Their clinical uses include indications similar to penicillin G as well as infections resulting from *enterococci, Listeria monocytogenes, Escherichia coli, Proteus mirabilis, Haemophilus influenzae,* and *Moraxella catarrhalis*, although resistant strains occur.

Oral a parenteral forms

When used in combination with inhibitors of beta lactameses (clavulanic acid, sulbactam, tazobactam), their antibacterial activity is often enhanced. In enterococcal and listerial infections, ampicillin is synergistic with aminoglycosides.

Ureidopenicillin – broad spectrum of activity

Piperacillin

These drugs have broad spectrum activity against several gram-negative rods, including *Pseudomonas, Enterobacter,* and in some cases *Klebsiella species*, also streptococci, enterococci, anaerobes

Piperacillin is susceptible to certain beta lactamases and are often used in combination with penicillinase inhibitors (eg, tazobactam and clavulanic acid) to enhance their activity.

It is used for the treatment of serious nosocomial infections (pneumonia, sepsis, complicated urinary tract infections, wound infections, abdominal infections) ...)

Penicillins – toxicity, side effects

Allergy—Allergic reactions include urticaria, severe pruritus, fever, joint swelling, hemolytic anemia, nephritis, and anaphylaxis.

Complete cross-allergenicity between different penicillins should be assumed.

2. Gastrointestinal disturbances— Nausea and diarrhea may occur with oral penicillins, especially with ampicillin.

Gastrointestinal upsets may be caused by direct irritation or by overgrowth of gram-positive organisms or yeasts.

Cephalosporins

The cephalosporins are β-lactam antibiotics that are closely related both structurally and functionally to the penicillins.

Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to 7-aminocephalosporanic acid.

Cephalosporins have the same mode of action as penicillins, and they are affected by the same resistance mechanisms.

However, they tend to be more resistant/stable than the penicillins to certain β-lactamases.

Mechanisms of Action and Resistance

Cephalosporins bind to PBPs on bacterial cell membranes to inhibit bacterial cell wall synthesis by mechanisms similar to those of the penicillins. Cephalosporins are bactericidal against susceptible organisms.

Cephalosporins less susceptible to penicillinases produced by staphylococci, but many bacteria are resistant through the production of other betalactamases that can inactivate cephalosporins.

Resistance can also result from decreases in membrane permeability to cephalosporins and from changes in PBPs.

Methicillin-resistant staphylococci (MRSA) are also resistant to cephalosporins.

Classification of cephalosporins

- **1-4. generation**
- **Division into generations determines :**

- spectrum of antimicrobial activity

- stability to the effect of beta lactamases

- **The higher the generation - the wider the spectrum of activity and the higher the stability to beta lactameses**

First generation

First-generation drugs—cefazolin, cefalotin (parenteral) and cephalexin (oral) are examples of this subgroup.

They are active against gram-positive cocci, including staphylococci and common streptococci. Many strains of *E coli* and *K pneumoniae* are also sensitive.

Clinical uses include treatment of infections caused by these organisms and surgical prophylaxis in selected conditions.

Second generation

Cefuroxim, cefprozil

Have slightly less activity against gram-positive organisms than the first-generation drugs but have an extended gram-negative coverage.

Examples of clinical uses *include infections* sinus,

ear, and respiratory infections caused by *H influenzae or M catarrhalis*

Urinary tract infections caused by *E. coli, Proteus spp...*

.. surgical prophylaxis in selected conditions

Third-generation

Ceftazidime, cefotaxime, ceftraixone

include increased activity against gram-negative organisms resistant to other beta-lactam drugs and ability to penetrate the blood-brain barrier

Most are active against *Providencia, Serratia marcescens..*, and beta-lactamase producing strains of *H. influenzae and Neisseria*

Ceftriaxone and cefotaxime are currently the

most active cephalosporins against penicillin-resistant pneumococci (PRSP strains)

- **Also have activity against *Pseudomonas* (cefoperazone, ceftazidime)**
- **Ceftriaxone (parenteral) and cefixime (oral), currently drugs of choice in gonorrhea.**

Fourth-generation

Cefepime is more *resistant to beta-lactamases* produced by gram-negative organisms, including

***Enterobacter, Haemophilus, Neisseria*, and some penicillin resistant pneumococci…**

Cefepime combines the gram-positive activity of first-generation agents with the wider gram-negative spectrum of third-generation cephalosporins.

CLINICAL USE OF BROAD SPECTRUM CEPHALOSPORINES (2-4. gen.)

- **Respiratory tract infections**
- **Urinary tract infections**
- **Neuroinfection**
- **Sepsis…**
  - **most often of hospital origin**
  - **…administered intravenously**

- **Resistance is most often mediated by beta lactamases with an extended spectrum of activity (ESBL, AmpC ...)**

Fifth generation ?

Ceftaroline has activity in infections caused by methicillin-resistant staphylococci

The only registered beta lactam antibiotic with an effect on MRSA

The spectrum of action corresponds to the 3rd generation

Side effects, toxicity

Allergy—Cephalosporins cause a range of allergic reactions from skin rashes to anaphylactic shock. These reactions occur *less frequently with cephalosporins than with penicillins*.

Complete cross-hypersensitivity between different cephalosporins should be assumed. Cross-reactivity between penicillins and cephalosporins

is incomplete (5–10%)

They may increase the nephrotoxicity of aminoglycosides when the two are administered together.

OTHER BETA-LACTAM DRUGS -

Aztreonam is a monobactam that is resistant to beta-lactamases produced by certain gram-negative rods, including *Pseudomonas aeruginosa*, *Serratia, Klebsiella…*

The drug has no activity against gram positive bacteria or anaerobes.

Aztreonam is administered intravenously

Carbapenems - Imipenem, Meropenem and Ertapenem

- **Chemically different from penicillins but retaining the beta-lactam ring structure**
- **Reserve antibiotics - Now used to treat gram negative infections due to so called ESBL producing organisms e.g., *E coli, Klebsiella…***
- **They are administered intravenously only**
- **They have wide activity against gram-positive cocci (including some penicillin-resistant pneumococci), gram-negative rods, and anaerobes.**
- **For pseudomonal infections, they are often used in combination with an aminoglycoside.**

Beta-Lactamase Inhibitors

. Clavulanic acid, sulbactam, and tazobactam are used in fixed combinations with certain hydrolyzable penicillins.

- amoxicilin/clavulanic acid, ampicilin/sulbactam, piperacilin/tazobactam

They are most active against plasmid-encoded beta lactamases such as those produced by *gonococci, staphylococci, E coli*, and *H influenzae..*

- **They are not good inhibitors of inducible chromosomal beta-lactamases (AmpC..) formed by *Enterobacter, Pseudomonas, and Serratia***
- **Inhibition of ESBL enzymes is not reliable**

BETA LACTAMS - MECHANISMS OF ACTION

Beta-lactam antibiotics are bactericidal drugs. They act to inhibit cell wall synthesis by the following steps:

(1) Binding of the drug to specific enzymes (penicillin-binding proteins [PBPs]) located in the bacterial cytoplasmic membrane;

(2) inhibition of the transpeptidation reaction that cross-links the linear peptidoglycan chain constituents of the cell wall; and

(3) activation of autolytic enzymes that cause lesions in the bacterial cell wall.

BETA LACTAMS - MECHANISM OF RESISTANCE

- **The formation of beta-lactamases**

  by most staphylococci and many gram-negative organisms.
- **Inhibitors of these bacterial enzymes (eg, clavulanic acid, sulbactam, tazobactam) are often used in combination with penicillins to prevent their inactivation.**
- **Structural change in target PBPs is responsible for methicillin resistance in staphylococci and for resistance to penicillin G in pneumococci (eg, PRSP, penicillin resistant *Streptococcus pneumoniae*) and enterococci.**
- **In some gram-negative rods (eg, *Pseudomonas aeruginosa*), changes in the porin structures in the outer cell wall membrane may contribute to resistance by impeding access of penicillins to PBPs., another option is efflux**

CLASSIFICATION OF BETA LACTAMASES

There have been a number of schemes for the classification of beta lactamases. The most often used scheme

Ambler classification [Molecular classification]

Groups β-lactamases into four major classes (A to D) based on genotypic relationships. Class A, C, and D enzymes which utilize serine for β-lactam hydrolysis and class B metalloenzymes which require divalent zinc ions for substrate hydrolysis.

EXTENDED-SPECTRUM B-LACTAMASES

- **Extended-spectrum ß-Lactamases (ESBLs) are extremely broad spectrum ß-Lactamase enzymes found in a variety of Enterobacteriaceae.**
- **The ESBLs are mutant forms of TEM-1, TEM-2 and SHV-1 enzymes. The ESBLs often differ from the original enzymes by only one to a few changes in their amino acid sequences.**
- **ESBLs are enzymes that mediate resistance to extended-spectrum (third generation) cephalosporins (e.g., ceftazidime, cefotaxime, and ceftriaxone) and monobactams (e.g., aztreonam) but do not affect carbapenems (e.g., meropenem or imipenem).**
- **ESBLs are generally encoded by plasmid-borne genes, characteristically hydrolyse oximino-cephalosporins (e.g. ceftriaxone), partly inhibited by clavulanic acid and sulbactam, The majority of ESBLs (SHV and TEM derivatives) contain a serine at the active site, and belong to Ambler's molecular class A**
- **The OXA type ESBLs (Amber class D) have more commonly been identified in *P. aeruginosa* and are another growing family of ESBLs.**

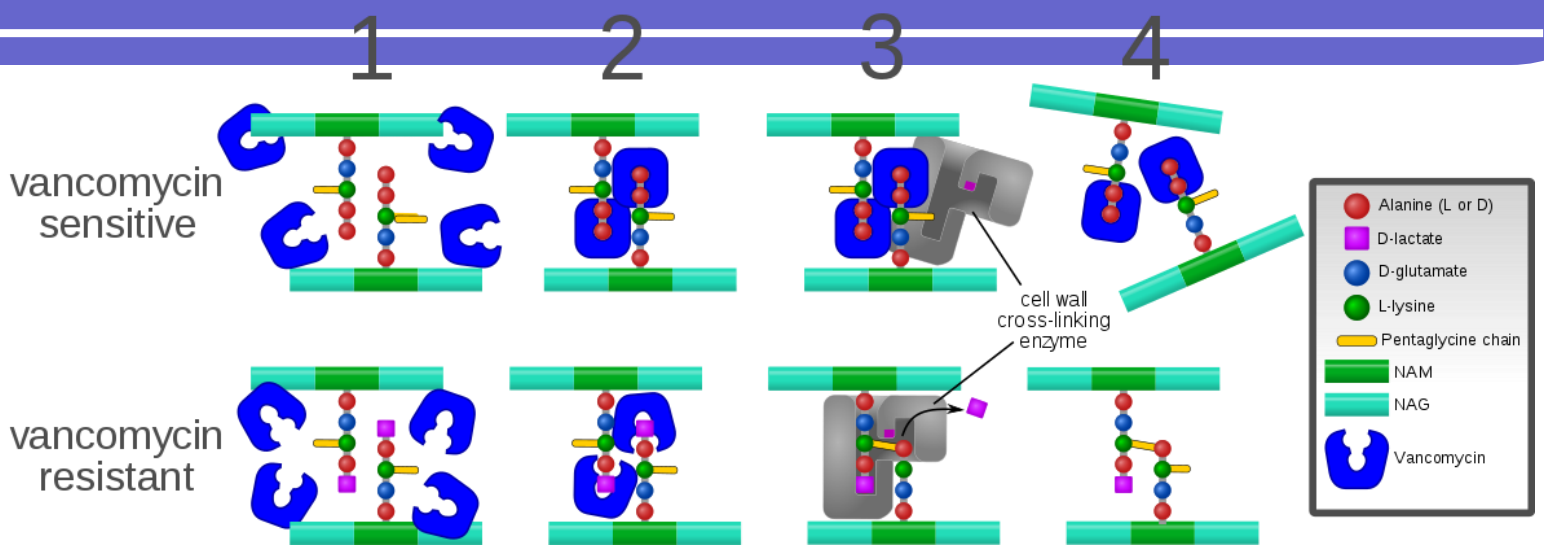
OTHER CELL WALL OR MEMBRANE-ACTIVE AGENTS: VANCOMYCIN, Teicoplanin

Vancomycin is a bactericidal glycoprotein that binds to the *d-Ala-d-Ala* terminal of the nascent peptidoglycan pentapeptide side chain and inhibits transglycosylation.

This action prevents elongation of the peptidoglycan chain and interferes with crosslinking.

Another less used glycoprotein is teicoplanin

•Resistance in strains of enterocci (vancomycin-resistant enterococci [VRE]) and staphylococci (vancomycin-resistant S aureus [VRSA]) involves a decreased affinity of vancomycin for the binding site



Mechanism of vancomycin action and resistance: This diagram shows only one of two ways vancomycin acts against bacteria (inhibition of cell wall cross-linking) and only one of many ways that bacteria can become resistant to it.
1.Vancomycin is added to the bacterial environment while it is trying to synthesize new cell wall. Here, the cell wall strands have been synthesized, but not yet cross-linked.
2.Vancomycin recognizes and binds to the two D-ala residues on the end of the peptide chains. However, in resistant bacteria, the last D-ala residue has been replaced by a D-lactate, so vancomycin cannot bind.
3.In resistant bacteria, cross-links are successfully formed. However, in the nonresistant bacteria, the vancomycin bound to the peptide chains prevents them from interacting properly with the cell wall cross-linking enzyme.
4.In the resistant bacteria, stable cross-links are formed. In the sensitive bacteria, cross-links cannot be formed and the cell wall falls apart.

VANCOMYCIN- CLINICAL USE

Vancomycin has a narrow spectrum of activity and is used for serious infections caused by drug-resistant gram-positive organisms (staphylococci, streptococci..),

including methicillin-resistant staphylococci (MRSA) – sepsis, infective endocarditis, serious wound infection…It is used intravenously

Vancomycin is drug of chice for oral treatment (it is not absorbed in the intestine) **of intestinal infections caused by *Clostridium difficile* – (CDI – Clostridium difficile Infection)**

SIDE EFFECTS, TOXICITY

- **Toxic effects of vancomycin include phlebitis, ototoxicity, and nephrotoxicity.**
- **Rapid intravenous infusion may cause diffuse flushing ("red man syndrome") from histamine release**
- **Treatment can be monitored by measuring serum levels to prevent toxic high levels of vancomycin**

Fosfomycin

Fosfomycin is an antimetabolite inhibitor of cytosolic enolpyruvate transferase. This action prevents the formation of N-acetylmuramic acid, an essential precursor molecule for peptidoglycan chain formation

Spectrum activity : enterobacteria, staphylococci, streptococci, enterococci

Fosfomycin is *excreted by the kidney*, with urinary levels exceeding the minimal inhibitory concentrations (MICs) for many urinary tract pathogens

AMINOGLYCOSIDES

- **Agents that bind to 30S ribosomal subunit & alter protein synthesis, which eventually leads to cell death**

Aminoglycosides

Bactericidal effect

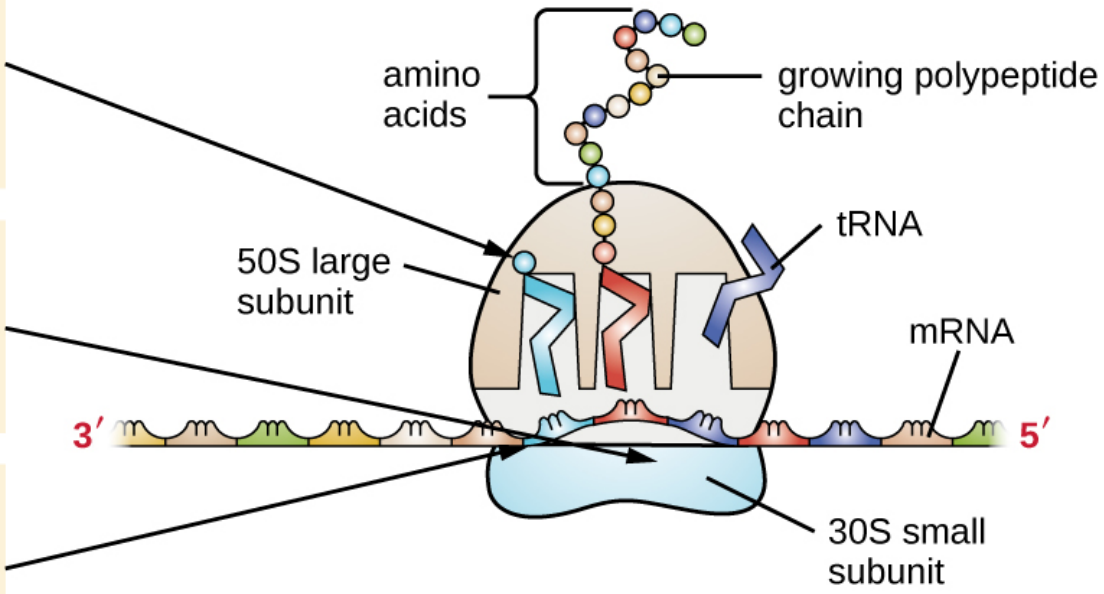
Protein synthesis inhibitors

Major classes of protein synthesis–inhibiting antibacterials

Chloramphenicol, macrolides, and lincosamides
- Bind to the 50S ribosomal subunit
- Prevent peptide bond formation
- Stop protein synthesis

Aminoglycosides
- Bind to the 30S ribosomal subunit
- Impair proofreading, resulting in production of faulty proteins

Tetracyclines
- Bind to the 30S ribosomal subunit
- Block the binding of tRNAs, thereby inhibiting protein synthesis



AMINOGLYCOSIDES – SPECTRUM ACITIVITY

- **Gentamicin, amikacin (tobramycin, streptomycin)**

- **Bacericidal, concentration dependent higher the concentration greater the rate at which bacteria are killed**
- **Mainly active against gram negative bacteria, *E. coli, Pseud. aeruginosa, Protues, Klebsiella, Eterobacter, Citrobacter..***
  partially staphylococci
- **Aminoglycosides and beta-lactams are synergistic and nearly always used in combination with a beta-lactam to extend coverage to possibly gram-positive microbes**

  - **Not effective against streptoccoci, and anaerobes**

Aminoglycosides – clinical use

- **Used to treat serious infection due to aerobic gram negative bacilli , because of serious toxicities it is replaced by safer drugs (if it is possible)**
- **used in most gram-negative aerobic bacillary infection, septicaemia, pelvic and abdominal sepsis, urosepsis**
- **Bacterial endocarditis**
- **Other infections: tuberculosis (streptomycin)**

POST ANTIBIOTIC EFFECT

- **They also exert a long & concentration dependent post antibiotic effect that is, residual bactericidal activity persisting after the serum concentration has fallen below the minimum inhibitory concentration**
- **Duration of this effect is concentration dependent**
- **They are applied once a day**

SIDE EFFECTS, TOXICITY

- **Ototoxicity (vestibular and cochlear)related to high peak plasma level and duration of treatment : deafness may be irreversible**
- **Nephrotoxicity : mild, reversible**
- **Neuromuscular blocade/paralysis**
- **Treatment can be monitored by measuring serum levels to prevent toxic high levels of gentamicin or amikacin**

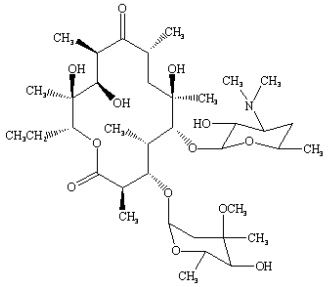
PROTEOSYNTHESIS INHIBITORS, (Bacteriostatic)

- **Agents that affect the function of 30S or 50S ribosomal subunits to cause a reversible inhibition of protein synthesis**
- Bacteriostatic drugs

  Chloramphenicol, Tetracyclines, Macrolides, Clindamycin

MACROLIDES

- **Basic structure macrocyclic lactone ring 14-, 15-, 16-membered**
- **The first member : eytromycin**



- **Modern derivatives : roxithromycin, clarithromycin, azithromycin…**
- **Broad spectrum activity : streptococci, staphylococci, pathogenic neisseria, chlamydia, mycoplasma, legionella, campylobacter…**
- **Possibility Intracellular penetration (chlamydia, legionella..)**

MACROLIDES – CLINICAL USE

- **Treatment of respiratory infections**
- **Skin and soft tissue infections**
- **Treatment of mycoplasma infection**
- **Chlamydial infections**
- **Legionellosis**
- **Treatment of *Helicobacter pylori* infections**
- **Treatment of campylobacter infections**
- **An alternative in case of penicillin allergy**

- **Oral and parenteral forms**

SIDE EFFECTS, TOXICITY, RESISTANCE

Hepatotoxicity

Drug interactions

Indigestion, nausea (erytromycin)

- **Resistance, alteration of 23S rRNA by adenine methylation. This confers resistance to type B macrolides, lincosamides and streptogramins and is referred to as the MLS_B phenotype. It is encoded by the erm (erythromycin ribosomal methylase) genes; : alteration of 23S rRNA by adenine methylation. This confers resistance to type macrolides, lincosamides and streptogramins and is referred to as the MLS_B phenotype. It is encoded by the erm (erythromycin ribosomal methylase) genes**

LINCOSAMIDES

- **Lincomycin and clindamycin**
- **Different structure, similar mechanism of action as macrolides**
- **Spectrum of activity : staphylococii, streptococii, anaerobes, *Gardnerella vaginalis*…**

CLINICAL USE

- **Infections in orthopedics and dentistry (high concentration in bone tissue)**
- **Intra-abdominal infections (in combination)**
- **Gynecological infections**
- **Abscessive infections (lungs, abdomen ..)**
- **Toxoplasmosis (pregnant)**

SIDE EFFECTS, RESISTANCE

- **Minimal toxicity**
- **For the first time, treatment-related *Cl.difficile* infection (CDI) has been demonstrated**
- **Resistance : often crossed with macrolides- MLS_B (macrolides, lincosamides, streptogramins- change of site configuration), streptococci, staphylococci, *Bacteroides fragilis* ..**