

# Antibiotics

destroy structures

- present in bacteria
- not present in host

## Antiseptics

Topical (e.g. skin)

- e.g. iodine or 70% alcohol
- “reduce” bacterial load

## Disinfection

Liquids that kill bacteria

- e.g. phenol based
- too toxic for skin surfaces

# Antibacterial chemotherapy

- Medications used to treat bacterial infections
- If bacteria multiply faster than the body's defenses can destroy them, *infectious disease develops with inflammatory* signs, e.g., wound infection or urinary tract infection.
- Ideally, before beginning antibiotic therapy, the suspected areas of infection should be cultured to identify the causative organism and potential antibiotic susceptibilities.

# Common Bacteria by Site of Infection

## Mouth

*Peptococcus*

*Peptostreptococcus*

*Actinomyces*

## Skin/Soft Tissue

*S. aureus*

*S. pyogenes*

*S. epidermidis*

## Bone and Joint

*S. aureus*

*S. epidermidis*

*Streptococci*

*N. gonorrhoeae*

*Gram-negative rods*

## Abdomen

*E. coli, Proteus*

*Klebsiella*

*Enterococcus*

*Bacteroides sp.*

## Urinary Tract

*E. coli, Proteus*

*Klebsiella*

*Enterococcus*

*Staph saprophyticus*

## Upper Respiratory

*S. pneumoniae*

*H. influenzae*

*M. catarrhalis*

*S. pyogenes*

## Lower Respiratory

### Community

*S. pneumoniae*

*H. influenzae*

*K. pneumoniae*

*Legionella pneumophila*

*Mycoplasma, Chlamydia*

## Lower Respiratory

### Hospital

*K. pneumoniae*

*P. aeruginosa*

*Enterobacter sp.*

*Serratia sp.*

*S. aureus*

## Meningitis

*S. pneumoniae*

*N. meningitidis*

*H. influenza*

*Group B Strep*

*E. coli*

# **Antibacterial chemotherapy**

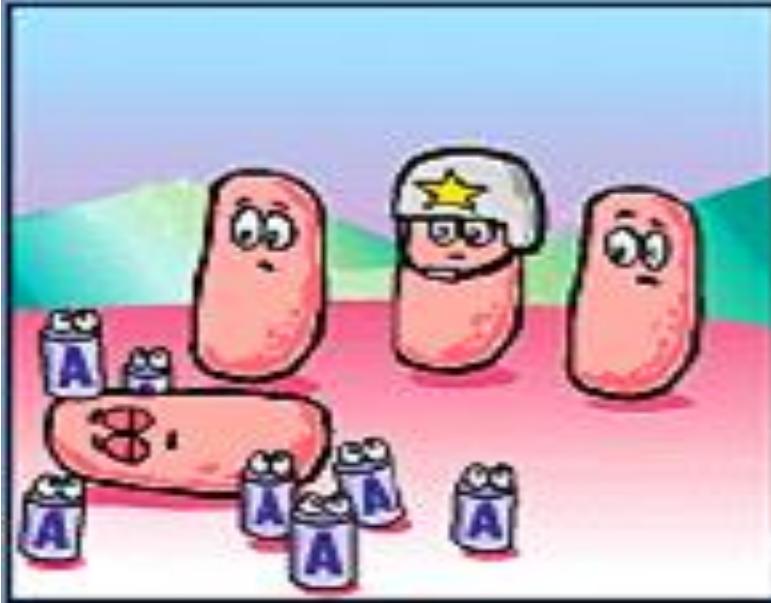
- Antibiotic also can be describe as:
  - a. narrow-spectrum that act only on a single or limited group of microorganism.
  - B. broad- spectrum : antibiotics that are effective against gram-positive organisms and also against a significant number of gram-negative bacteria.
  - C. Extended-spectrum: that effect wide variety of microbial species. However, this can be severely alter the nature of the normal bacterial flora (GI), and precipitate superinfection.

# Superinfection

- When administration of antibiotics kills off the normal flora, pathogenic drug-resistant organisms can increase due to the absence of competition.
- This is considered a superinfection (i.e., an infection on top of another infection).
- For example, administration of antibiotics can lead to the overgrowth of the gastrointestinal pathogen *Clostridium difficile*, which is resistant to most antibiotics.
- *C. difficile* can cause diarrhea and life-threatening bowel inflammation.

# Superinfection

- Another example is the administration of broad-spectrum antibacterial drugs can select for the overgrowth of fungi, most commonly yeasts of the genus *Candida*.
- So, the most narrow-spectrum agents appropriate to the infection should be administered .



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2



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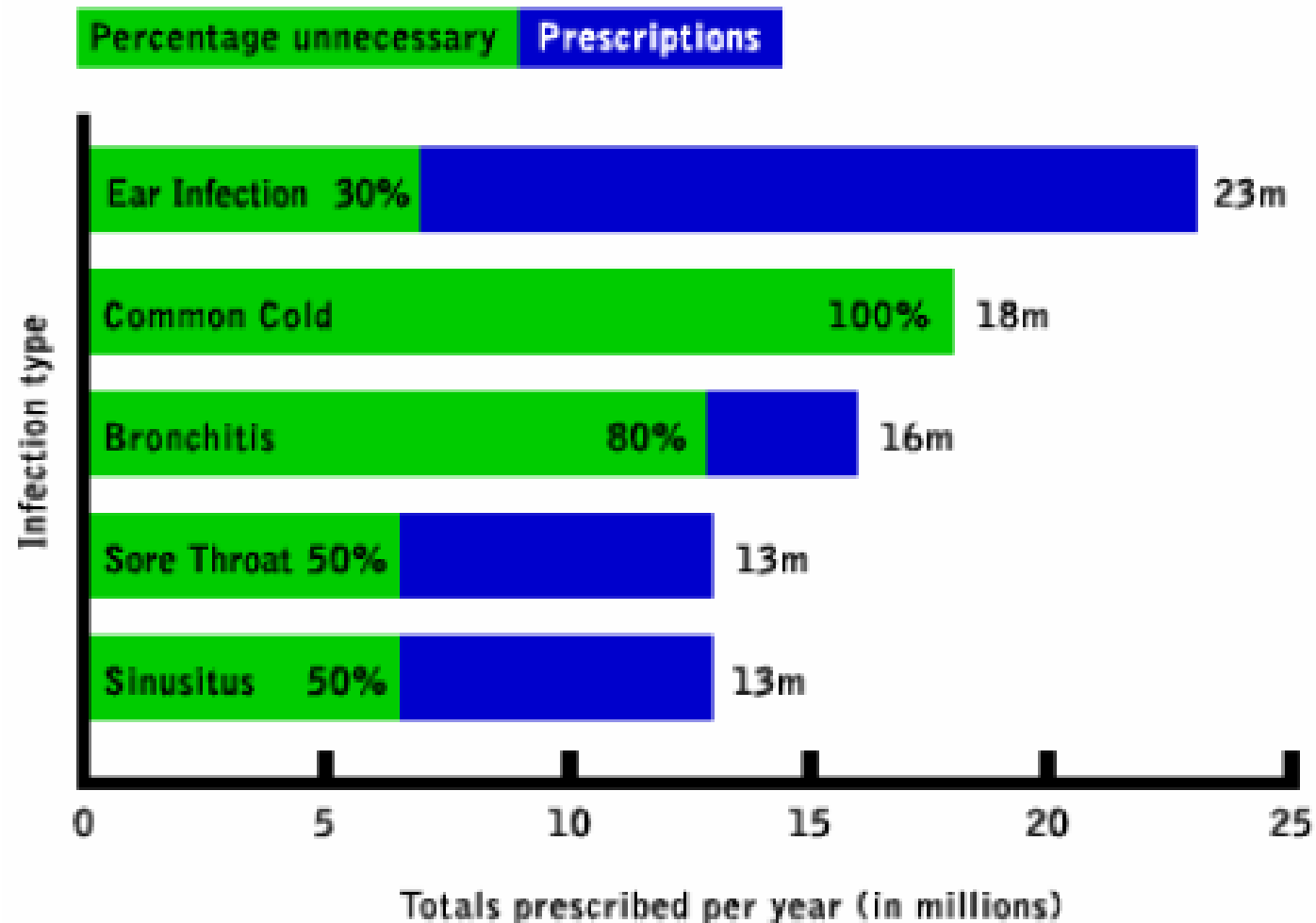
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# Antibiotic Misuse

- **Taking antibiotics when they are not needed:**
  - for viral infections
- **When needed, taking antibiotics incorrectly:**
  - stopping the medicine when you feel better - not finishing the prescription
  - saving antibiotics for a future illness
  - sharing or using someone else's medicine



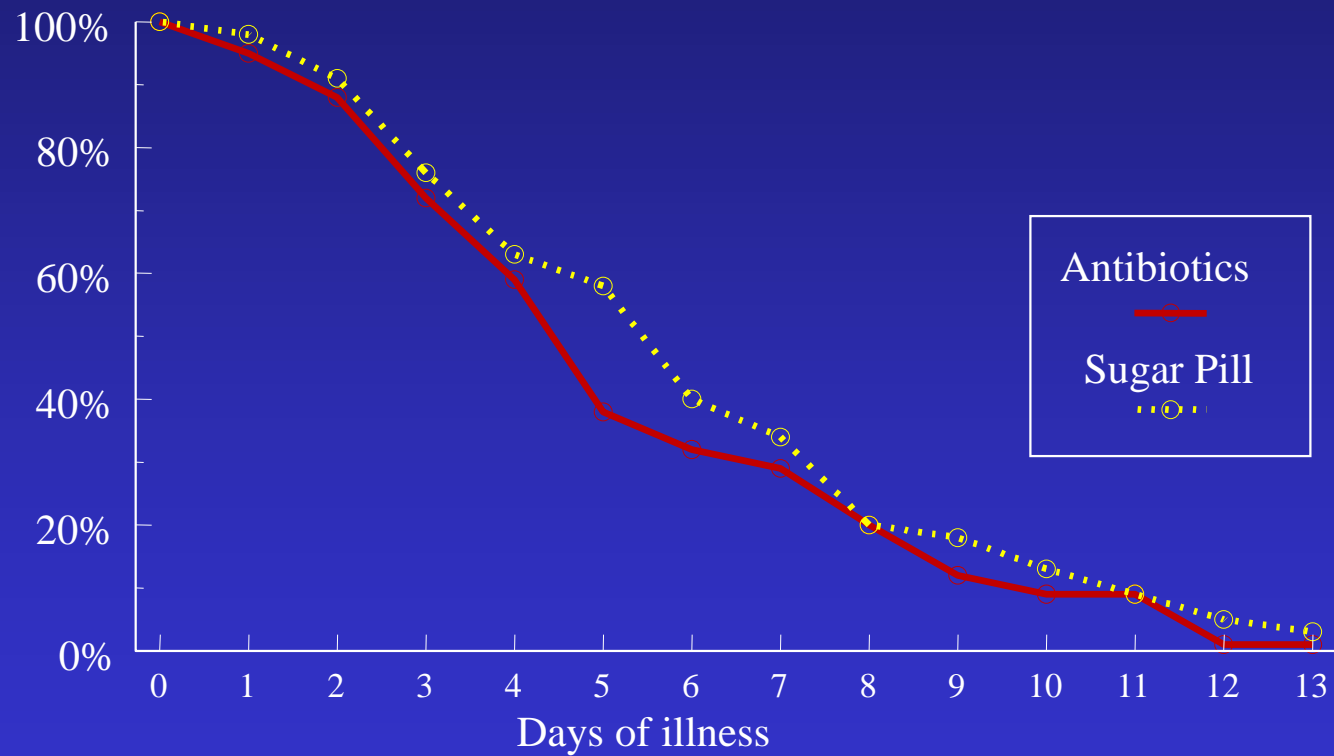
# Unnecessary Antibiotic Prescriptions



More than 50 million unnecessary antibiotic prescriptions are written each year in the United States for patients outside of hospitals, according to the Centers for Disease Control and Prevention

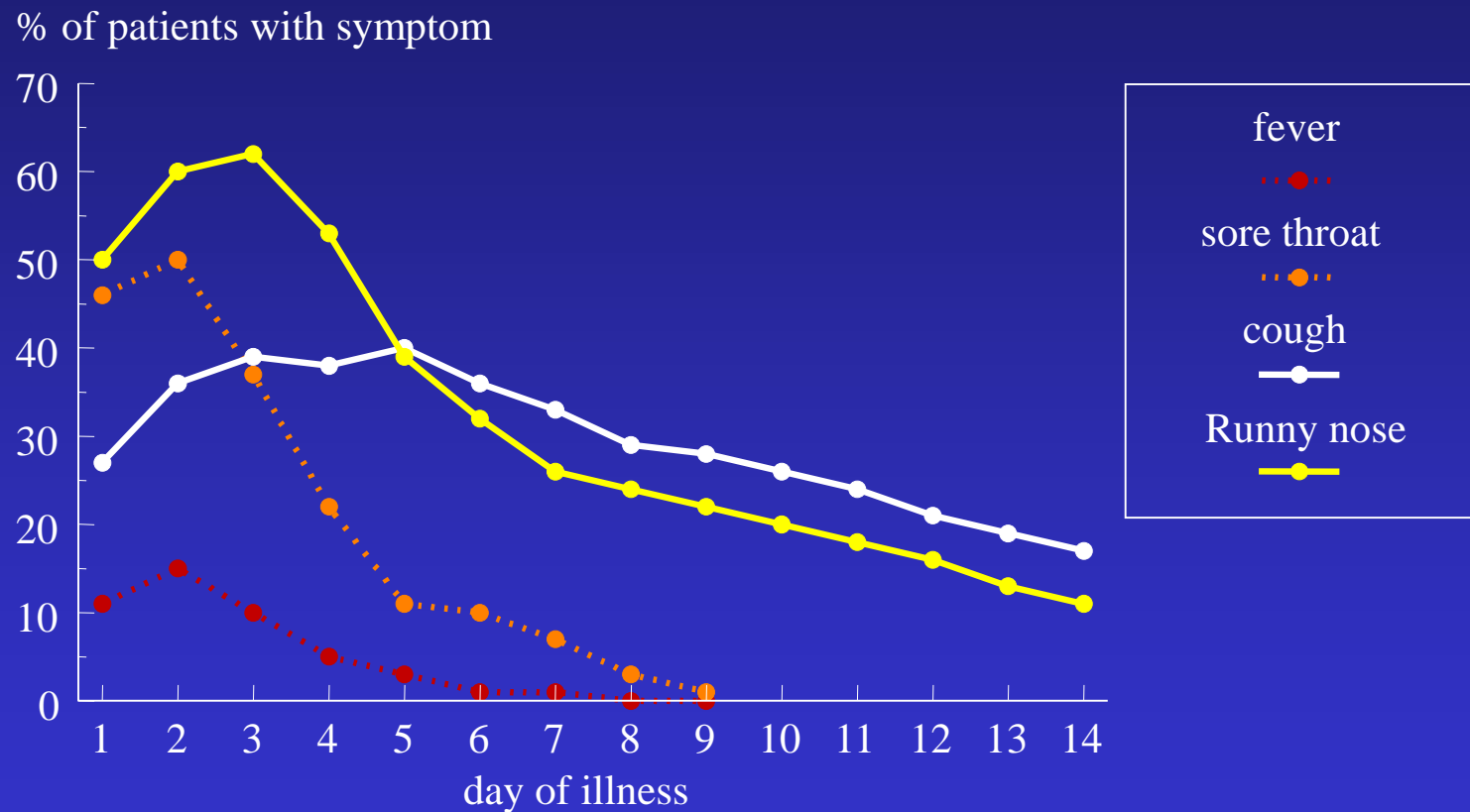
# The Green Mucus Myth

Patients recording yellow sputum



Stott BMJ 1976;2:556

# Be Realistic: It Takes Time to Get Over a Virus!



# **Why is Antibiotic Misuse a Problem?**

- (1) Antibiotics become less effective and may not work the next time you use them.**
- (2) Improper use of antibiotics leads to more antibiotic resistant bacteria.**
- (3) Antibiotic resistant bacteria can be spread throughout the community and from person to person.**

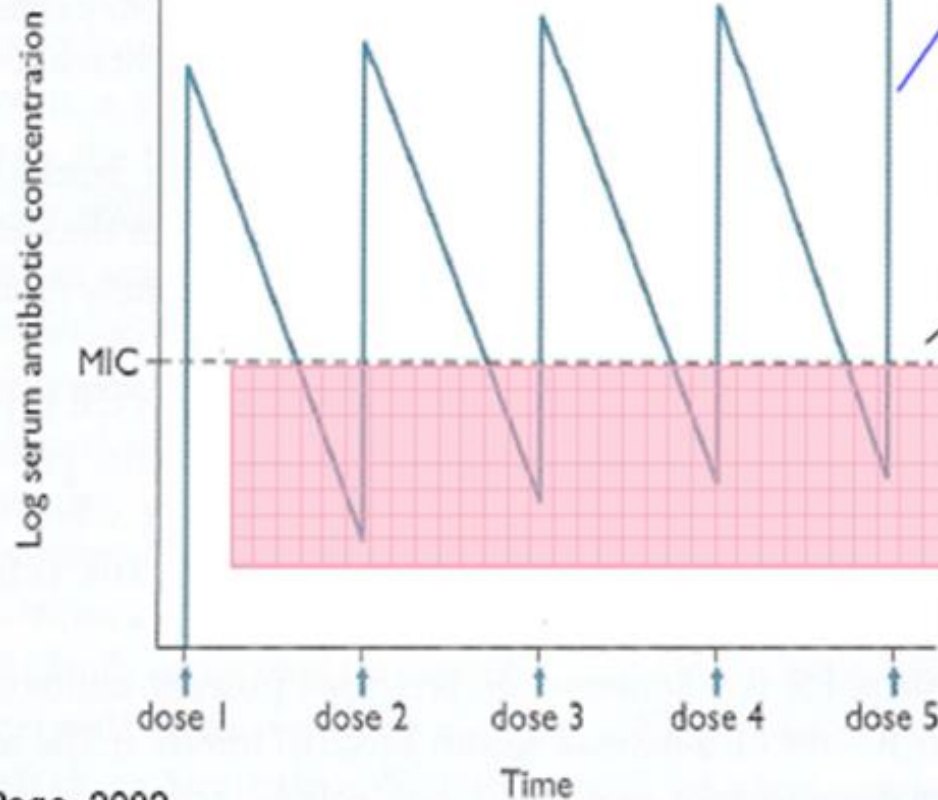
# Therapeutics: Keeping above the MIC

Successive doses of drug

Antibiotic concentration in serum

MIC: Minimal Inhibitory Concentration

Antibiotic level has fallen





# Therapies

- **Prophylaxis**
- **Empirical**
- **Definite therapy**
- **Post-treatment suppression therapy.**

# Bacterial resistance mechanisms

- The spontaneous rate of mutation in bacteria is very low; about 1 in 10 million cells per division will be a mutant.
- The clinical difficulty arises when the infecting bacteria are already drug resistant.
- The four main mechanisms of resistance include:
  - A. Production of an enzyme that inactivates the drug
  - B. Mutations in the target macromolecule (Receptors)
  - C. Induction of mechanisms to reduce accumulation of the drug
  - D. Multiple drug resistance involving all these mechanisms



# **Antibacterial chemotherapy**

- **Main Molecular Targets**

- A. External integrity of the bacterial cell**

- 1. Cell wall synthesis (Penicillins, Cephalosporins.....)**

- B. Protein Synthesis (Tetracyclines, Aminoglycosides, Macrolides)**

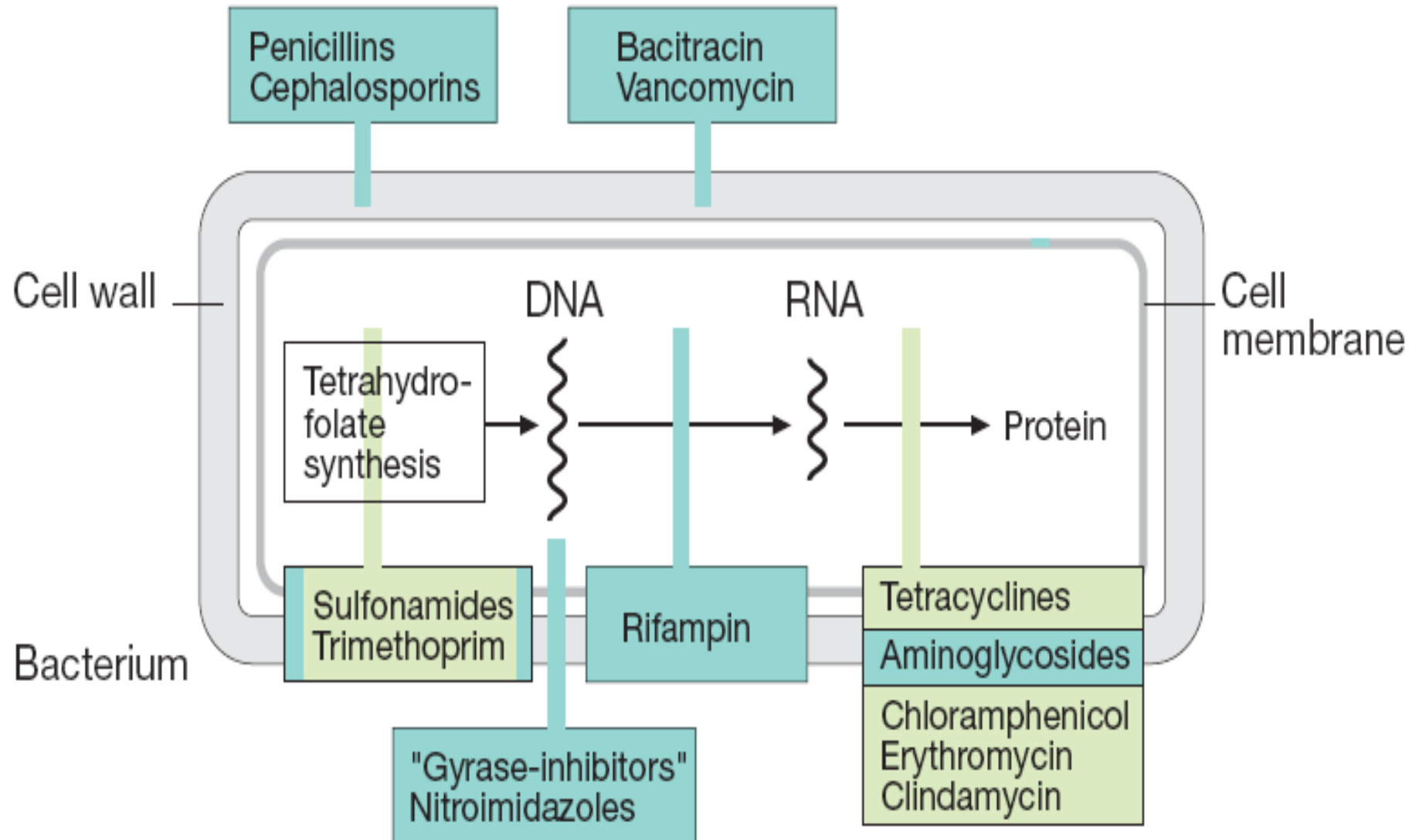
- C. Perturbation of nucleic acid synthesis**

- 1. Inhibition of the synthesis and function of folic acid (Sulphonamides, Trimethoprim )**

- 2. Inhibition of DNA gyrase (Fluoroquinolones, Nalidixic acid)**

- 3. Inhibition of RNA polymerase (Rifampicin)**

# Main Molecular Targets



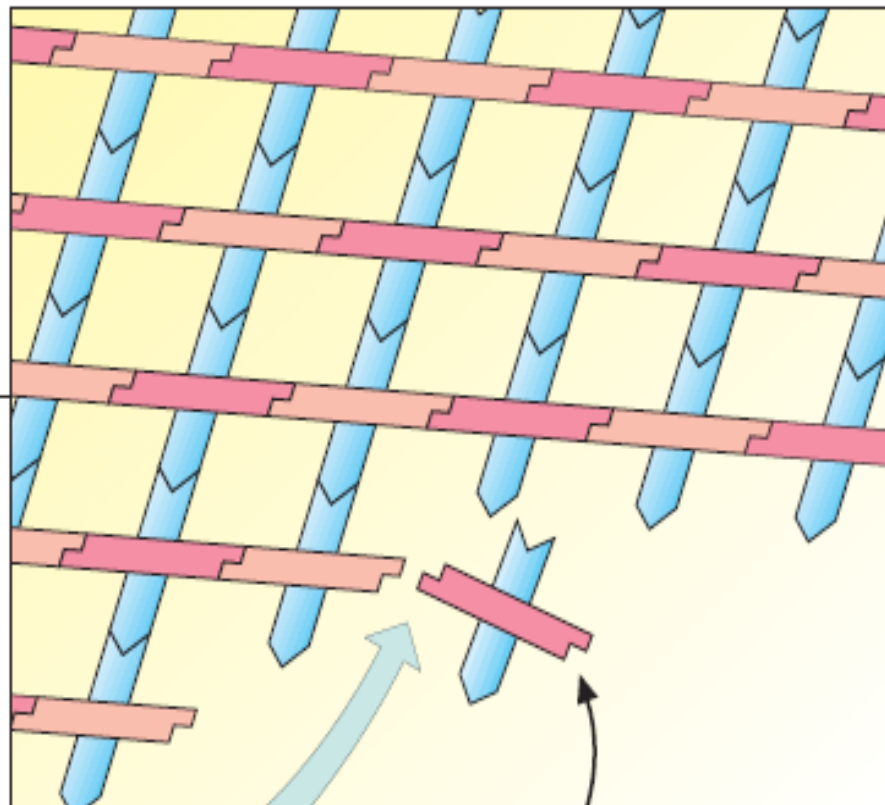
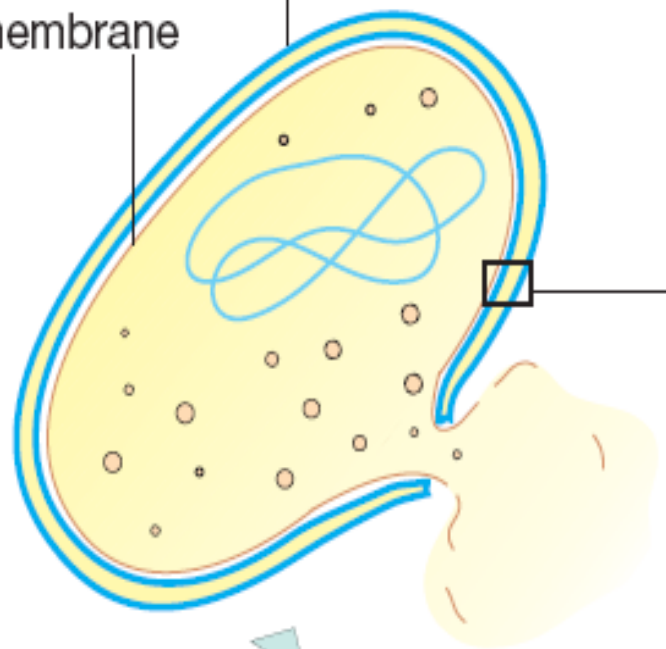
# **Antibiotic brands**

- **50 penicillins**
- **71 cephalosporins**
- **12 tetracyclines**
- **8 aminoglycosides**
- **1 monobactam**
- **3 carbapenems**
- **9 macrolides**
- **3 dihydrofolate reductase inhibitors**
- **1 oxazolidinone**
- **30 quinolones**

# Cell wall inhibitors

- These agents interfere with synthesis of the bacterial cell wall (mammalian cells do not have it).
- To be maximally effective, cell wall inhibitors require actively proliferating (multiplying) microorganism.
- The cell wall inhibitors include :  
  
Penicillins, Cephalosporins,, Monobactams, Carbapenems,  
  
and Vancomycin. ....

Cell wall  
Cell membrane



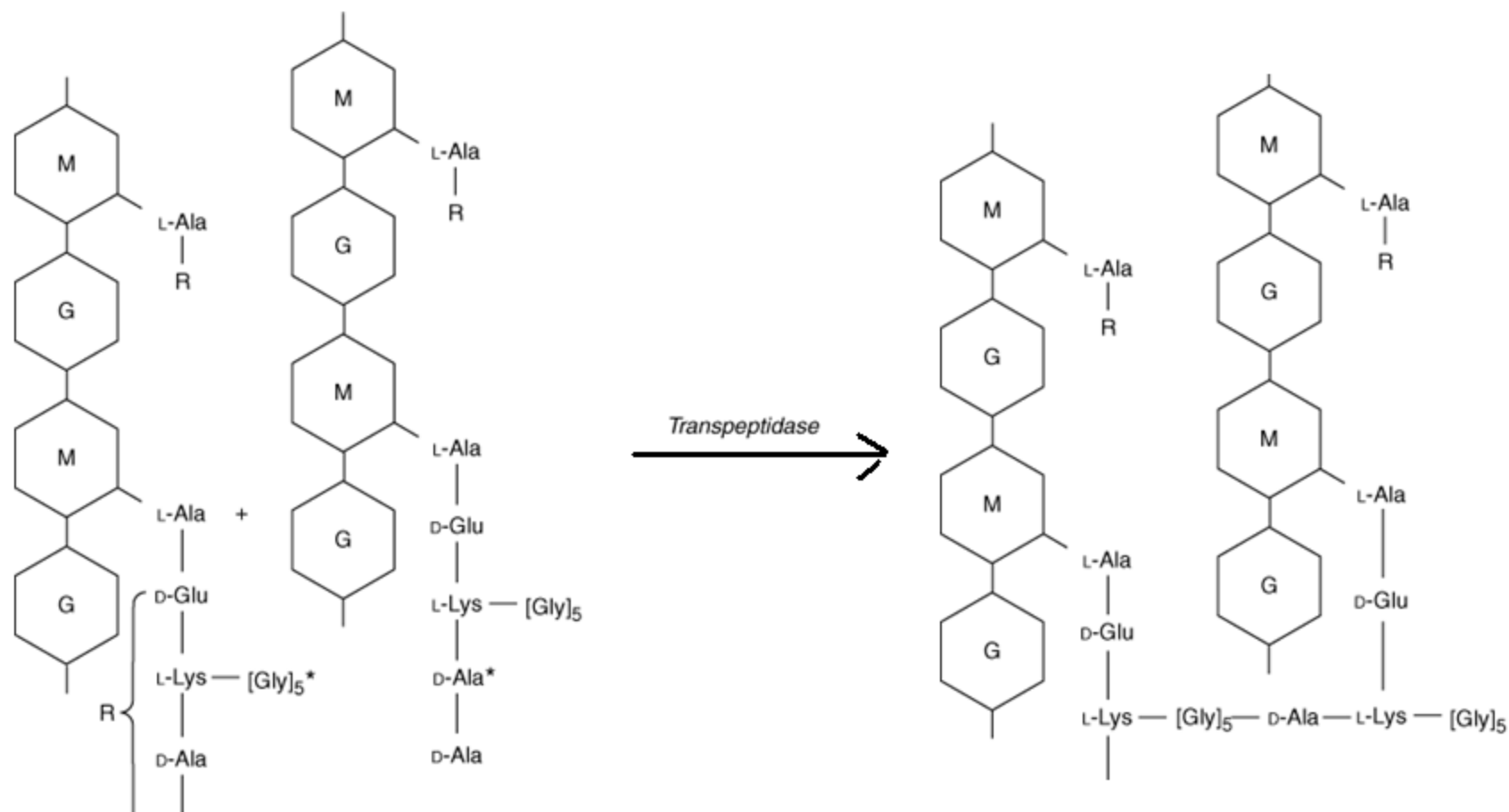
Cross-linked  
by  
transpeptidase

Inhibition of  
cell wall synthesis

Amino acid  
chain

Sugar

Cell wall  
building block



# **The main forms of Penicillins resistance**

**A. b-lactamases (penicillinases) which hydrolyse the lactam ring.**

**b-lactamase production is particularly important in staphylococci, but they are not made by streptococci.**

**At least 90% of staphylococcus species in the West now produce b-lactamases.**

**One strategy to overcome the problem is the development of b-lactamase antagonists such as clavulanic acid which is a suicide inhibitor of the enzyme.**

**B. reduction in the permeability of the outer membrane in Gram-negative bacteria.**

**C. mutations to the penicillin-binding proteins.**

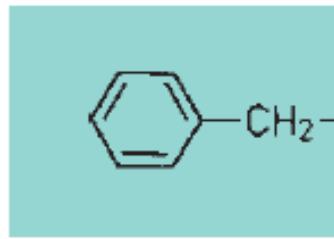
# Natural penicillin

- Naturally-occurring benzylpenicillin (penicillin G) is active against some organisms but their main drawbacks are
  - a. penicillin G Sensitivity to acid hydrolysis in the stomach, which means it has to be administered by injection,
  - b. Its susceptibility to b-lactamases.
  - c. Limited activity against gram negatives.
- These, and other, difficulties gave inspiration to the development of the semi-synthetic agents designed to be :
  1. b-lactamase resistant
  2. broad spectrum
  3. extended spectrum (extended to include pseudomonads)

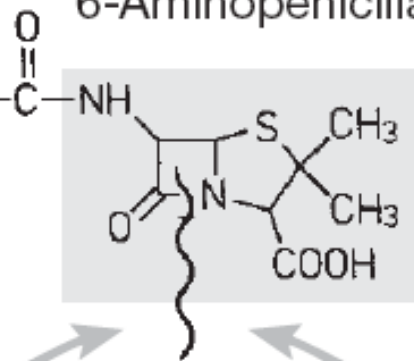


# Natural penicillin

- **Benzylpenicillin (Penicillin G) is Given IM or IV.**
- **Active against:**
  - **most gram-positive bacteria with the exception of penicillinase-producing *S. aureus***
  - **most *Neisseria species* and some gram-negative anaerobes**
  - **Not active against most gram-negative aerobic organisms**

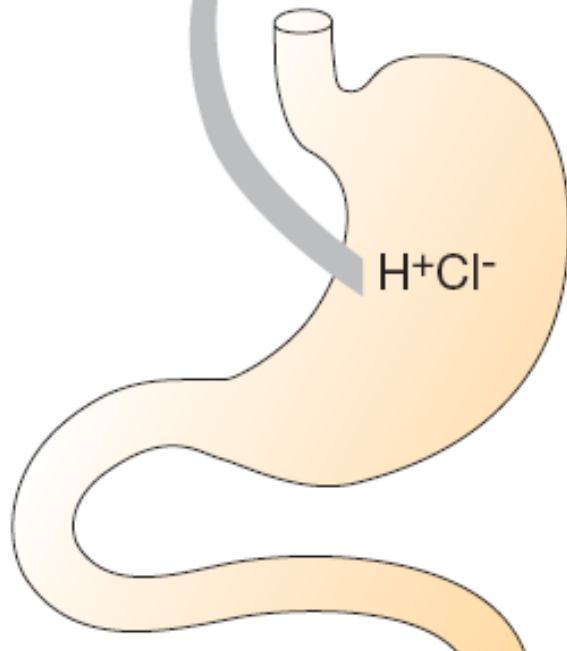


6-Aminopenicillanic acid



Penicillin G

**Acid sensitivity**



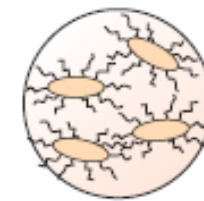
**Penicillinase sensitivity**



Penicillinase



Staphylococci



Salmonella typhi



E. coli

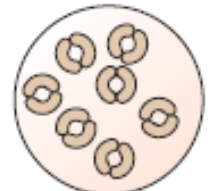
Gram-negative

Not active

**Narrow-action spectrum**

Active

Gram-positive



Gonococci



Pneumococci



Streptococci

# Penicillin G clinical uses

- Treatment for beta-hemolytic streptococcal pharyngitis (Empirical).
- Streptococcal infections that include pneumonia, otitis media, meningitis, and septic arthritis. **Only as definitive therapy.**
- In addition, penicillin G is effective against **Neisseria meningitidis (definitive for meningitis)**
- and **Clostridium tetani**, and **Corynebacterium diphtheriae**, **Treponema pallidum**, and **Listeria monocytogenes**.

# **Benzathine penicillin**

- **Benzathine penicillin for intramuscular injection yield low but prolonged drug levels.**
- 1. A single intramuscular injection of benzathine penicillin, 1.2 million units, is effective treatment for beta-hemolytic streptococcal pharyngitis.**
  - 2. Also prophylactic, given intramuscularly once every 3–4 weeks, it prevents re-infection..**
  - 2. Reoccurrence of rheumatic fever.**
  - 2. Benzathine penicillin G, 2.4 million units intramuscularly once a week for 1–3 weeks, is effective in the treatment of syphilis. Also prophylactic.**

# Natural penicillin

- Benzylpenicillin (Penicillin V) is more acid stable, is orally active but is less potent than penicillin G.
- Treatment for beta-hemolytic streptococcal pharyngitis (Empirical).
- Penicillin V often employed in the treatment of oral infection, where it is effective against **some anaerobic organism**.
- *Penicillin V is the most frequently prescribed* antibiotic for oral infections.
- It is the first choice in the treatment of odontogenic infections.
  - (1) post extraction infection,
  - (2) pericoronitis and
  - (3) salivary gland infection

# **b-lactamase-resistant Penicillins**

- These include Cloxacillin, Flucloxacilin, Oxacillin which are well-absorbed orally.
- They also includes methicillin (not available any more).
- Antibacterial spectrum is the same as for penicillin G, but less potent and does cover staph producing beta-lactamase.
- Their use is restricted to treatment of infections caused by penicillins-resistant bacteria. Nonetheless, Many *Staphylococci* are now resistant to them.
- **MRSA is very common.**

# Extended Spectrum Penicillins

- These include Ampicillin, which is fairly well absorbed orally, Amoxicillin which is very well absorbed, and is prodrug to ampicillin.
- Their antibacterial spectrum is the same as for penicillin G plus some Gram-negative bacteria. (Enhanced ability to penetrate the gram-negative outer membrane).
- Ampicillin and amoxicillin are among the most useful antibiotics for treating children suffering from infections caused by sensitive gram-negative aerobic bacteria, *enterococci*, and  $\beta$ -lactamase-negative *H. influenzae*.

# Aminopenicillins

(ampicillin, amoxicillin)

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Developed to increase activity against gram-negative aerobes

## Gram-positive

pen-susc *S. aureus*

Pen-susc streptococci

viridans streptococci

**Enterococcus** sp.

*Listeria monocytogenes*

## Gram-negative

***Proteus mirabilis***

***Salmonella*,**

**some *E. coli***

**$\beta$ L- *H. influenzae***



# $\beta$ -Lactamase Inhibitor Combos

(Unasyn, Augmentin, Timentin, Zosyn)

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Developed to gain or enhance activity against  $\beta$ -lactamase producing organisms (some better than others). Provides some or good activity against:

## Gram-positive

*S. aureus* (MSSA)

## Anaerobes

*Bacteroides* sp.

## Gram-negative

*H. influenzae*

*E. coli*

*Proteus* sp.

*Klebsiella* sp.

*Neisseria gonorrhoeae*

*Moraxella catarrhalis*

# Extended Spectrum Penicillins

- They are widely used in the treatment of **respiratory infections**.
- Are given orally to treat **sinusitis, otitis, and lower respiratory tract infections**.
- **Amoxicillin is the favored drug for the treatment of acute otitis. Empirical (Increase the dose to 80-90 mg/kg/day).**
- Amoxicillin is employed prophylactically, for patient with abnormal heart valves who are undertaken extensive oral surgery. (the drug of choice for prophylaxis of infective endocarditis).

# Broad Spectrum Penicillins

- These include Carbenicillin, Ticarcillin, and **Piperacillin**.
- All are very poorly absorbed from the gut. They are susceptible to b-lactamases.
- Their antibacterial spectrum is the same as the broad-spectrum drugs plus **pseudomonads**.
- These antibiotics are used in the treatment of urinary tract, lung, and bloodstream infections caused by ampicillin-resistant enteric gram-negative pathogens.

# Broad Spectrum Penicillins

Piperacillin has increased potency against common Gram-negative organisms.

Its main uses are in intensive care medicine (pneumonia, peritonitis)

- Although supportive clinical data are lacking for superiority of combination therapy over single-drug therapy, because of the propensity of *P aeruginosa* to develop resistance during treatment, an antipseudomonal penicillin is frequently used in combination with an aminoglycoside or fluoroquinolone for pseudomonal infections outside the urinary tract.

# Ureidopenicillins (piperacillin, azlocillin)

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Developed to further increase activity  
against resistant gram-negative aerobes

## Gram-positive

viridans strep

Group strep

some Enterococcus

## Anaerobes

*Fairly good activity*

## Gram-negative

*Proteus mirabilis*

*Salmonella, Shigella*

*E. coli*

$\beta$ L- *H. influenzae*

*Enterobacter sp.*

*Pseudomonas aeruginosa*

*Serratia marcescens*

some *Klebsiella sp.*

# Unwanted effects

- Penicillins are remarkably free of direct toxic effects.
- The main unwanted side-effects are hypersensitivity reactions which derive from the fact that degradation products of penicillins combine with host proteins and become antigenic.
- They cause alteration of bacterial flora in the gut and this can be associated with GI disturbances, such as Diarrhoea. (happened to a greater extent with those have an extended antibacterial spectrum).
- All Penicillins, particularly Methicillin, have the potential to cause acute nephritis, thus Methicillin is no longer available.

# Unwanted effects

- Antipseudomonal penicillins (Carbenicillin and Ticarcillin), to some extent Penicillin G, may decrease agglutination.
- All oral penicillins are best given on an empty stomach to avoid the absorption delay caused by food. **Exception being amoxicillin.**

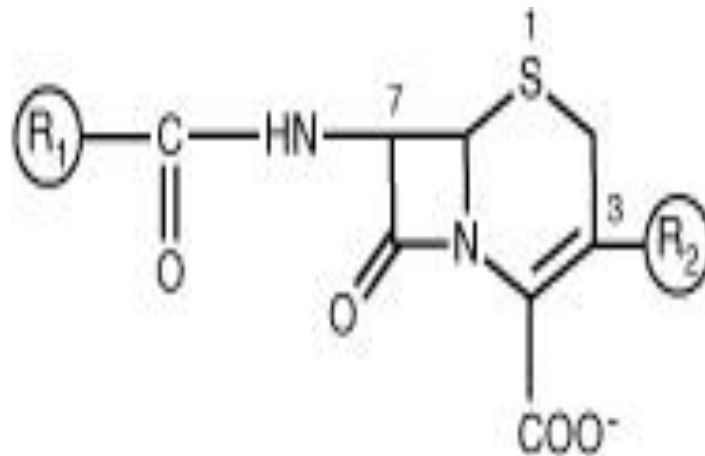
# Cephalosporins

- Are also  $\beta$ -lactam antibiotics isolated from a strain of *Streptomyces*.
- There are a large number available for clinical use, variously termed “first- second- third- fourth generations.
- They are bactericidal and work in the same way as the penicillins.
- Resistance is due to  $\beta$ -lactamases, permeability mutants and mutations to the target proteins.



# Cephalosporins

- **Bicyclic ring structure**
  - **beta-lactam ring (in common with penicillins)**
  - **6 membered sulfur containing dihydrothiazine ring**
- **Changes in side chain R groups gives changes in spectrum of activity, pharmacokinetics, etc.**



# Cephalosporins

## 1st gen

- Cefadroxil
- Cefazolin
- Cephalixin
- Cephalothin

## 2nd gen

- Cefaclor
- Cefoxitin
- Cefuroxime

## 3rd gen

- Cefnidir
- Cefixime
- Cefotaxime
- Ceftazidime
- Ceftibuten
- Ceftriaxone

4th gen  
Cefepime

# 1st generation

- Act as penicillin G, but they are resistant to the staphylococcal penicillinase.

have good activity against gram-positive bacteria and relatively modest activity against gram-negative microorganisms.

Most gram-positive cocci (with the exception of enterococci, methicillin-resistant *S. aureus*, and *S. epidermidis*) are susceptible.

# First Generation Cephalosporins

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Best activity against gram-positive aerobes,  
with limited activity against a few gram-  
negative aerobes

## Gram-positive

meth-susc *S. aureus*

pen-susc *S. pneumoniae*

Group A/B/C/G streptococci

viridans streptococci

## Gram-negative

*E. coli*

*K. pneumoniae*

*P. mirabilis*

- The first-generation cephalosporins are excellent agents for skin and soft tissue infections owing to *S. aureus* and *S. pyogenes*.



- A single dose of cefazolin just before surgery is the preferred prophylaxis for procedures in which skin flora are the likely pathogens .



- For colorectal surgery, where prophylaxis for intestinal anaerobes is desired, the second-generation agents cefoxitin or cefotetan are preferred.

# Cephalosporins generations

**Second generation: have greater activity against three additional gram-negative organism : *H influenzae*, *Neisseria*, and *Enterobacter aerogenes*. However, the activity against gram positive bacteria is weaker.**

**A subset of second-generation agents ( *cefoxitin*, *cefotetan*, and *cefmetazole* ) also is active against the *B. fragilis* group.**

**so can be used to treat mixed anaerobic infections such as peritonitis or diverticulitis.**

**Cefuroxime is used to treat community-acquired pneumonia because it is active against beta-lactamase-producing *H influenzae* or *K pneumoniae* and penicillin-resistant pneumococci.**

# Second Generation Cephalosporins

## Spectrum of Activity

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### Gram-positive

meth-susc *S. aureus*

pen-susc *S. pneumoniae*

Group A/B/C/G strep

viridans streptococci

### Gram-negative

*E. coli*

*K. pneumoniae*

*P. mirabilis*

*H. influenzae*

*M. catarrhalis*

*Neisseria sp.*

# Second Generation Cephalosporins

## Spectrum of Activity

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The cephamycins (cefoxitin and cefotetan) are the only 2nd generation cephalosporins that have activity against anaerobes

### Anaerobes

*Bacteroides fragilis*

Bacteroides fragilis group



# Third Generation Cephalosporins

## Spectrum of Activity

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- In general, are even less active against gram-positive aerobes, but have greater activity against gram-negative aerobes
- Ceftriaxone and cefotaxime have the best activity against gram-positive aerobes, including pen-resistant *S. pneumoniae*

# Third Generation Cephalosporins

## Spectrum of Activity

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### Gram-negative aerobes

*E. coli*, *K. pneumoniae*, *P. mirabilis*

*H. influenzae*, *M. catarrhalis*, *N. gonorrhoeae* (including beta-lactamase producing); *N. meningitidis*

*Citrobacter* sp., *Enterobacter* sp., *Acinetobacter* sp.

*Morganella morganii*, *Serratia marcescens*, *Providencia*

*Pseudomonas aeruginosa* (ceftazidime and cefoperazone)

# Clinical uses

- The third-generation cephalosporins, with or without aminoglycosides, have been considered to be the drugs of choice for serious infections caused by *Klebsiella*, *Enterobacter*, *Proteus*, *Serratia*, and *Haemophilus* spp.
- They may be particularly useful in treating hospital-acquired infections,

although increasing levels of extended-spectrum beta-lactamases are reducing the clinical utility of this class of antibiotics.

# Clinical uses

- In neutropenic, febrile immunocompromised patients, third-generation cephalosporins are often used in combination with an aminoglycoside.
- Other potential indications include empirical therapy of sepsis of unknown cause in both the immunocompetent and the immunocompromised patient

# Third Generation Cephalosporins

## Spectrum of Activity

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### Gram-negative aerobes

*E. coli*, *K. pneumoniae*, *P. mirabilis*

*H. influenzae*, *M. catarrhalis*, *N. gonorrhoeae* (including beta-lactamase producing); *N. meningitidis*

*Citrobacter* sp., *Enterobacter* sp., *Acinetobacter* sp.

*Morganella morganii*, *Serratia marcescens*, *Providencia*

*Pseudomonas aeruginosa* (ceftazidime and cefoperazone)

# Clinical uses

- Ceftriaxone and cefotaxime
  1. are used for the initial treatment of meningitis in nonimmunocompromised (**in combination with vancomycin**)

because of their antimicrobial activity, good penetration into CSF, and record of clinical success.

2. are the most active cephalosporins against penicillin-resistant strains of pneumococci and are recommended for empirical therapy of serious infections that may be caused by these strains.
3. Ceftriaxone is the therapy of choice for all forms of gonorrhea and for severe forms of **Lyme disease**.

# ***Fourth-generation cephalosporins***

- ***cefepime***, have an extended spectrum of activity compared with the third generation.
- The fourth-generation cephalosporins are indicated for the empirical treatment of nosocomial infections

particularly useful when gram-positive microorganisms, Enterobacteriaceae, and *Pseudomonas* all are potential etiologies.

# Fourth Generation Cephalosporins

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- 4th generation cephalosporins for 2 reasons
  - Extended spectrum of activity
    - ♦ gram-positives: similar to ceftriaxone
    - ♦ gram-negatives: similar to ceftazidime, including *Pseudomonas aeruginosa*; also covers beta-lactamase producing *Enterobacter* sp.
  - Stability against  $\beta$ -lactamases; poor inducer of extended-spectrum  $\beta$  -lactamases
- Only cefepime is currently available



# Clinical uses

- For example, cefepime has superior activity against nosocomial isolates of *Enterobacter*, *Citrobacter*, and *Serratia* spp. compared with ceftazidime and piperacillin (Jones *et al.*, 1998).
- Cross blood-brain barrier and are effective in meningitis.

# Cephalosporins adverse effects

- Hypersensitivity, patient who has an anaphylactic response to penicillin should avoid cephalosporins.
- **N-methyl-thiotetrazole-containing cephalosporins**
- **cefamandole, cefotetan, cefditoren, cefoperazone, and only**
  - 1) A disulfiram-like effect: happened when some cephalosporins is indigested with alcohol, because of the blockade to the alcohol metabolism, which result in accumulation of acetaldehyde.
  - 2) Bleeding: some cephalosporins have an anti vitamin K effect, and may cause bleeding (hypoprothrombinemia )

# Cephalosporins interactions

- Ceftraixone and calcium product , FDA warning.

- **Note**

cefoperazone and ceftriaxone are exceptions because they are excreted predominantly in the bile.

# Carbapenem

- Doripenem, ertapenem, **imipenem**, and meropenem are licensed for use in the USA.
- Imipenem has a wide spectrum with good activity against many gram-negative rods, including *P aeruginosa*, gram-positive organisms, and anaerobes.
- Imipenem is inactivated by dehydropeptidases in renal tubules, so administered together with an inhibitor of renal dehydropeptidase, cilastatin, for clinical use.

# Carbapenem

- A carbapenem is indicated for infections caused by susceptible organisms that are resistant to other available drugs, eg, *P aeruginosa*, and for treatment of mixed aerobic and anaerobic infections.
- it is also the treatment of choice for infections caused by extended-spectrum beta-lactamases–producing gram-negatives.

## Example:

A carbapenem is the beta-lactam antibiotic of choice for treatment of **enterobacter** infections because it is resistant to destruction by the lactamase produced by these organisms;

# Carbapenem

- Its side-effects are similar to those seen with other  $\beta$ -lactam antibiotics,
- Nausea and vomiting been the most frequently encountered.
- At high doses neurotoxicity can occur.

# Vancomycin

- Vancomycin is bactericidal and acts by inhibiting cell wall synthesis.
- it is active only against gram-positive bacteria, particularly staphylococci.
- Its special clinical use is in treating **methicillin-resistant staphylococci**, **resistant enterococci** and ***Clostridium difficile*** (which causes pseudomembranous colitis).
- The main indication for parenteral vancomycin is sepsis or endocarditis caused by methicillin-resistant staphylococci.

# Vancomycin

- It is also valuable in severe staphylococcal infections in patients allergic to penicillins and cephalosporins.
- Vancomycin in combination with gentamicin is used for treatment of enterococcal endocarditis in a patient with serious penicillin allergy.
- It is not absorbed from the gut and is only given orally for treatment of GI infections. It is generally administered intravenously.
- Resistance can be caused by changing the permeability to the drug and by decreasing the binding of Vancomycin to receptors.



# Vancomycin

- **Vancomycin must be administered in a dilute solution slowly, over at least 60 minutes.**

**This is due to the high incidence of pain and thrombophlebitis and to avoid an infusion reaction known as the red man syndrome or red neck syndrome.**

- **Unwanted effects are a serious problem and include fever, rashes and local phlebitis.**
- **Ototoxicity and nephrotoxicity can occur and hypersensitivity reactions are occasionally encountered.**

- Nephrotoxicity and Ototoxicity
  - rare with monotherapy, more common when administered with other nephro- or ototoxins
  - risk factors include renal impairment, prolonged therapy, high doses, ? high serum concentrations, other toxic meds

# Monobactams

**Their spectrum of activity is limited to aerobic gram-negative rods (including pseudomonas). Unlike other beta-lactam antibiotics, they have no activity against gram-positive bacteria or anaerobes.**

- The main monobactam is Aztreonam which is a monocyclic b-lactam resistant to most b-lactamases.**
- Penicillin-allergic patients tolerate aztreonam without reaction.**

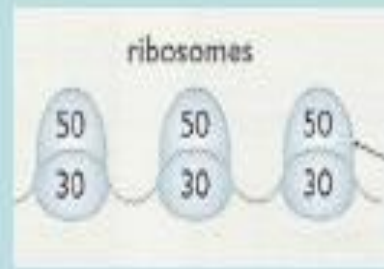
**In which used to treat serious infections such as pneumonia, meningitis, and sepsis caused by susceptible gram-negative pathogens.**

- Its unwanted side-effects are similar to the other b-lactam antibiotics.**

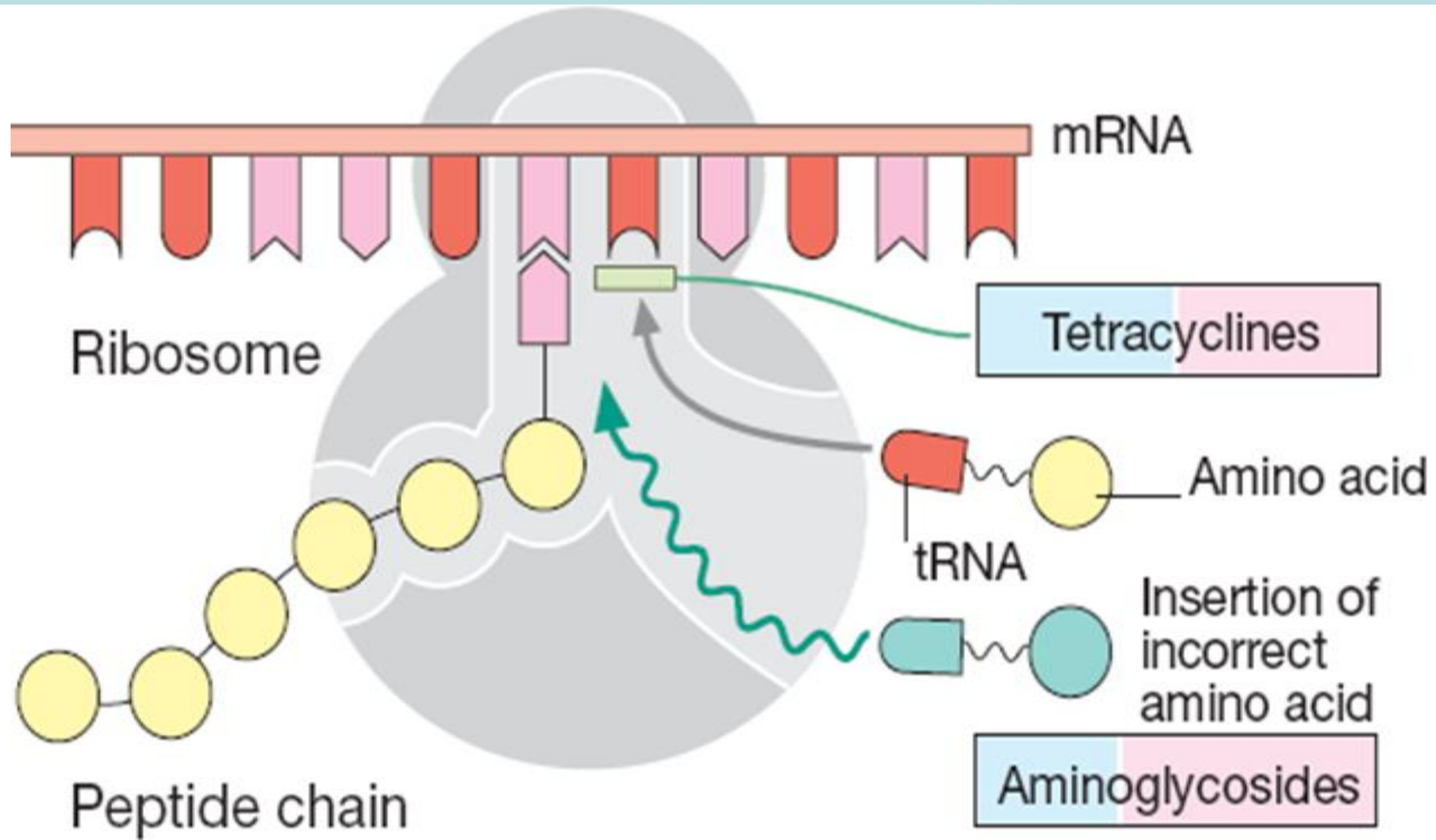
# Protein Synthesis Inhibitors

- They are active against a wide variety of organisms (broad spectrum).
  - Most are bacteriostatic but a few are bactericidal against certain organisms.
  - Because of overuse, resistance is common.
- 
- ❖ Bacterial ribosomes differ in molecular detail from eukaryotic ones enabling antibiotics to exhibit selective toxicity.
  - ❖ The main ribosomal processes they interfere with are :
    - (1) binding of aminoacyl-tRNA
    - (2) normal codon:anticodon recognition
    - (3) transpeptidation

DNA → mRNA →



→ proteins



# Tetracyclines

- Tetracycline, Methacycline, Moxycycline, doxycycline minocycline and **Tigecycline**.
- They bind to both mRNA and the ribosomal 30S subunit where they prevent the binding of aminoacyl-tRNA.
- They are bacteriostatic not bacteriocidal.
- Their spectrum of activity is very wide and includes Gram-positive and Gram-negative bacteria, some spirochaetes and some protozoa (eg amoebae).

## CHLAMYDIAL INFECTIONS

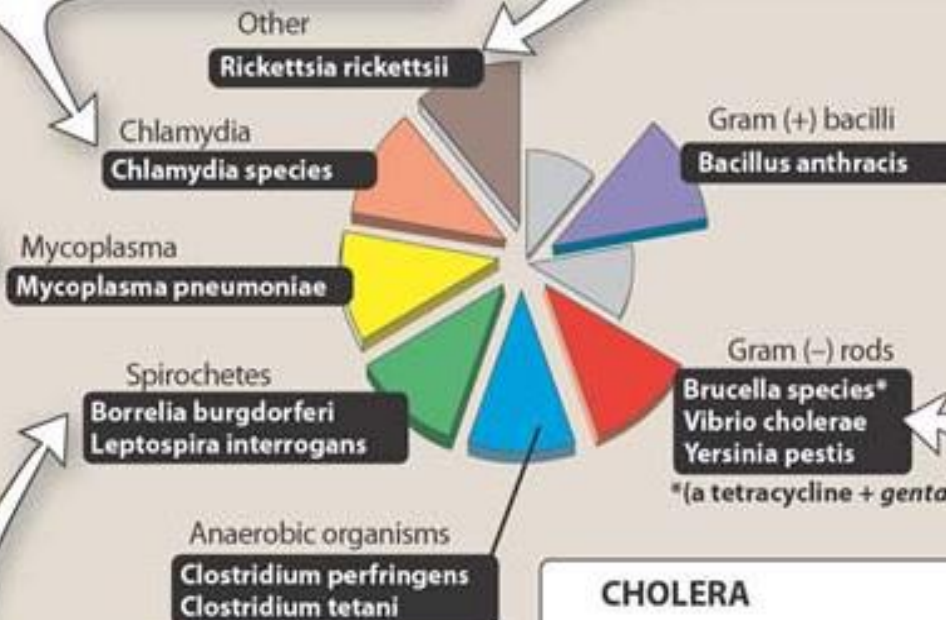
- *Chlamydia trachomatis* is the major cause of sexually transmitted disease in the United States. It causes nongonococcal urethritis, pelvic inflammatory disease, and lymphogranuloma venereum.
- *Chlamydia psittaci* causes psittacosis, which usually takes the form of pneumonia. Other clinical forms include hepatitis, myocarditis, and coma.
- Doxycycline or azithromycin is used to treat chlamydial infections.

## ROCKY MOUNTAIN SPOTTED FEVER

- This disease, caused by *Rickettsia rickettsii*, is characterized by fever, chills, and aches in bones and joints.
- Response to tetracyclines is prompt if the drug is started early in the disease process.

## MYCOPLASMA PNEUMONIA

- *Mycoplasma pneumoniae* is a common cause of pneumonia in young adults and in people who live in close confines, such as in military camps.
- Treatment leads to a shorter duration of fever, cough, and malaise.
- Treatment with macrolides is also effective.



## LYME DISEASE

- This is a spirochetal infection caused by *Borrelia burgdorferi*. The disease is transmitted by the bite of infected ticks.
- Infection results in skin lesions, headache, and fever, followed by meningoenitis and, eventually, arthritis.
- A single, 200-mg dose of doxycycline, given within 72 hours after a tick bite, can prevent development of the disease.

## CHOLERA

- Cholera is caused by *Vibrio cholerae* ingested as part of fecally contaminated food or water.
- The organism multiplies in the gastrointestinal tract, where it secretes an enterotoxin that produces diarrhea.
- Treatment includes doxycycline, which reduces the number of intestinal vibrios, and fluid replacement.

# Tetracyclines

- Their main clinical uses are :

(1) mycoplasma and chlamydia infections

(2) A tetracycline—usually in combination with an aminoglycoside—is indicated for brucellosis

(3) They are used in combination regimens to treat gastric and duodenal ulcer disease caused by *Helicobacter p*

(4) Acne

(5) syphilis



# Tetracyclines

- Resistance is common and is mainly due to a plasmid-mediated energy-dependent efflux pump, (typical of the multiple drug resistance type). Mutations in the tetracycline target site are also found.
- The Tetracyclines are usually administered orally but can be given parenterally.
- Absorption from the gut is irregular and better in the absence of food.
- Since Tetracyclines chelate di- and trivalent metal ions, forming insoluble complexes, absorption is decreased in the presence of milk, certain antacids and iron preparations.

# Tetracyclines

- The most Common side-effects are GI disturbances, due initially to direct irritation and later to modification of gut flora.
- They are deposited in growing bones and teeth, causing staining and sometimes dental hypoplasia and bone deformities.
- Phototoxicity: for example, severe sunburn, occurs when the patient receiving a tetracycline is exposed to sun or ultra-violet rays.
- They shouldn't be given to children, pregnant women or nursing mothers. (may causes hepatotoxicity in pregnant women).

# Tetracyclines

- **Tetracycline is a broad spectrum antibiotic that is occasionally used in Dentistry to treat bacterial infections.**
- **This antibiotic has a natural tendency to concentrate in the gingival fluids around the teeth so it is often used to treat gingivitis and gum disease.**
- **It is one of the first choices for the treatment of ANUG.**
- **Acute Necrotizing Ulcerative Gingivitis appears with stress. College students can get it during finals and people breaking up can get it.**

# Macrolides

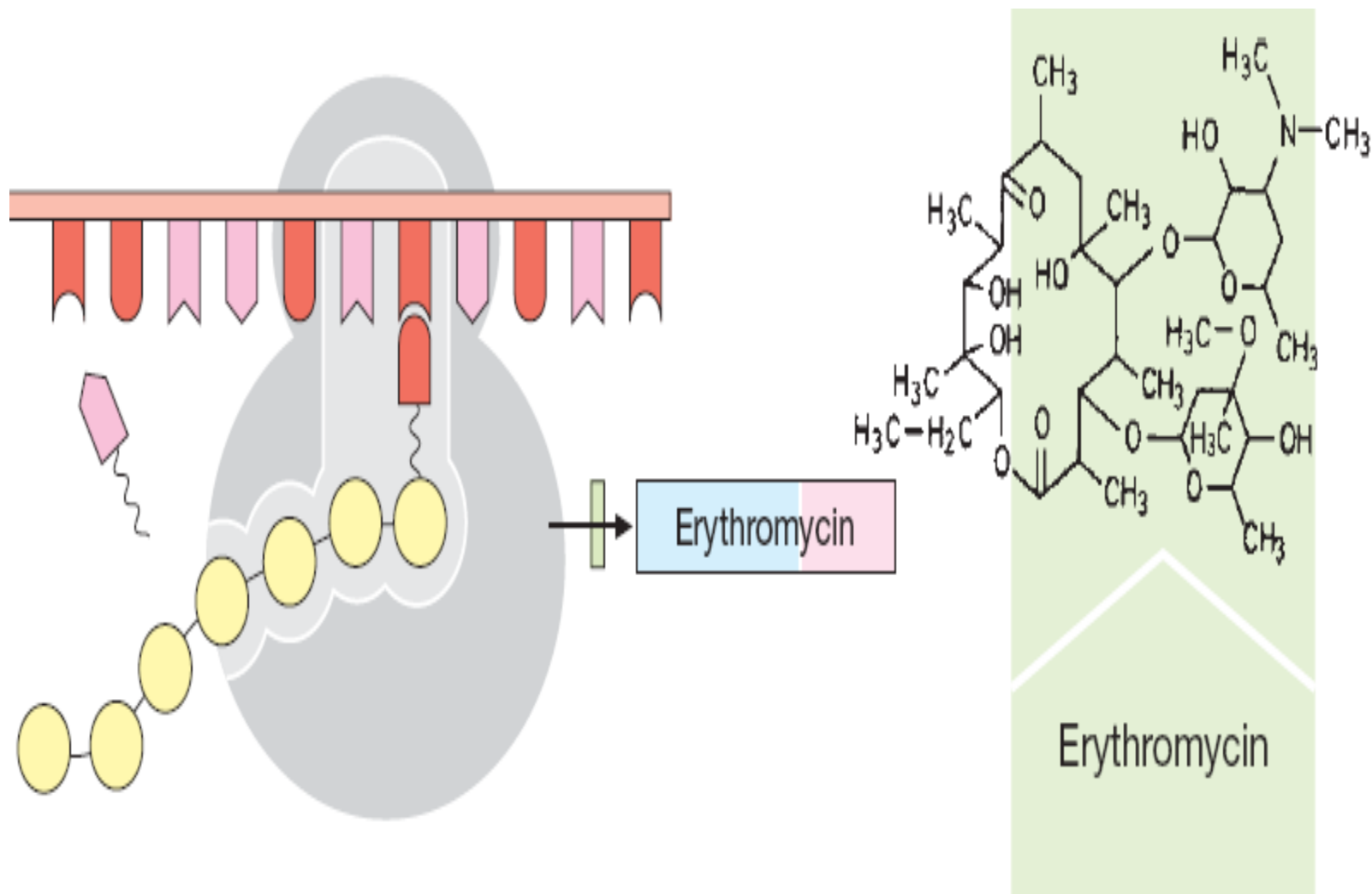
- The best known example is Erythromycin, modern clinical members being Clarithromycin, Azithromycin, **Telithromycin**.
- They bind to the 50S ribosomal subunit and inhibit protein synthesis.
- Erythromycin is active against Gram-positive bacteria and spirochaetes but not against most Gram-negative organisms.
- **Azithromycin far more active against respiratory infections due to Haemophilus influenzae and E. coli.**

## **Approval of Antibiotic Worried Safety Officials**

"How does one justify balancing the risk of fatal liver failure against one day less of ear pain?"

David Ross and Rosemary Johann-Liang

- [http://www.nytimes.com/2006/07/19/health/19fda.html?\\_r=0](http://www.nytimes.com/2006/07/19/health/19fda.html?_r=0)



## CHLAMYDIAL INFECTIONS

- *Azithromycin* is an alternative to *tetracycline* in treating uncomplicated urethral, endocervical, rectal, or epididymal infections due to Chlamydia.
- *Erythromycin* is the drug of choice for urogenital infections due to Chlamydia occurring during pregnancy.

## CORYNEBACTERIUM DIPHTHERIAE

- *Erythromycin* or *penicillin* is used to eliminate the carrier state.

## LEGIONNAIRES' DISEASE (LEGIONELLOSIS)

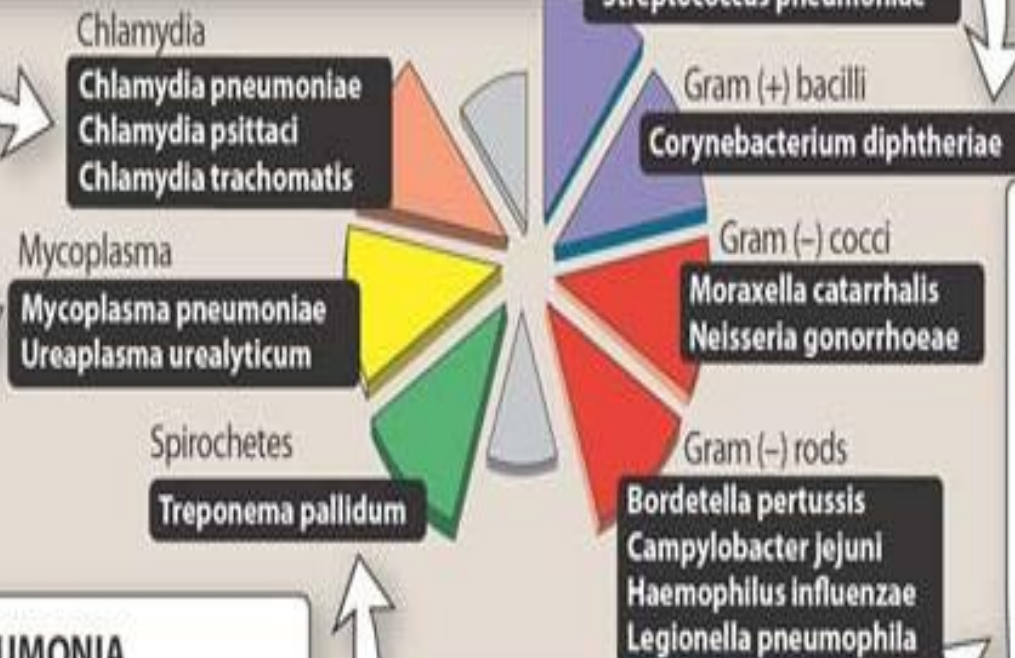
- Legionellosis represents 0.5 to 2.0 percent of all pneumonia in the United States. Undiagnosed or asymptomatic infections are common.
- *Azithromycin* is the therapy of choice.

## SYPHILIS

- *Erythromycin* is used to treat syphilis in patients who are allergic to *penicillin G*.

## MYCOPLASMAL PNEUMONIA

- Called "atypical" pneumonia because causative mycoplasma escape isolation by standard bacteriologic techniques.
- *Erythromycin* or *tetracycline* is effective.



# Macrolides clinical uses

- Its antibacterial spectrum is very similar to that of penicillins and it has proved a very useful penicillin substitute in penicillin-sensitive patient
- drug of choice in corynebacterial infections (diphtheria, corynebacterial sepsis);
- Azithromycin drug of choice in respiratory, neonatal, ocular, or genital chlamydial infections; and
- Azithromycin drug of choice in treatment of community-acquired pneumonia because its spectrum of activity includes pneumococcus, mycoplasma, and legionella.



# Macrolides clinical uses

- Clarithromycin is effective against *Mycobacterium avium* *cellulare* which can cause chronic lung disease in elderly or immunologically compromised individuals.
- Clarithromycin : Adjunct in treatment of duodenal ulcer ( *H. pylori* )
- Azithromycin shows particularly good activity against chlamydial urethritis

Except for its cost, it is now the preferred therapy for urethritis

# Macrolides

- The macrolides are administered orally, although they can be given parenterally.
- Azithromycin differs from erythromycin and clarithromycin mainly in pharmacokinetic properties
- Gastrointestinal disturbances are common side effects, but not serious. The newer agents seem to have less GI effects. Erythromycin has been reported to cause skin rashes and fever, transient hearing disturbances.

# **Azithromycin**

- **azithromycin penetrates into most tissues (except cerebrospinal fluid), with tissue concentrations exceeding serum concentrations by 10- to 100-fold.**
- **The drug is slowly released from tissues (tissue half-life of 2–4 days) to produce an elimination half-life approaching 3 days.**

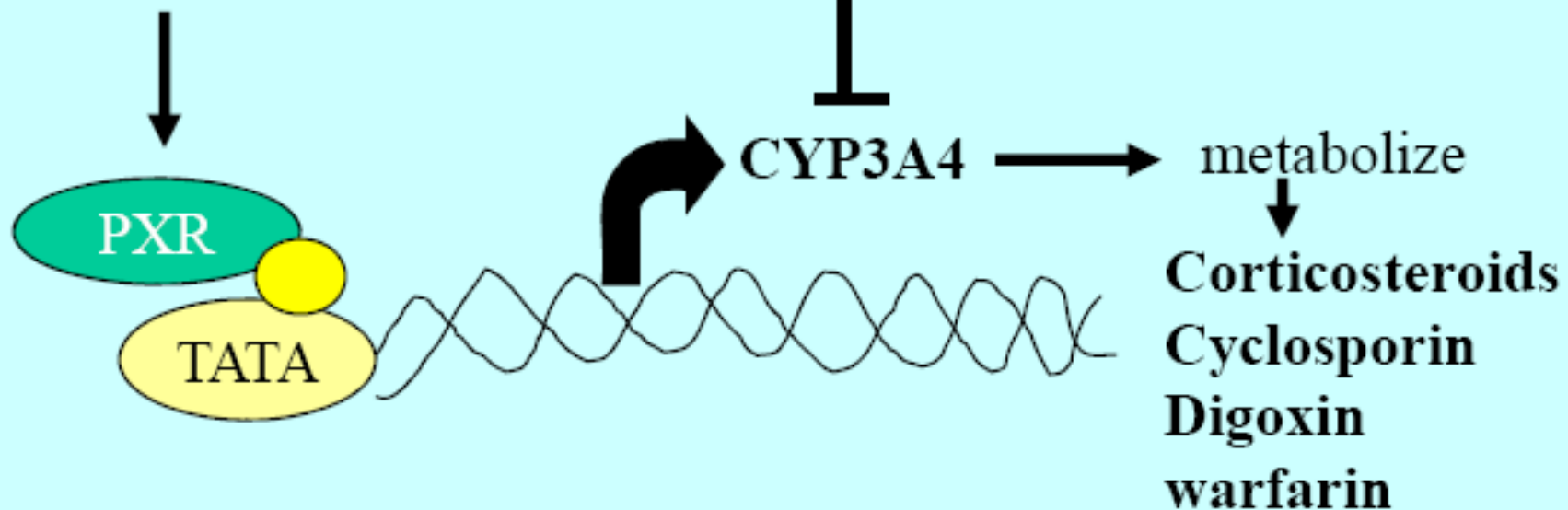
# Macrolides

- **Ototoxicity:** Transient deafness has been associated with erythromycin, especially at high dosages.
- **Cholestatic jaundice** especially with the estolate form of erythromycin

# Drug Interactions of Macrolides

Mainly Erythromycin  
and (to a lesser extent Clarithromycin)  
(use caution with Azithromycin)

Ligand i.e. inducers, subs)

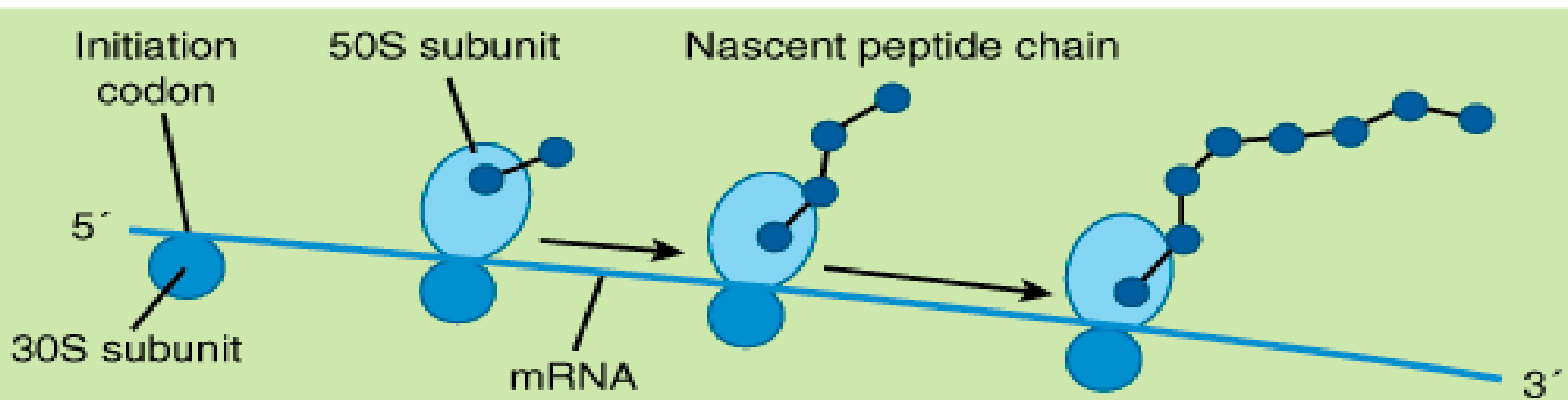


# Aminoglycosides

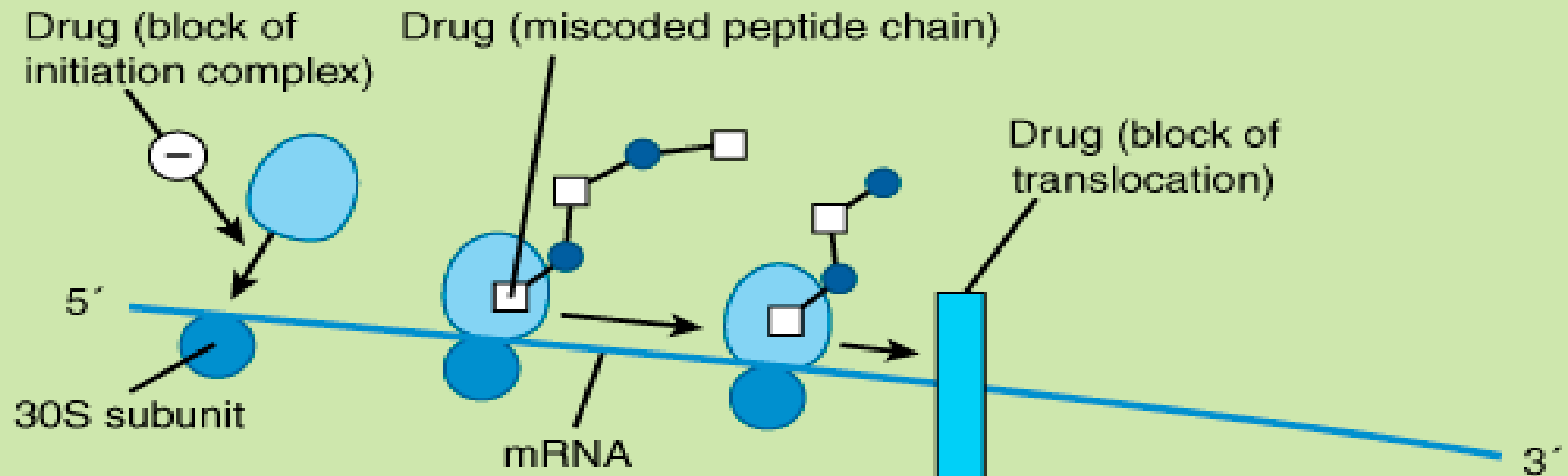
## (only bactericidal protein synthesis inhibitor)

- bind to the ribosomal 30S subunit
- inhibit initiation of peptide synthesis and cause misreading of the genetic code.
- Streptomycin is the best known member of the group which also includes **amikacin**, **Gentamicin**, **Tobramycin**, Netilmycin, and Neomycin.
- They are effective against many aerobic Gram-negative and some Gram-positive bacteria, finding their greatest use against Gram-negative enteric organisms and in sepsis.

## Normal bacterial cell



## Aminoglycoside-treated bacterial cell



# Clinical uses

- 1) Gram –ve bacillary infection – septicemia, pelvic & abdominal sepsis
- 2) Bacterial endocarditis – enterococcal, streptococcal or staphylococcal.
- 3) Pneumonias, Tuberculosis
- 4) Plague, Brucellosis
- 5) To sterilize the bowel of patients who receive immunosuppressive therapy, before surgery & in hepatic coma



# Points

- **First choice gentamycin due to low cost, reliable activity and long experience of use.**
- **Used in infected burns, otitis externa, acute pyelonephritis**
- **Tobramycin is the most active against Pseudomonas infections**
- **Amikacin is the Broadest antibacterial spectrum Preferred in serious nosocomial G –ve bacillary infection in hospitals where Tobramycin & Gentamicin have developed resistance**

# Aminoglycosides

- They are effective in the empirical treatment of infections suspected of being due to aerobic gram-negative bacilli.
- Neomycin is reserved for topical applications because of their systemic toxicity.

# Aminoglycosides

- Aminoglycosides are not absorbed from the GI tract.
- They are usually administered intramuscularly or intravenously.
- Serious dose-related side-effects occur with the aminoglycosides, The main hazards and nephrotoxicity.
- Ototoxicity

Subclass	Mechanism of Action	Effects	Clinical Applications	Toxicities, Interactions
<b>Aminoglycosides &amp; Spectinomycin</b>				
<b>Gentamicin</b>	<b>Prevents bacterial protein synthesis by binding to the 30S ribosomal subunit</b>	<b>Bactericidal activity against susceptible bacteria. synergistic effects against gram-positive bacteria when combined with lactams or vancomycin. demonstrate concentration-dependent killing and a significant postantibiotic effect</b>	<b>Sepsis caused by aerobic gram-negative bacteria synergistic activity in endocarditis caused by streptococci, staphylococci, and enterococci</b>	<b>once-daily dosing at 5–7 mg/kg as effective and may have less toxicity than conventional dosing <i>Toxicity:</i> Nephrotoxicity (reversible), ototoxicity (irreversible), neuromuscular blockade</b>
<b><i>Tobramycin: Intravenous; more active than gentamicin versus pseudomonas; may also have less nephrotoxicity</i></b>				
<b><i>Amikacin: Intravenous; resistant to many enzymes that inactivate gentamicin and tobramycin; higher doses and target peaks and troughs than gentamicin and tobramycin</i></b>				
<b><i>Neomycin: Oral or topical, poor bioavailability; used before bowel surgery to decrease aerobic flora; also used to treat hepatic encephalopathy</i></b>				

# Clindomycin

- Binds to the 50S ribosomal subunit and inhibit the correct attachment of the amino acid end of aminoacyl-tRNA.
- Is active against Gram-positive cocci, including penicillin-resistant staphylococci, and many **anaerobic bacteria**.
- Clindomycin finds its main clinical use in infections caused by *Bacteroides* organisms and for staphylococcal infections of bones and joints.
- Clindamycin is also indicated for treatment of anaerobic infection caused by bacteroides and other anaerobes that often participate in mixed infections.

# Clindomycin

- Clindamycin, sometimes in combination with an aminoglycoside or cephalosporin, is used to treat
  - (1) penetrating wounds of the abdomen and the gut;
  - (2) infections originating in the female genital tract, eg, septic abortion.
  - (3) and **aspiration pneumonia**.
- Side-effects generally are limited to GI upsets.

However, a potentially lethal pseudomembranous colitis can occur.

# Dental pharmacologic features of clindamycin

1. Wide spectrum of in vitro antimicrobial activity that includes those species implicated as pathogens in dental infections
2. Achievement of high levels in saliva, gingival crevicular fluid, and bone
3. Reduction of the expression of virulence factors (M protein, capsule, and toxins)
4. Increased bacterial phagocytosis and killing
5. Activity in conjunction with the host defense system
6. Suppression of the adherence of bacteria to the mucosal epithelial cells and the expression of virulence factors
7. Postantibiotic effect

# Clindamycin

## Spectrum of Activity

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Anaerobes – activity against Above the Diaphragm  
Anaerobes (ADA)

*Peptostreptococcus*

some *Bacteroides sp*

*Actinomyces*

*Prevotella sp.*

*Propionibacterium*

*Fusobacterium*

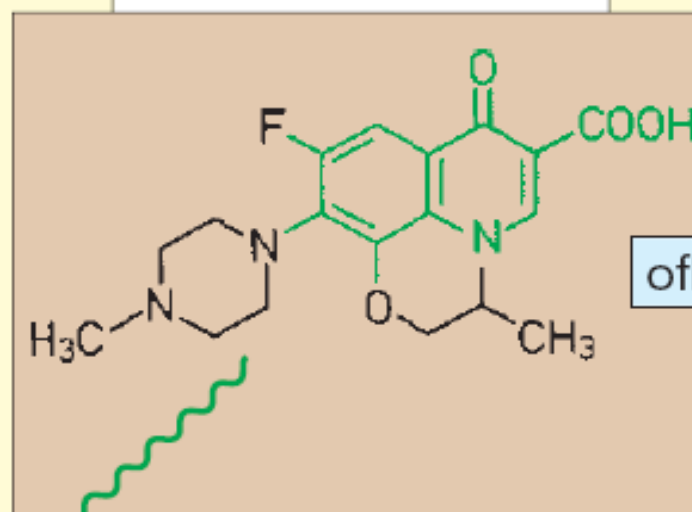
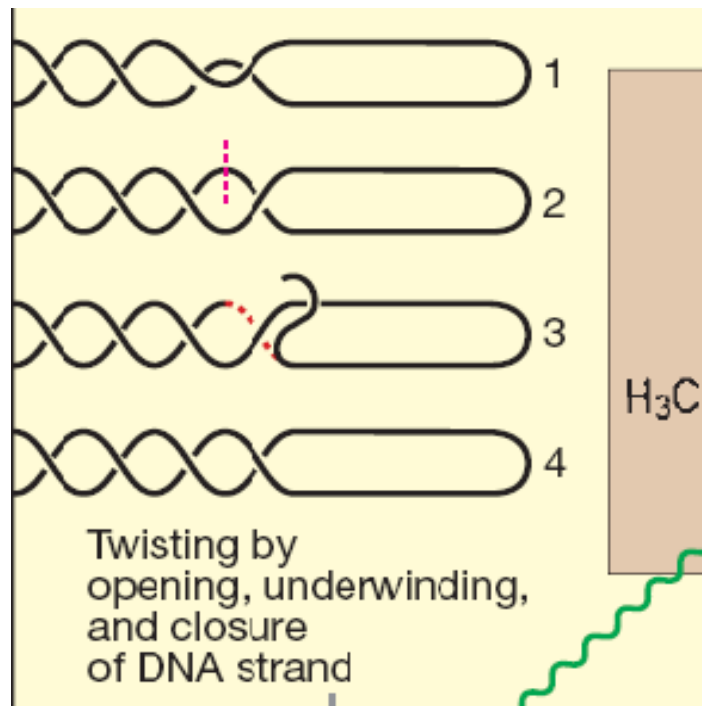
*Clostridium sp.* (not *C. difficile*)

Other Bacteria – *Toxoplasmosis gondii*, Malaria



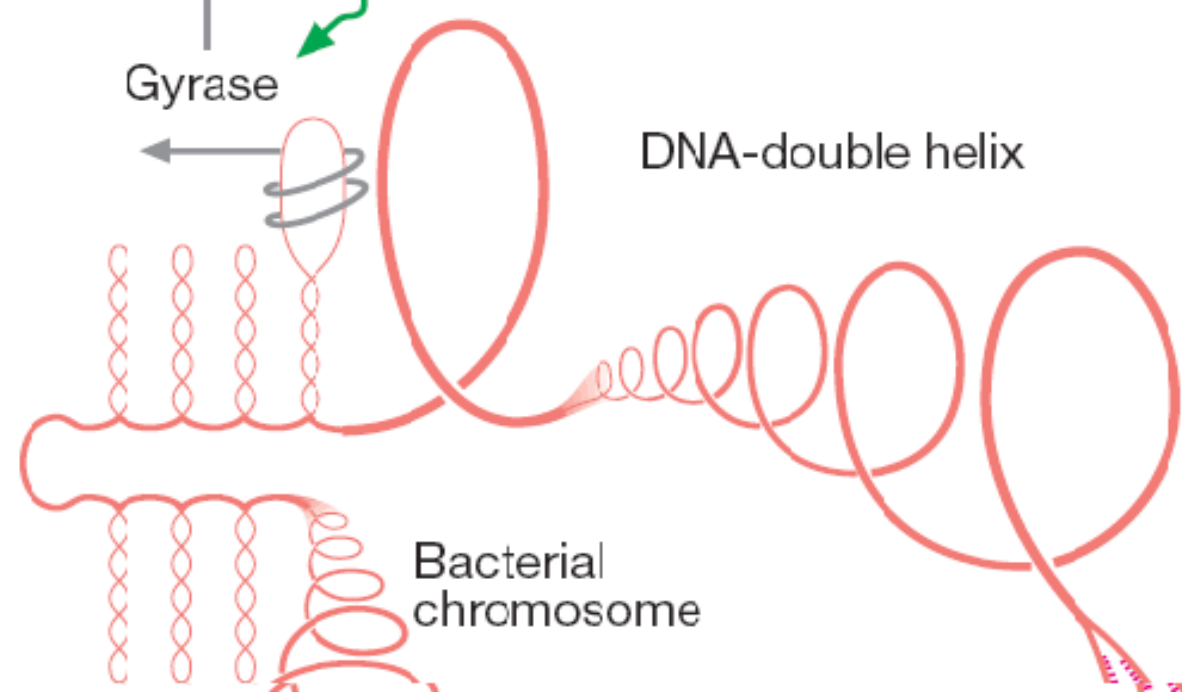
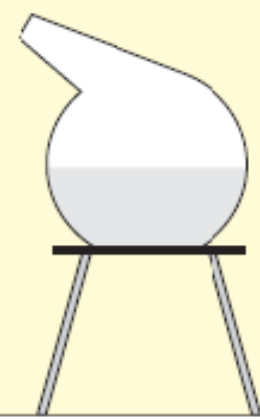
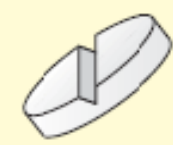
# Inhibition of DNA Gyrase

- bacterial DNA gyrase is a type II topoisomerase that produces transient double strand breaks in DNA.
- The best example is the fluoroquinolones, which are specific inhibitors of DNA gyrase that trap the enzyme in its cleavable complex.
- Inhibition of DNA gyrase prevents the relaxation of positively supercoiled DNA that is required for normal transcription and replication.
- Its a broad spectrum antibiotic active against both Gram-negative and Gram-positive bacteria. It is more active against Gram-negative species.



Gyrase inhibitors

ofloxacin



# Quinolones

- First oral antibiotics effective against gram-negative bacteria.
- Ciprofloxacin is the most commonly used fluoroquinolone.
- Ciprofloxacin most active agent against gram-negatives, *Pseudomonas aeruginosa* in particular
- Levofloxacin, gemifloxacin, and moxifloxacin: improved activity against gram-positive organisms, particularly *S. pneumoniae* and some staphylococci.

# Quinolone

- Their main uses are:

**(1) complicated urinary tract infections**

**(2) respiratory infections in patients with cystic fibrosis**

Levofloxacin,, gemifloxacin, and moxifloxacin, so-called respiratory fluoroquinolones, with their enhanced gram-positive activity and activity against atypical pneumonia agents (eg, chlamydia, mycoplasma, and legionella), are effective and used increasingly for treatment of upper and lower respiratory tract infections.

**(3) Infections of soft tissues, bones, and joints and in intra-abdominal**

**(4) bacterial prostatitis and cervicitis**

**(5) Also used in bacterial diarrhoea caused by shigella, salmonella, *E. coli*.**

# Quinolone

- Side-effects are infrequent and usually mild. They consist mainly of GI disorders (nausea, vomiting, and diarrhea) and skin rashes.
- Arthropathy, Fluoroquinolones may damage growing cartilage and cause an arthropathy. particularly in young individuals.

So contraindicated in children (under 18) except in special cases.

# Perturbation of nucleic acid synthesis

- Sulphonamides have a similar structure to p-aminobenzoic acid (PABA), which is a precursor of Folic acid.
- These agents compete with PABA for the bacterial enzyme, dihydropteroate synthetase. Thus, they inhibit the synthesis of the bacterial folic acid, and the end result is interfering in nucleic acid synthesis
- The sulphonamides are bacteriostatic rather than bacteriocidal so the host must have effective immune function.
- Resistance is common, mainly via up-regulation of the synthesis of PABA and by mutations in dihydropteroate synthetase.



p-Aminobenzoic acid



Sulfonamides

Folic acid

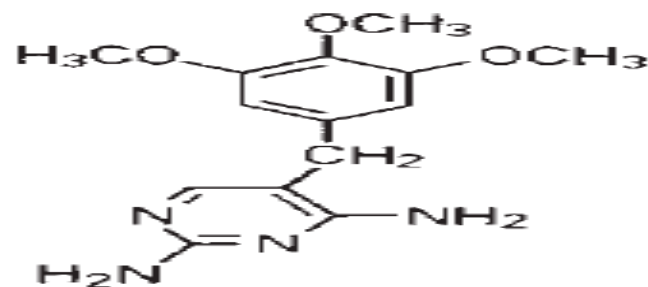
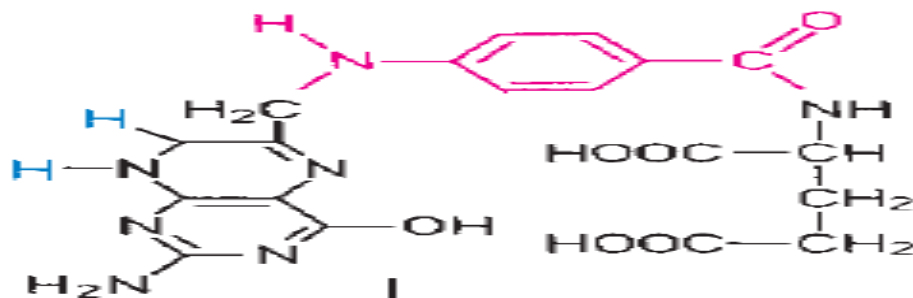
(Vitamin)

Dihydro-folic acid (DHF)

DHF-Reductase

Tetrahydro-folic acid

Synthesis of purines  
Thymidine



Trimethoprim

# **Sulphonamides are available as:**

## **(1) Oral Absorbable Agents:**

**Sulfisoxazole and sulfamethoxazole. almost exclusively to treat urinary tract infections.**

## **(2) Oral Nonabsorbable Agents**

**Sulfasalazine (salicylazosulfapyridine) is widely used in ulcerative colitis, enteritis, and other inflammatory bowel disease**

## **(3) Topical Agents**

**Silver sulfadiazine is used for prevention of infection of burn wounds.**



# Sulphonamides

- Sulphonamides have mild to moderate side-effects including, nausea, vomiting, headaches, and depression.
- More serious side-effects include hepatitis, hypersensitivity reactions, bone marrow depression, and aplastic anemia
- Sulfonamides may provoke hemolytic reactions in patients with glucose-6-phosphate dehydrogenase deficiency.

# Oral Trimethoprim-Sulfamethoxazole (TMP-SMZ)

- is the drug of choice for infections such as *Pneumocystis jiroveci* (formerly *P carinii*) pneumonia, toxoplasmosis, nocardiosis, and occasionally other bacterial infections.
- effective treatment for urinary tract infections and prostatitis.
- prophylaxis in recurrent urinary tract infections of some women.

# VRE and more

- **Teicoplanin** is used in the prophylaxis and treatment of serious infections caused by Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecalis*.
- **Linezolid** is approved for **vancomycin-resistant *E faecium* infections**; nosocomial pneumonia; community-acquired pneumonia; and skin infections, complicated or uncomplicated.

It should be reserved for treatment of infections caused by multidrug-resistant gram-positive bacteria.
- **Daptomycin** is active against vancomycin-resistant strains of enterococci and *S aureus*.

# Oxazolidinones

---

- Linezolid (Zyvox<sup>®</sup>) is the first available agent which received FDA approval in April 2000; available PO and IV
- Developed in response to need for agents with activity against resistant gram-positives (MRSA, GISA, VRE)

# Linezolid

## Adverse Effects

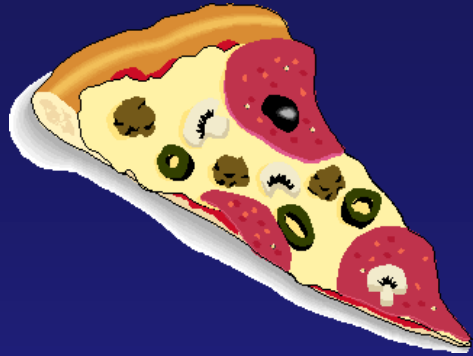
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- Gastrointestinal – nausea, vomiting, diarrhea (6 to 8 %)
- Headache – 6.5%
- Thrombocytopenia – 2 to 4%
  - Most often with treatment durations of > 2 weeks
  - Therapy should be discontinued – platelet counts will return to normal

# Linezolid (Zyvox®)

## Drug–Drug/Food interactions

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Tyramine rich foods, adrenergic drugs and serotonergic drugs should be avoided due to the potential drug-food and drug-drug interactions. A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of more than 100 mg. Therefore, patients receiving linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content.



# Linezolid and Tyramine

## *cont*

Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats such as pepperoni (0.1 to 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5 mg tyramine per 1 teaspoon); tap beers (4 mg tyramine per 12 ounces); red wines (0 to 6 mg tyramine per 8 ounces). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated.

# Antibiotics in Pregnancy

FDA Category	Antibiotics in Category
A	
B	Penicillins, Cephalosporins, Carbapenems (except Imipenem), Daptomycin, Vancomycin (oral), Clindamycin, Erythromycin, Azithromycin, Metronidazole (avoid first trimester),
C	Quinolones, Chloramphenicol, Clarithromycin, Imipenem, Linezolid, Trimethoprim/Sulfa (D if used near term), Vancomycin (IV), Rifampin
D	Tetracyclines (Doxy, Tige, Mino), Aminoglycosides (some put gentamicin as a category C)
X	