

Antibiotics Lecture 1

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.

Antibacterial chemotherapy

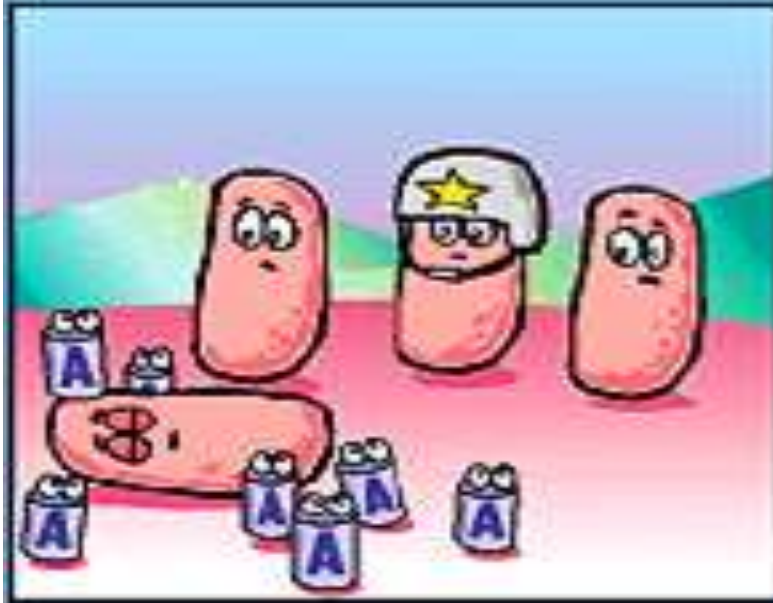
- Antibiotic also can be describe as:
 - a. **narrow-spectrum** that act **only on a single or limited group of microorganism.** *best*
 - B. **broad- spectrum**: antibiotics that are **effective against gram-positive organisms and also against a significant number of gram-negative bacteria.**
 - C. **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.**
↳ explained in the next slides

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

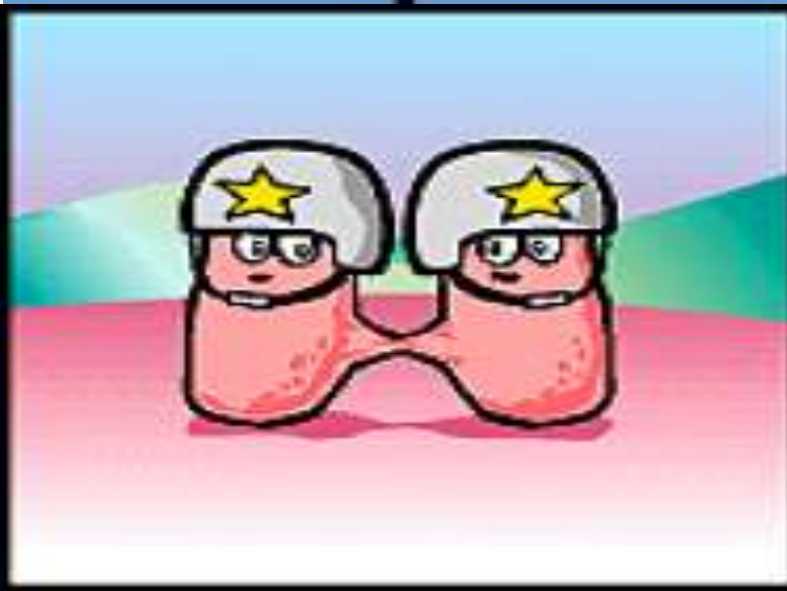
- Another example is the administration of broad-spectrum antibacterial drugs can select for the overgrowth of fungi, most commonly yeasts of the genus *Candida*.
- So, the most narrow-spectrum agents appropriate to the infection should be administered. *Stewardship*



1



2



3



4

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 : no compliance → can't reach steady state.
 - saving antibiotics for a future illness
 - sharing or using someone else's medicine
 - unnecessary A.b increase the Risk ratio of colorectal cancer

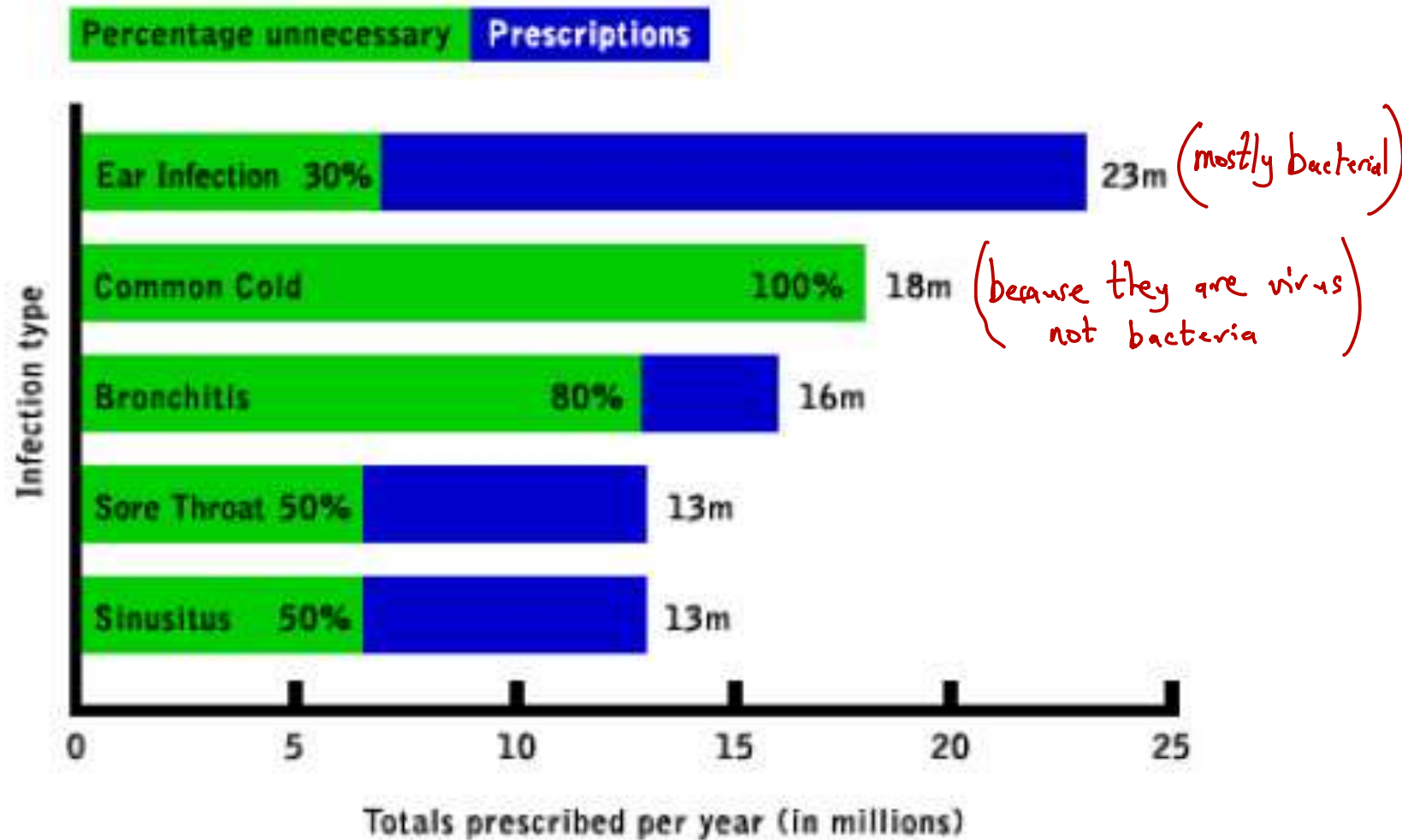
Viral Infection & Antibiotic Timeline

- **After 48 Hours:** The virus uses your cells to cause infection, but then the immune system activates and symptoms (the "flair") naturally begin to decrease.
- **Days 3–4 (Self-Healing):** As the body heals itself, we often go to the pharmacy on Day 3 to take antibiotics.
- **The Misconception:** We think the antibiotics made us feel better, but it was actually our body's natural recovery.
- **Days 4–5 (The Consequence):** The antibiotics end up killing our microflora instead of helping.

— **saving antibiotics for a future illness**

— **sharing or using someone else's medicine**

Unnecessary Antibiotic Prescriptions



that why culturing is important.

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

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.

Misuse: using a drug without knowing that it's harmful.

Abuse: using a drug knowing that it's harmful. (smoking)

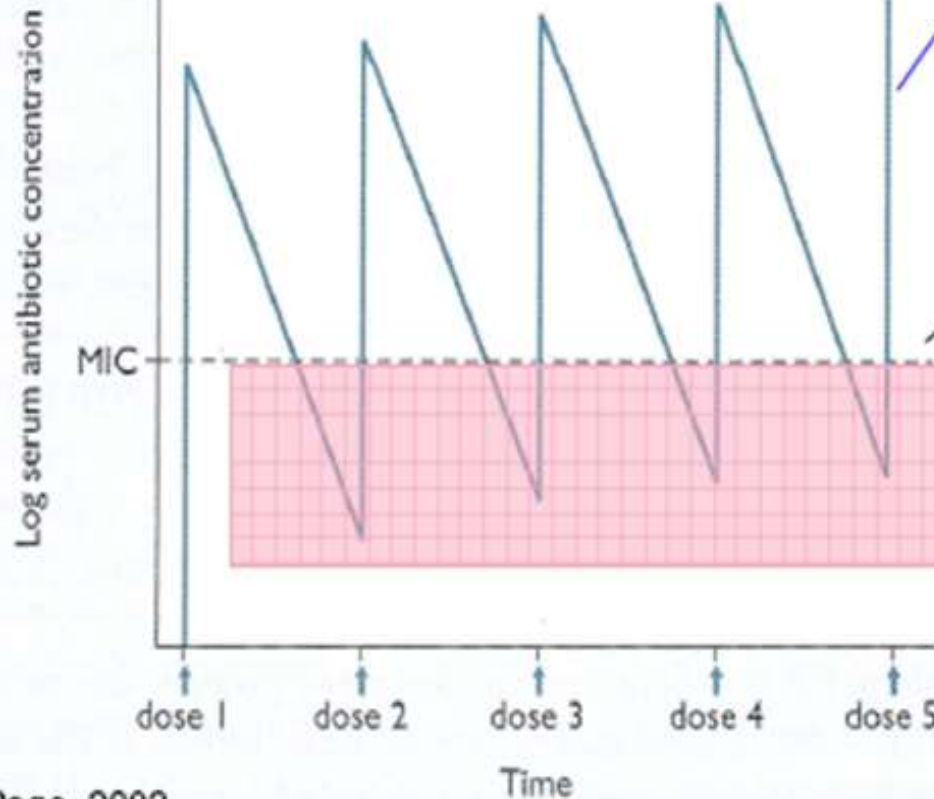
Therapeutics: Keeping above the MIC

Successive doses of drug

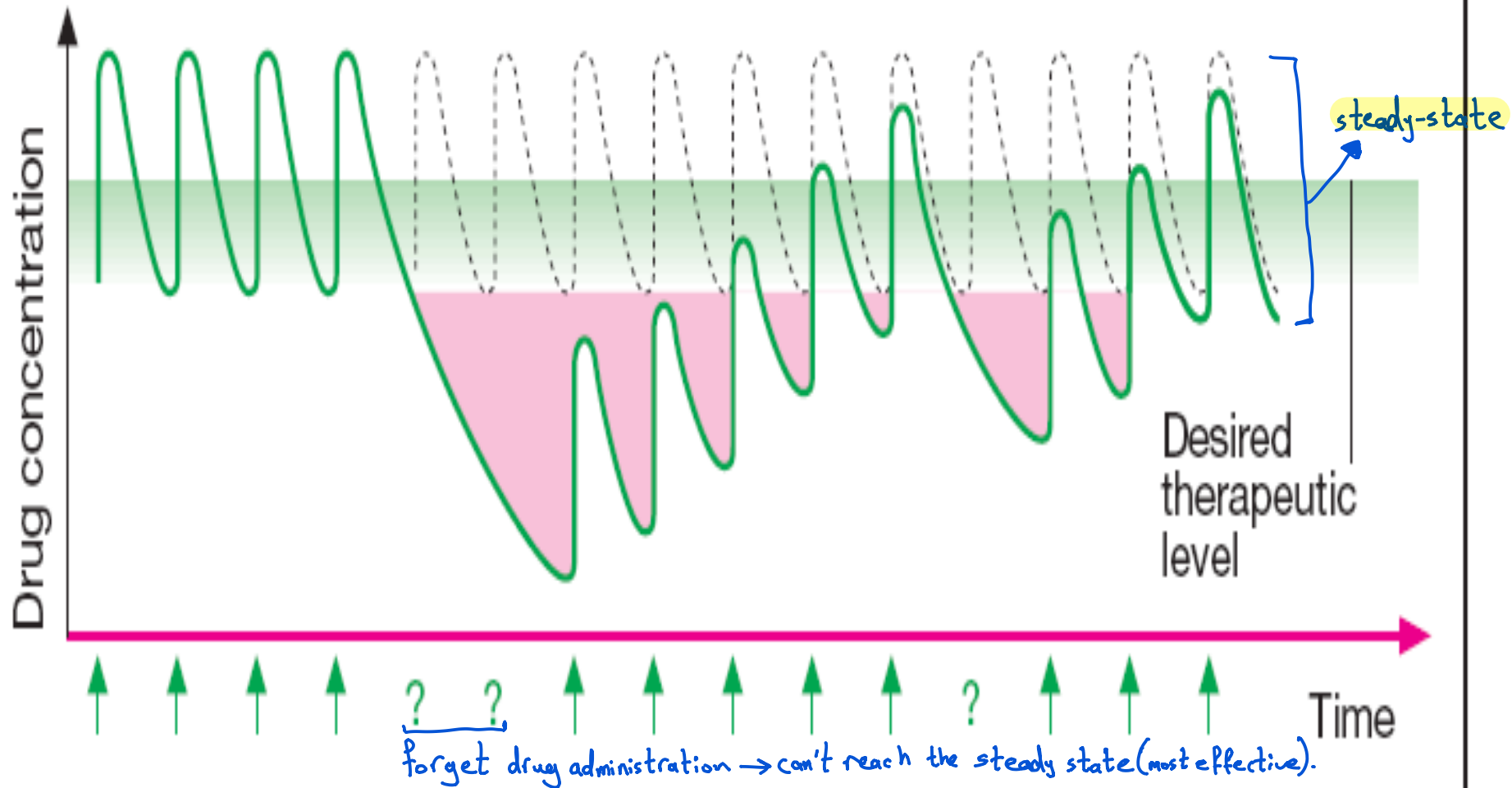
Antibiotic concentration in serum

MIC: Minimal Inhibitory Concentration

Antibiotic level has fallen



• MIC (Minimum Inhibitory Concentration):
The lowest amount of a drug needed to stop bacteria from growing (visible growth). The bacteria might still be alive, just "frozen" in place.



Time course of drug concentration with irregular intake

Therapies (Next slide)

- Prophylaxis
- Empirical → we must know:
- Definite therapy
- Post-treatment suppression therapy.



1. Prophylaxis (الوقاية)

- Definition: Treatment given before an infection occurs to prevent it from starting.
- Difference: There is no active infection yet; the goal is protection.
- Example: Taking an antibiotic before a dental surgery or a malaria pill before traveling to a high-risk area.

2. Empirical Therapy (العلاج التجريبي) *Covers all bacteria in a particular site.*

- Definition: Treatment started immediately based on a doctor's "best guess" before lab results are ready, *before culturing.*
- Difference: An infection is present, but we don't know the exact germ yet. Doctors usually use broad-spectrum drugs here.
- Example: Giving a general antibiotic for a high fever and cough while waiting 48 hours for blood test results.

3. Definite Therapy (العلاج المحدد)

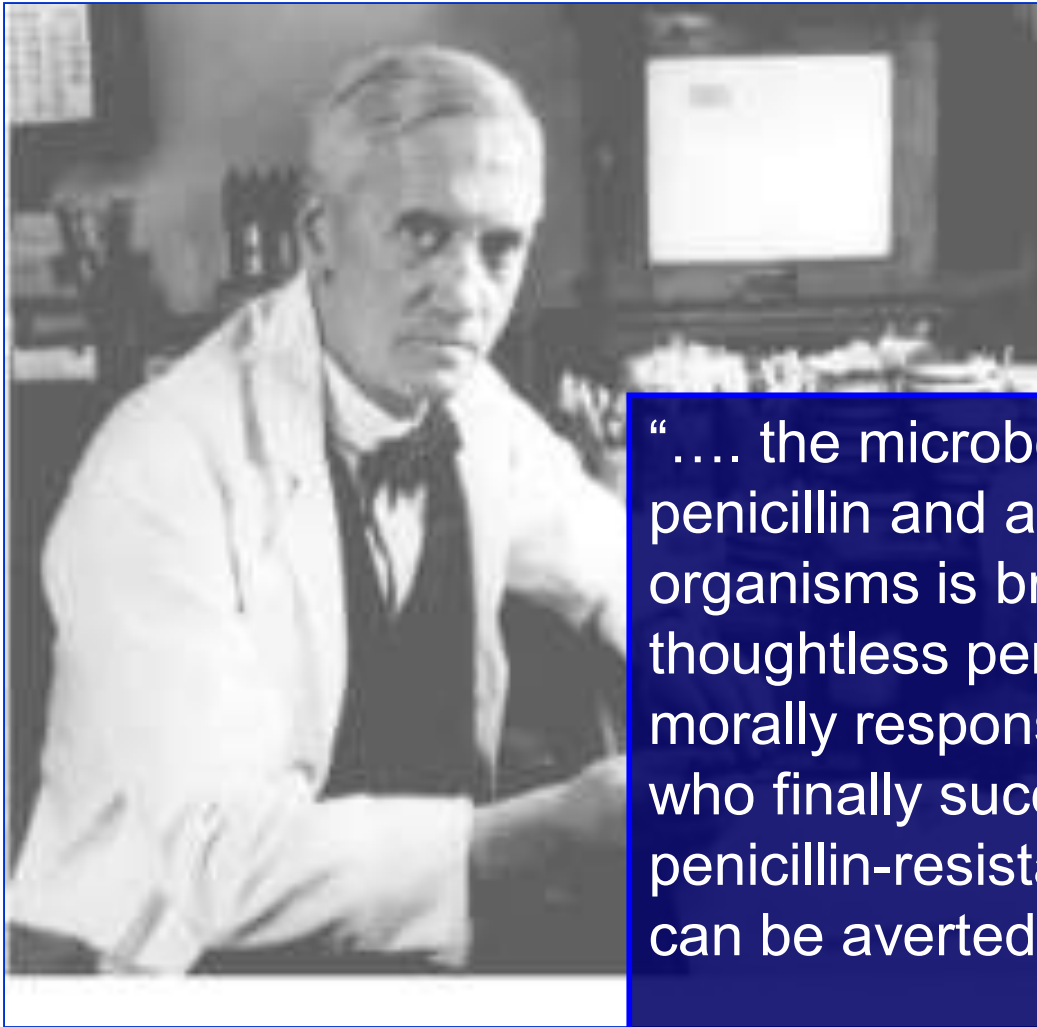
- Definition: Targeted treatment chosen after lab results identify the specific germ and which drug kills it, *after culturing.*
- Difference: This is precise medicine based on evidence. Doctors usually switch to narrow-spectrum drugs here.
- Example: Switching from a general antibiotic to a specific one once the lab confirms you have Strep throat.

4. Post-treatment Suppression Therapy (العلاج القمعي)

- Definition: Low-dose treatment continued after the main infection is cleared to keep it from coming back, *prevent recurrence.*
- Difference: The main "fire" is out, but you are keeping the "coals" from reigniting.
- Example: A patient taking a low-dose antibiotic daily for several months because they suffer from chronic, recurring urinary tract infections (UTIs).

Antibiotics Lecture 2

Antimicrobial Stewardship



“.... the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out... In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted.”

- Sir Alexander Fleming, June 1945

Major influencing factors for antibiotic prescribing.

OTC: Over The Counter



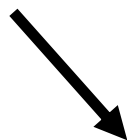
Reasons for Antibiotic Overuse :

Patient Concerns

- Want clear explanation
- Green nasal discharge
- Need to return to work

Physician Concerns

- Patient expects antibiotic
- Diagnostic uncertainty
- Time pressure



Antibiotic Prescription

Higher doses improve antibiotic penetration into target tissues. Furthermore, dosing must be adjusted because different bacteria require specific Minimum Inhibitory Concentrations (MIC) to be effectively killed.

RESISTANCE TO ANTIBIOTIC

Antibiotic	Year Deployed	Resistance Observed
Sulfonamides	1930s	1940s
Penicillin	1943	1946
Streptomycin	1943	1959
Chloramphenicol	1947	1959
Tetracycline	1948	1953
Erythromycin	1952	1988
Vancomycin	1956	1988
Methicillin	1960	1961
Ampicillin	1961	1973
Cephalosporins	1960s	late 1960s

Table 20.2 Microbiology: A Clinical Approach (© Garland Science)

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

Antibiotic brands

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

Common Bacteria by Site of Infection (First step)

Mouth

Peptococcus
Peptostreptococcus
Actinomyces

Skin/Soft Tissue

S. aureus
S. pyogenes
S. epidermidis
Pasteurella

Bone and Joint

S. aureus
S. epidermidis
Streptococci
N. gonorrhoeae
Gram-negative rods

Abdomen

E. coli, *Proteus*
Klebsiella
Enterococcus
Bacteroides sp. (anaerobes)

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 (superbugs)

K. pneumoniae
P. aeruginosa (worst)
Enterobacter sp.
Serratia sp.
S. aureus (MRSA)
E. coli
(after 3 days from hospital entry)

Meningitis

S. pneumoniae
N. meningitidis
H. influenza
Group B Strep
E. coli
Listeria

(The drug administered must cross BBB)

Dosing Matters – Penicillin Example

- Penicillin half-life is only 30-45 minutes
- Retrospective review of Streptococcal infective endocarditis
 - Penicillin given every 4 hours was associated with successful treatment vs every 6 hours (OR 2.79; 95%CI 1.43-5.62)

Deescalation: (empirical → definitive): to decrease antibiotic resistance bacteria strains.

When to combine more than one antibiotic: if one can't kill all the bacteria needed + to not give it a chance to become resistance.

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

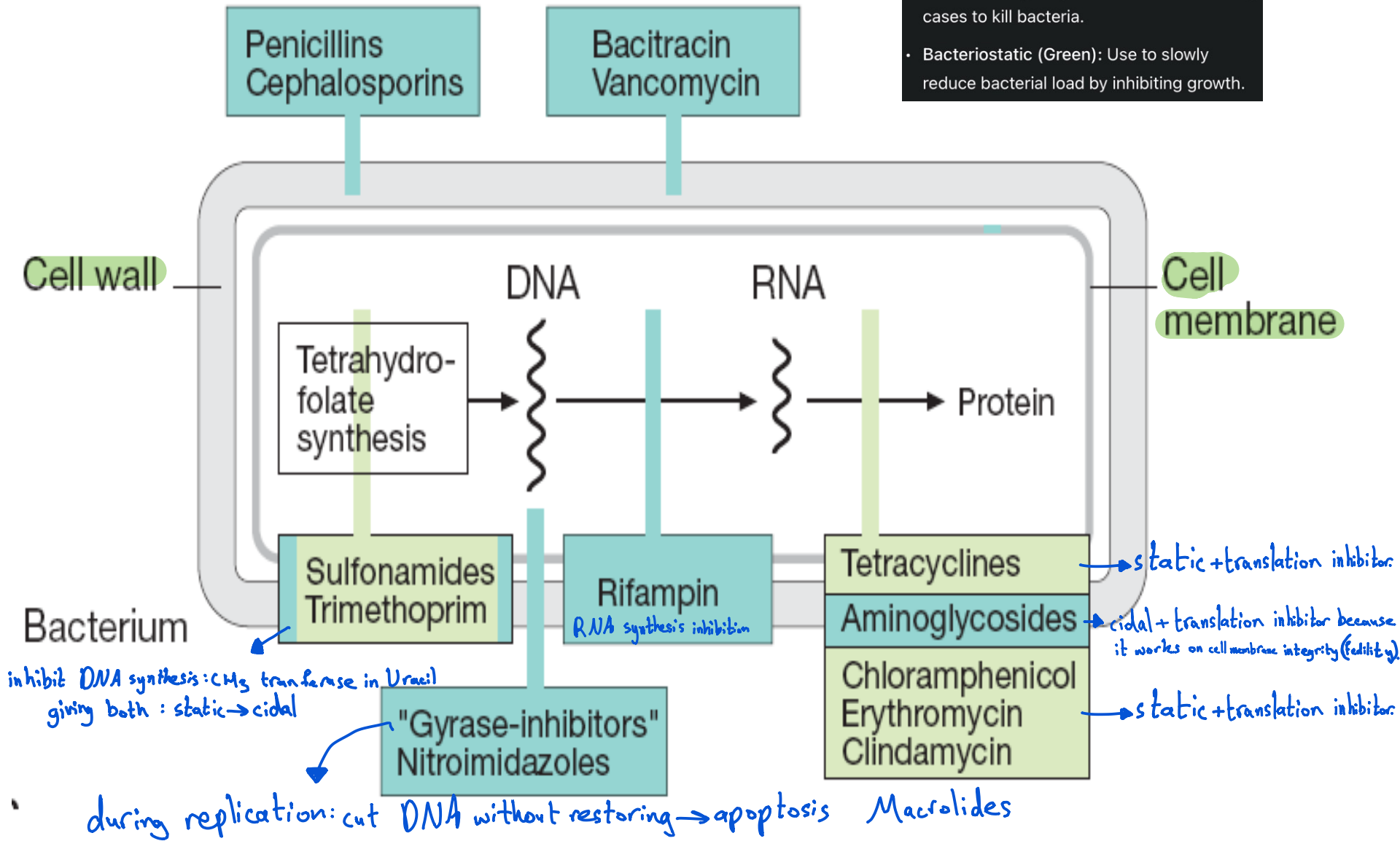
1. Inhibition of the **synthesis and function of folic acid** (Sulphonamides, Trimethoprim)

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

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

Main Molecular Targets

- Bactericidal (Blue): Use for life-threatening cases to kill bacteria.
- Bacteriostatic (Green): Use to slowly reduce bacterial load by inhibiting growth.



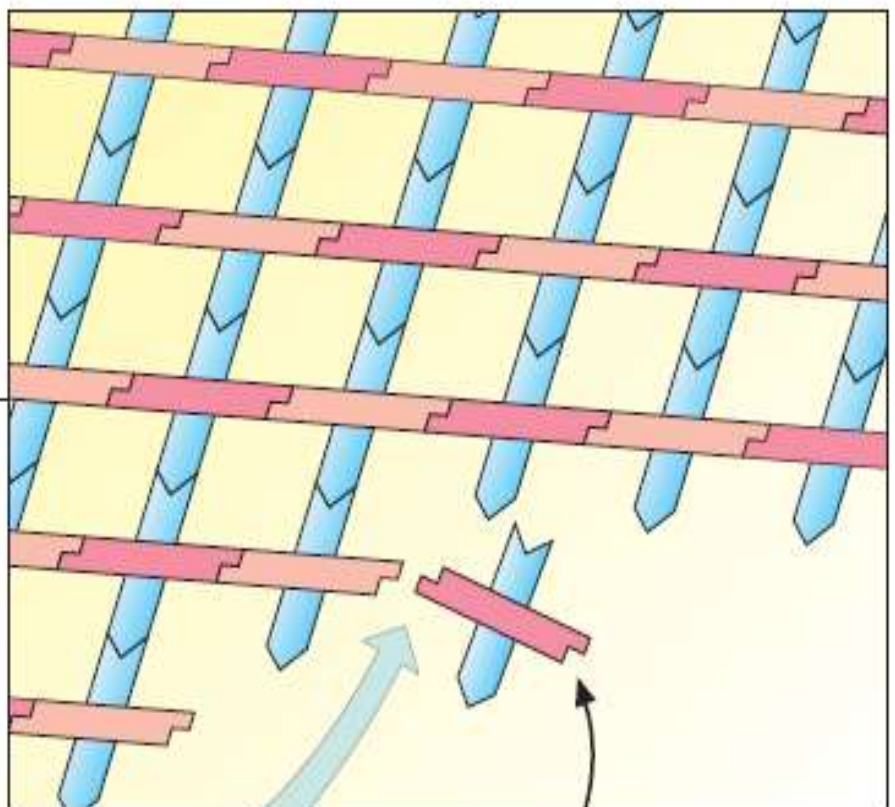
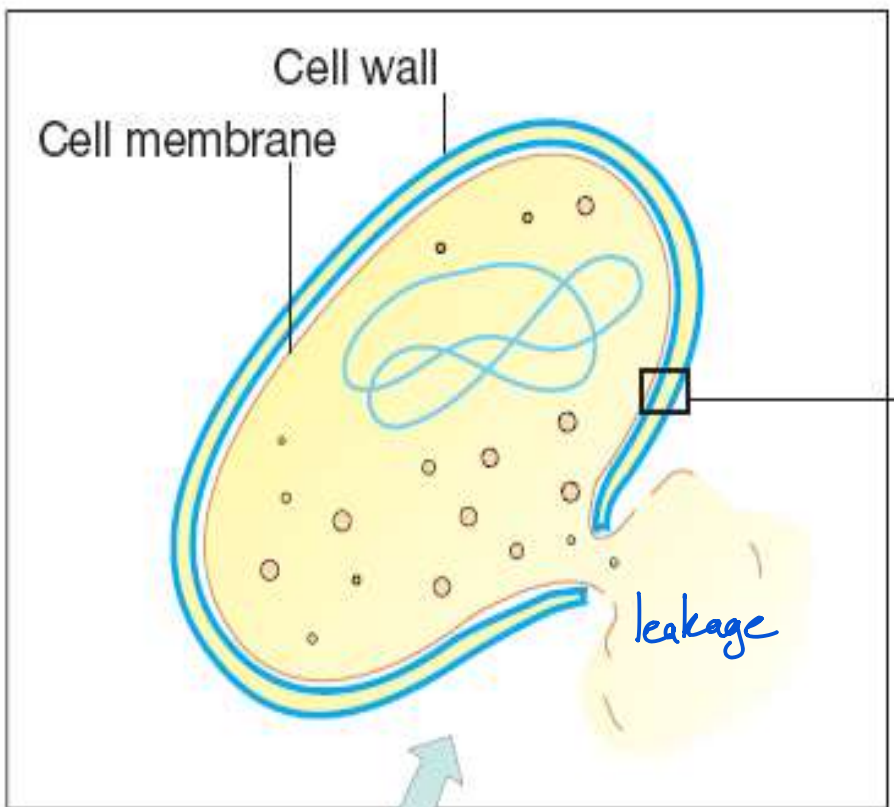
Cell wall inhibitors

- These agents interfere with synthesis of the bacterial cell wall (mammalian cells do not have it). *inhibit Peptidoglycan cross-linking in cell wall leading to cell burst.*
- To be maximally effective, cell wall inhibitors require actively proliferating (multiplying) microorganism.

- The cell wall inhibitors include :

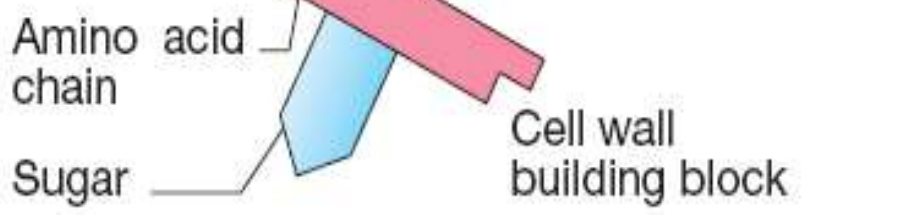
While most cell wall inhibitors target cross-linking, vancomycin and teicoplanin (glycopeptides) differ by directly inhibiting peptidoglycan synthesis.

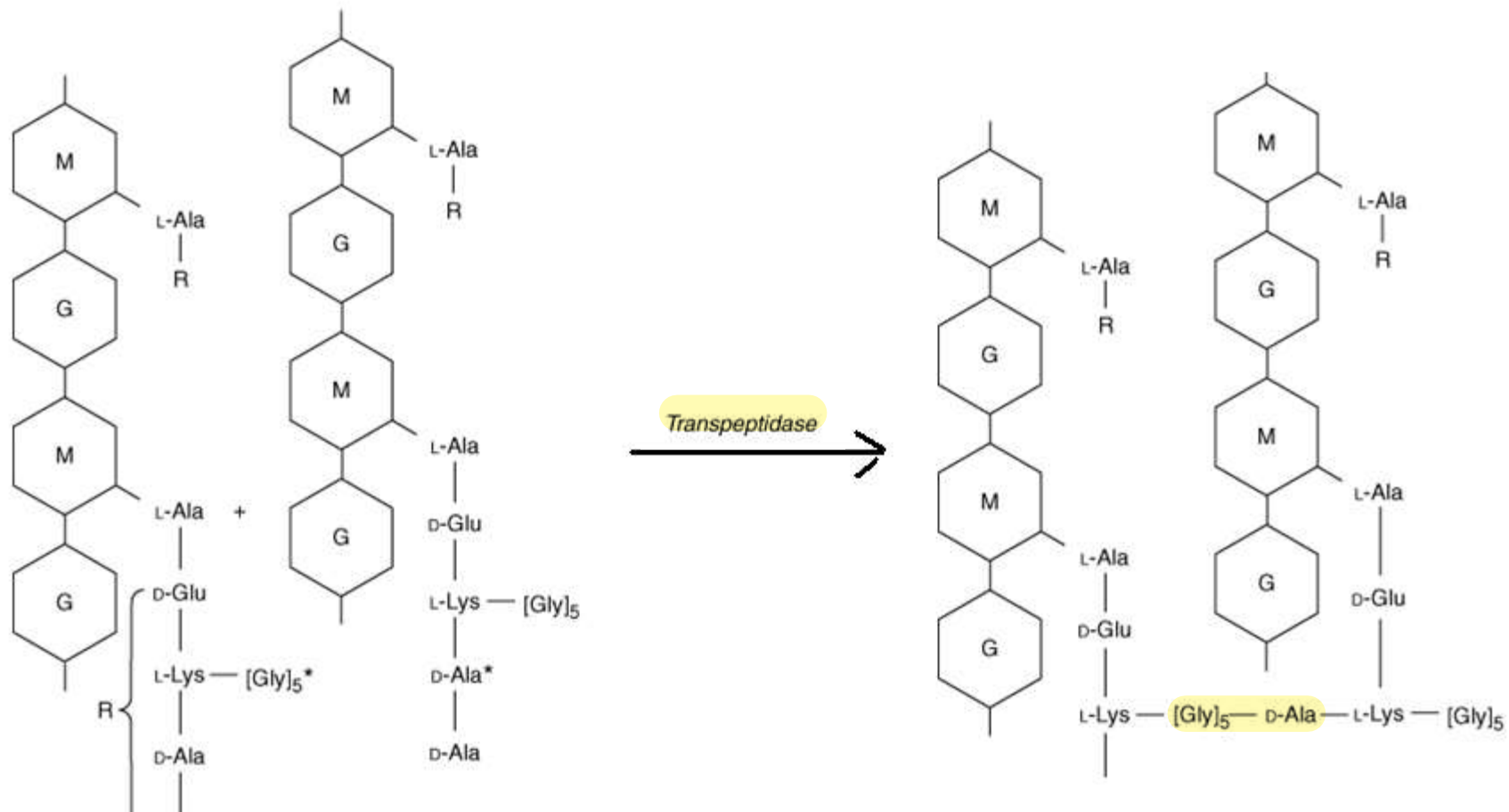
Penicillins, Cephalosporins,, Monobactams, Carbapenems,
and Vancomycin.



Bacterium

Inhibition of cell wall synthesis





The main forms of Penicillins resistance

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

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**. *Augmentin → next lecture.*

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

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

Penicillins classes

- 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 β -lactamases.  Penicillin G, V
 - c. Limited activity against gram negatives.

Antibiotics Lecture 3

IM+IV: destroyed by stomach acid
narrow spectrum

Natural Penicillins

(penicillin G, penicillin VK)

orally + pills: counters stomach acidity.

Gram-positive

pen-susc *S. pneumoniae*

Group A/B/C/G strep

viridans streptococci

Enterococcus

Other

Treponema pallidum (syphilis)

Gram-negative

Neisseria sp. meningitis

Anaerobes

Above the diaphragm

Clostridium sp.

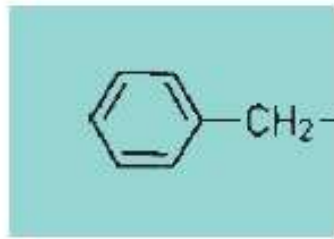
Mouth (Penicillin V empirical cover all 3)

Peptococcus

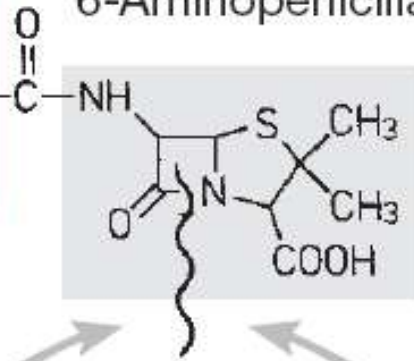
Peptostreptococcus

Actinomyces

*oral odontogenic: narrowest antibiotic: Penicillin G, V.

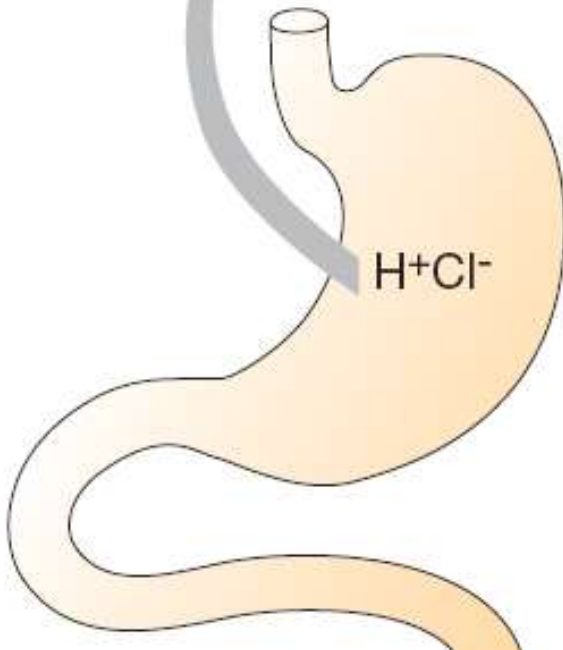


6-Aminopenicillanic acid

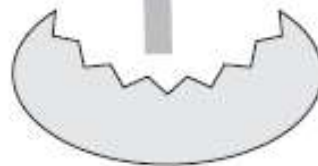


Penicillin G

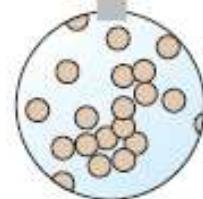
Acid sensitivity



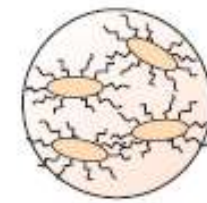
Penicillinase sensitivity



Penicillinase



Staphylococci



Salmonella typhi



E. coli

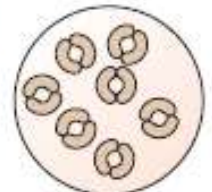
Gram-negative

Not active

Narrow-action spectrum

Active

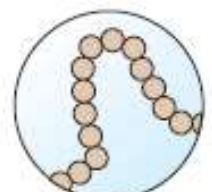
Gram-positive



Gonococci



Pneumococci



Streptococci

Penicillin G clinical uses

- Streptococcal infections that include pneumonia, otitis media, meningitis, and septic arthritis.
- In addition, penicillin G is effective against *Neisseria meningitidis* and *Clostridium tetani*, and *Corynebacterium diphtheriae*, *Treponema pallidum*, and *Listeria monocytogenes*.

Benzathine penicillin

- Benzathine penicillin for intramuscular injection yield low but prolonged drug levels.
- A single intramuscular injection of benzathine penicillin, 1.2 million units, is effective treatment for beta-hemolytic streptococcal pharyngitis; *strep. throat*
- Also prophylactic, given intramuscularly once every 3–4 weeks, it prevents re-infection..
- Reoccurrence of rheumatic fever.
- 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

Benzathine penicillin (Penicillin G)

- Benzylpenicillin (Penicillin V) is more acid stable, is orally active but is less potent than penicillin G.
- 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

Resistance Mechanisms: 1- β -lactamase production
2- protein change: MSSA $\rightarrow$ MRSA

b-lactamase-resistant Penicillins FNCOM

- These include ¹Cloxacillin, ²Flucloxacilin, ³Oxacillin which are well-absorbed orally.
- They also includes ⁴methicillin (not available any more), ⁵na^pcillin.
- Antibacterial spectrum is the same as for penicillin G, but less potent.
- Their use is restricted to treatment of infections caused by penicillins-resistant bacteria. Nonetheless, Many *Staphylococci* are now resistant to them.

Penicillinase-Resistant Penicillins

(nafcillin, oxacillin, methicillin)

Developed to overcome the penicillinase enzyme of *S. aureus* which inactivated natural penicillins, prophylaxis for skin.

Gram-positive

Methicillin-susceptible *S. aureus*

Penicillin-susceptible strains of Streptococci

Skin/Soft Tissue	
<i>S. aureus</i>	empirically
<i>S. pyogenes</i>	↓
<i>S. epidermidis</i>	res
<i>Pasteurella</i>	↓
	cover staph

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 β -lactamase-negative *H. influenzae*.

Aminopenicillins (ampicillin, amoxicillin)

broaderally

Developed to increase activity against
gram-negative aerobes : (Penicillin G + some G-).

Gram-positive

pen-susc *S. aureus*

Pen-susc streptococci

viridans streptococci

Enterococcus sp. ✓

Listeria monocytogenes

Gram-negative

Proteus mirabilis

Salmonella,

some *E. coli*

β L- *H. influenzae* ✓

not active against: 1. b. lactamase staphylococcus.
2. b. lactamase *H. influenzae*.

Upper Respiratory

S. pneumoniae

H. influenzae x

M. catarrhalis x

S. pyogenes

definitive

β -Lactamase Inhibitor Combos

(Unasyn, Augmentin, Timentin, Zosyn)

amoxicillin + clavulanic acid

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

Gram-positive Gram-negative

S. aureus (MSSA)

H. influenzae

E. coli

Proteus sp.

Klebsiella sp.

Neisseria gonorrhoeae

Moraxella catarrhalis

Anaerobes

Bacteroides sp.

"Augmentin is used for children to treat infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* (H. inf), which are frequently found in children who spend a lot of time indoors or in close contact with others (such as in households or daycares)." **not mycoplasma (schools)**

Upper Respiratory

S. pneumoniae
H. influenzae
M. catarrhalis
S. pyogenes

(empirical narrowest possible)

* if culture indicated *Strp. pyog*
definitive treatment: Penicillin V (narrowest)
↓ not available
amoxicillin

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). *endocarditis prophylaxis.*
- Ampicillin is the most active of the oral beta-lactam antibiotics against penicillin-resistant pneumococci and are the preferred beta-lactam antibiotics for treating infections suspected to be caused by these resistant strains.

Extended Spectrum Penicillins

- 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).
- All oral penicillins are best given on an empty stomach to avoid the absorption delay caused by food. **Exception being amoxicillin.**

While most oral penicillins require an empty stomach for optimal absorption, amoxicillin is an exception because it penetrates bacteria so effectively that food intake does not significantly hinder its clinical success.

Extended 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.

Extended 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. (treated with excretion)

Combination therapy: Using more than one drug from different groups; ex: cell wall inhibitor + translation inhibitor.

Carboxypenicillins (carbenicillin, ticarcillin)

The Extended
Spectrum Pen.

Developed to further increase activity against resistant gram-negative aerobes (more penetration for negative and aerobic)

Gram-positive

marginal

Gram-negative

Proteus mirabilis

Salmonella, Shigella

some *E. coli*

β L- *H. influenzae*

Enterobacter sp.

Pseudomonas aeruginosa ✓

Ureidopenicillins (piperacillin, azlocillin)

widest
spectrum
penicillin

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

β L- *H. influenzae*

Enterobacter sp.

Pseudomonas aeruginosa

Serratia marcescens ✓

some *Klebsiella sp.* ✓

β -Lactamase Inhibitor Combos

(Unasyn, Augmentin, Timentin, Zosyn)

Tazosyn $\rightarrow$ piperacillin + Tazobactam
Developed to gain or enhance activity against β -
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 ✓

• Hospital acquired patients: piperacillin + vancomycin

Unwanted effects

- MRSA changed the Penicillin binding protein and became resistant to all cell wall inhibitors.

- 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. (haptin), new protein → produce antibodies. (allergic)

10% common
↑
rbc
metabolites

- 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). The widest spectrum is the one that can mostly cause diarrhoea.

So why Oral Augmentin > Tazosyn? because Tazosyn is diluted until reaching GIT, but Aug not absorbed 100% and directly attack flora.
↓
IV

- All Penicillins, particularly Methicillin, have the potential to cause acute nephritis, thus Methicillin is no longer available.

Sensitivity reactions → anaphylaxis, hypotension, bronchoconstriction, ↑ histamine.
→ skin rash, fever.

Sensitivity test: حساسية
↓
immune reaction: Hypersensitivity
Swelling

Antibiotics Lecture 4

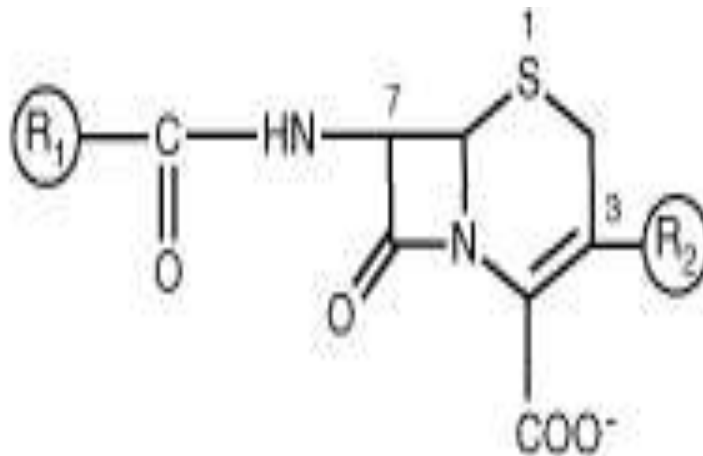
Cephalosporins

(for penicillin hypersensitive people): 10%

- Are also b-lactam antibiotics isolated from a strain of *Streptomyces*.
- There are a large number available for clinical use, variously termed “first- second- third- fourth generations. based on the year: 1 → 4
- They are bactericidal and work in the same way as the penicillins.
- Resistance is due to ¹b-lactamases, ²permeability mutants and ³mutations 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.**



β -lactam antibiotic
isolated from *Streptomyces*

Cephalosporins

(All 4 generations are
not active against enterococci)

increasing gram(-) resistance

1st gen (dzll)

- Cefadroxil (oral)
- Cefazolin (injectable)
- Cephalexin (oral)
- Cephalothin (oral)

* 1st gen $\approx$ methicillin-like
* For penicillinase resistance.
* Skin best: strep, staph.
* Prophylaxis:

- oral: for small injuries.
- injected: better penetration than methicillin (presurgery)

2nd gen (ctrx)

- Cefaclor
- Cefoxitin
- Cefuroxime
- Cefotetan

anaerobes

* Cefuroxime (Zinat) $\approx$ Augmentin-like
* staph; strep; gram-; abdominal anaerobes

3rd gen

- Cefnidir: oral
- Cefixime: oral
- Cefotaxime: inject
- Ceftazidime: *P. aeruginosa*
- Ceftibuten
- Ceftriaxone: inject

BBB permeable

* Ceftazidime $\approx$ Tazosyn-like

* For Meningitis if patient is >42 weeks;
because if we give Ceftriaxone to baby
 <42 week with hyperbilirubinemia $\rightarrow$ bilirubin precipitate
drug physiological interact $\rightarrow$ death, so we will
give him cefotaxime instead.

* Misuse of 3rd gen cephalosporin can induce ESBL gene on plasmid: ¹proteus, ²ecoli, ³k.pneumonia.

* Ceftazidime + Avibactam $\rightarrow$ inhibits β -lactamase.

* cefoperazone + ceftazidime $\rightarrow$ for *P. aeruginosa*.

4th gen

Cefepime

* Cefamandole: Extended;
gram (+, -) and *P. aeruginosa*
* Be careful when using; used
for multiple organ infection.
* It doesn't induce ESBL.

Cephalosporins clinical uses

- Some cephalosporins are given orally, eg. cephalexin, but most are administered intramuscularly or intravenously.
- Cephalosporins are second choice antibiotics for many infections including Gram-positive cocci such as *Staphylococcus*, *Streptococcus* and *Pneumococcus*, and Gram-positive rods such as *Clostridium*.
- They are first choice agents against Gram-negative rods of the *Enterobacteriaceae* such as *E. coli*, *Enterobacter* and *Klebsiella*.

1st generation ^(act as methicillin)

- 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 ²*S. aureus*, and ³*S. epidermidis*) are susceptible.

First Generation Cephalosporins

Methicillin-like

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 ✓

Doesn't include: H. inf and catralasis.

- 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. Abdominal surgeries where anaerobics live.

Cephalosporins generations

Second generation: have greater activity against ² three additional gram-negative organism : H¹ influenza, Neiseria, and ³ Enterbactor erogenes. 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. *for children with no mycoplasma.*

Second Generation Cephalosporins

Spectrum of Activity (Augmentin-like)

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. ✓

enterobacter ✓

} → 1st gen

Second Generation Cephalosporins

Spectrum of Activity

The cephamycins (¹cefoxitin and ²cefotetan)
are the only 2nd generation cephalosporins
that have activity against anaerobes

Anaerobes (lower diaphragm)

Bacteroides fragilis

Bacteroides fragilis group

Third-generation cephalosporins

- generally are less active than first-generation agents against gram-positive cocci,
- but they are much more active against the Enterobacteriaceae, including beta-lactamase-producing strains.
- A subset of third-generation agents (*ceftazidime* and *cefoperazone*) also is active against *P. aeruginosa*.

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 ^{few neutrophils} 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

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.

Antibiotics Lecture 5

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
↳ hospital acquired

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

Fourth Generation Cephalosporins

- 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 β -lactamases; poor inducer of extended-spectrum β -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

People $\begin{cases} \rightarrow 90\% \text{ not hypersensitive from Penicillin} \\ \rightarrow 10\% \text{ hypersensitive from Penicillin} \end{cases}$ $\begin{cases} \rightarrow 10\% \text{ also hypersensitive from cephalosporins. (1\% of people)} \\ \rightarrow 90\% \text{ not hypersensitive from cephalosporins.} \end{cases}$

- **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. *Because ceftriaxone (disulfiram-like) is similar to ADH, it'll bind to acetaldehyde instead of the ADH, leading to not metabolizing acetaldehyde $\rightarrow$ nausea (stop wine addicts).*

2) **Bleeding**: some cephalosporins have an **anti vitamin K effect**, and may cause bleeding (**hypoprothrombinemia**). *How?*

Ceftriaxone binds to prothrombin, which won't allow prothrombin to become thrombin (platelet-aggregation coagulation factor).

Cephalosporins interactions

- Ceftriaxone and calcium product, FDA warning. (Food and drug administration)

- **Note**

cefoperazone and ceftriaxone are exceptions because they are

excreted predominantly in the bile, not in kidney like other Cephalosporins.

So Ceftriaxone is good for people with kidney failure, and better because ²no need to adjust the dose.

↓
because no relationship with glomerular filtration in renal failure.

Cephalosporins Interactions & Excretion

- Interaction Warning: There is an FDA warning regarding the use of Ceftriaxone combined with calcium products.
- Excretion Exception: Unlike other Cephalosporins (which go through the kidneys), Cefoperazone and Ceftriaxone are excreted predominantly in the bile.
- Kidney Failure Benefit: Because Ceftriaxone relies on bile rather than glomerular filtration, it is safe for patients with kidney failure and requires no dose adjustment.

not required



Ceftobiprole – Injectable Anti-MRSA Cephalosporin Antibiotic

**US approval date:
2011**

not required

Ceftobiprole coverage and pharmacokinetic

- ✓ Ceftobiprole, a novel, broad-spectrum, parenteral cephalosporin, inhibits the cell-wall synthesis of penicillin-binding proteins (pbps) pbp2a and pbp2x, responsible for the resistance in staphylococci and pneumococci, respectively.
- ✓ Ceftobiprole has good activity against :
 - Gram-positive aerobes and anaerobes; methicillin-resistant staphylococcus aureus (MRSA) and methicillin-resistant staphylococcus epidermidis (MRSE), penicillin-resistant streptococcus pneumoniae, enterococcus faecalis as well as many gram-negative bacilli

↓
No cephalosporine is active against it.
 - Ceftobiprole is relatively **inactive against acinetobacter** species.
 - Its ability to bind relevant pbps of resistant gram-positive and gram-negative bacteria indicates **its potential use in the treatment of hospital-acquired pneumonia and complicated skin and skin-structure infections (CSSSIS).**

Carbapenem (best drugs) → Me

- 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,** *avoid its metabolism, excretion.*
Potentiation Synergism

Carbapenems

(broader than cefapime in enterococcus)

(Imipenem, Meropenem and Ertapenem)

Tinam

- All are injectable
- Most broad spectrum of activity of all antimicrobials
- Have activity against gram-positive and gram-negative aerobes and anaerobes, ESBL
- Bacteria not covered by carbapenems include MRSA, VRE, coagulase-negative staph, *C. difficile*, *Nocardia*
- Additional ertapenem exceptions:
 - ***Pseudomonas* and *Enterococcus***

* Imipenem misused instead of Meropenem increases death (x3).

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;

• Giving anti-cancer drugs causes febrile neutropenia (low immunity) $\xrightarrow{\text{treatment}}$ carbapenem.

Carbapenem

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

• Neurotoxicity, Nausea, and vomiting are mostly side-effects of: Imipenem/cilistatin

Class A Carbapenemases

(Ticam misuse)

- Most common in *Klebsiella pneumoniae* (KPC)
- Also seen in *E. coli*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Serratia*, *Pseudomonas* and *Proteus spp.*
- Very often with multiple other drug resistance mechanisms, resistance profile similar to ESBL but also carbapenem resistant
- Became problem in New York City first in 2002-2003 and is being increasingly recognized in Mid-Atlantic US.
 - Meropenem: not susceptible to carbapenemases.
 - so it can be used to kill bacteria that produce carbapenemase
- Spreading across species to other gram-negatives and enterobacteriaceae

Antibiotics Lecture 6

Vancomycin

- Vancomycin is bactericidal and acts by inhibiting cell wall synthesis. *inhibits cross-linking and takes place of alanine → part of a base peptidoglycan.*
- it is active only against gram-positive bacteria, particularly staphylococci.
- Its special clinical use is in treating ¹methicillin-resistant staphylococci, ²*Ampicillin* resistant enterococci and ³*Clostridium difficile* (which causes pseudomembranous colitis). *orally for G.I.T.*
Metronidazole drug is better for C.difficile.
- The main indication for parenteral vancomycin is sepsis or endocarditis caused by methicillin-resistant staphylococci.
↓
due to enterococci

Vancomycin

better than Carbapenems for
Staphs because it's narrower.
(Achieve Stewardship)

- 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. Next slide:
and cephalosporins 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.

The Core Concept: Synergistic Treatment for Endocarditis

1. The Goal: Treat Enterococcal Endocarditis (an infection of the heart caused by Enterococcus, a Gram-positive bacteria).
2. The Mechanism (Synergy): You need two drugs working together:
 - Cell Wall Inhibitor: Breaks open the bacteria. (Ampicillin)
 - Protein Synthesis Inhibitor: Enters through the holes and kills the bacteria from the inside. (Gentamicin)

The Two Treatment Options: /

- Plan A (Standard "AmpGent"): /

Use Ampicillin (Cell Wall) + Gentamicin (Protein Synthesis).

- Note: Even though Ampicillin is famous for Gram-negative coverage, it is also the standard choice for Enterococci (Gram-positive).
- Plan B (The Exception in the Image):

If the patient has a serious Penicillin Allergy, you cannot use Ampicillin.

Instead, you use Vancomycin (Cell Wall) + Gentamicin.

²
"vancgents"

We started using vancgents because:

- ² Gentamicin acts only on Gram-negative bacteria and cannot kill the Gram-positive enterococci.
- ³ Enterococci became resistant to ampicillin.

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. → histamine released → anaphylaxis ^{so} → stop vancomycin administration.

- Unwanted effects are a series problem and include fever, rashes and local phlebitis.

- ¹Ototoxicity and ²nephrotoxicity can occur and ³hypersensitivity reactions are occasionally encountered.

mainly because of gentamicin

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.

Monobactams

Spectrum of Activity

Aztreonam bind preferentially to PBP 3 of gram-negative aerobes; has little to no activity against gram-positives or anaerobes

Gram-negative

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

H. influenzae, *M. catarrhalis*

Enterobacter, *Citrobacter*, *Providencia*, *Morganella*

Salmonella, *Shigella*

Pseudomonas aeruginosa

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.

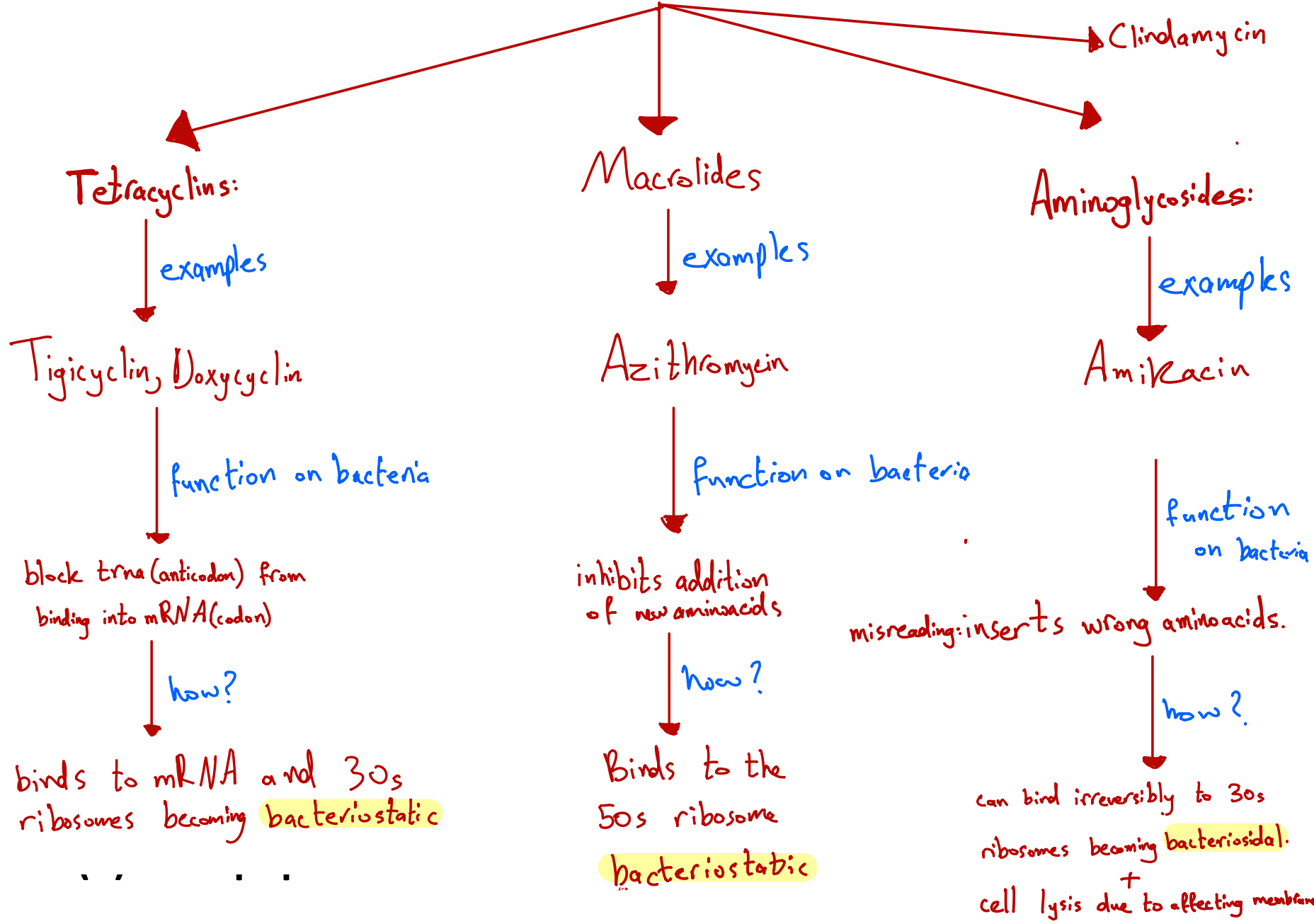
Protein synthesis inhibitors

- Tetracyclins: block tRNA from binding into mRNA.
- Aminoglycosides: inserts wrong amino acids.

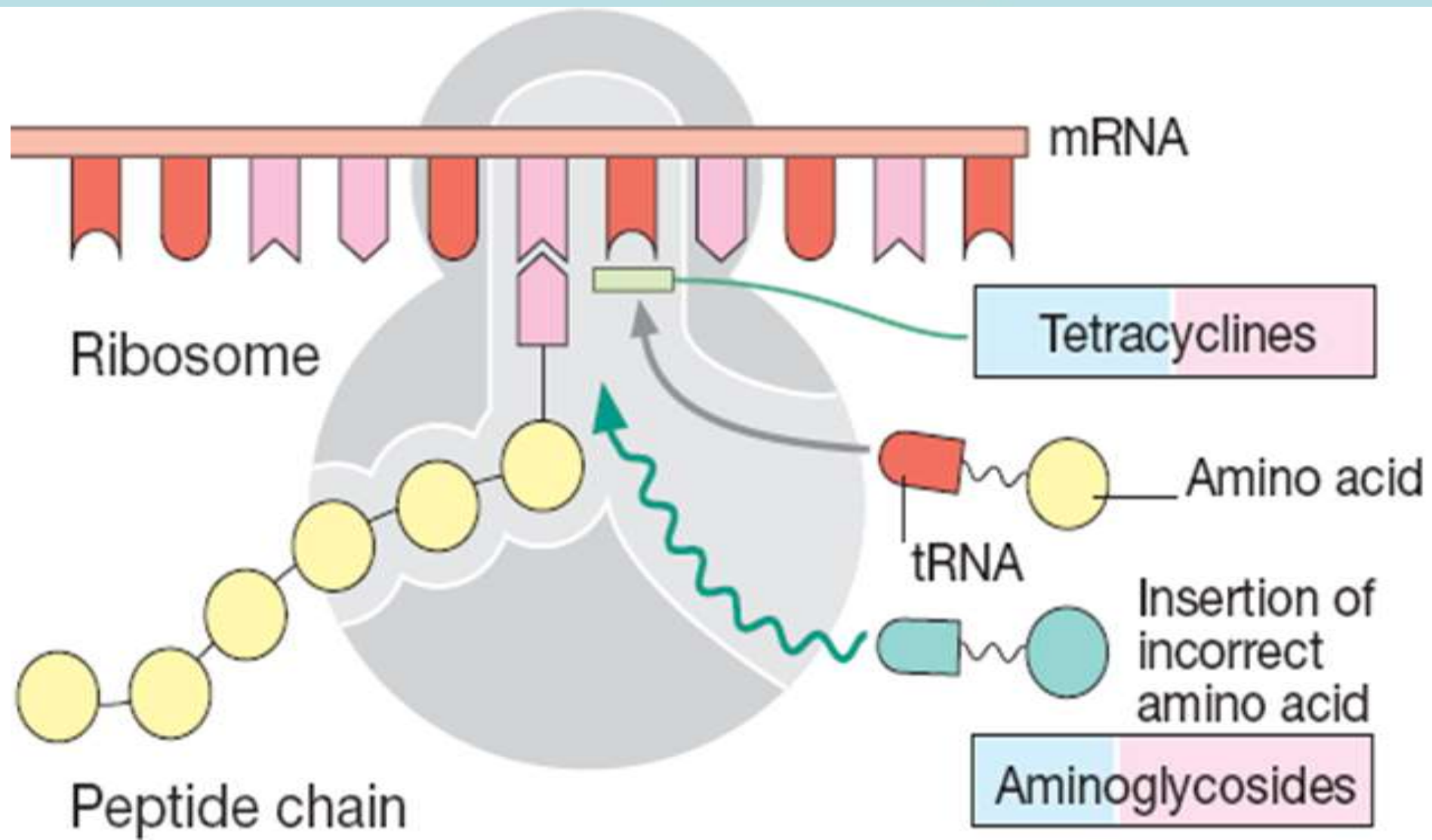
❖ The main ribosomal processes they interfere with are :

- (1) binding of aminoacyl-tRNA
- (2) normal codon:anticodon recognition
- (3) transpeptidation

Protein Synthesis Inhibitors (In following lectures)



DNA → mRNA →  → proteins



Tetracyclines

- Tetracycline, Methacycline, Moxycycline, doxycycline, minocycline and **Tigecycline**. → overcomes the multi-drug resistant pump → covers most bacteria except: *p.aeruginosa* and enterobacter
- 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).

Note for the next slide: Doxycycline is a tetracycline.
Azithromycin is a macrolide (discussed next lecture).

CHLAMYDIAL INFECTIONS

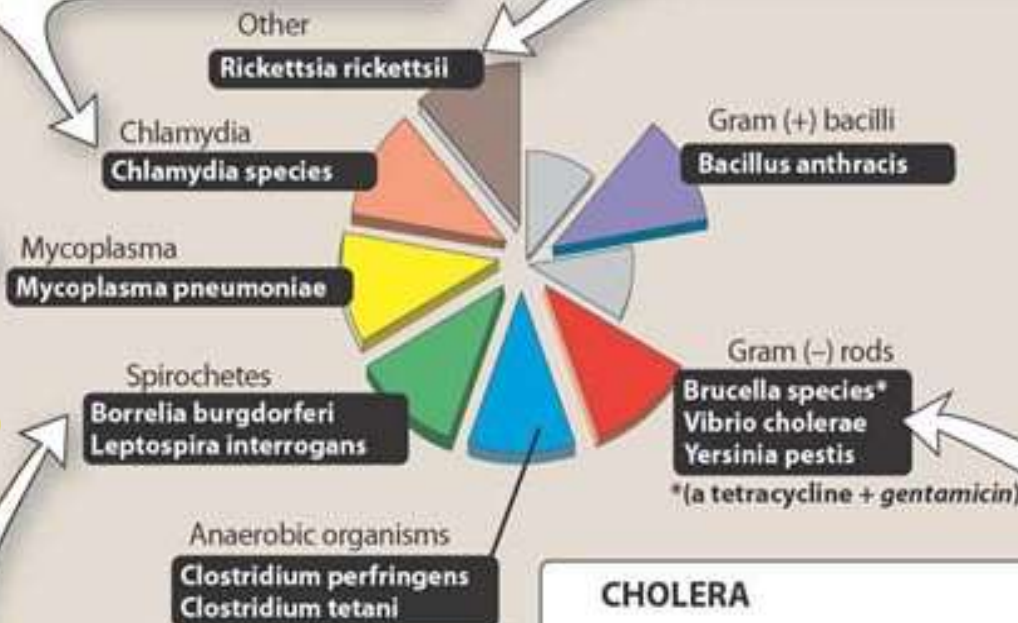
- **Chlamydia trachomatis** is the major cause of sexually transmitted disease in the United States. It causes nongonococcal urethritis, pelvic inflammatory disease, and lymphogranuloma venereum.
- **Chlamydia psittaci** causes psittacosis, which usually takes the form of pneumonia. Other clinical forms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

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. *by ties*

MYCOPLASMA PNEUMONIA

- **Mycooplasm 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. *by Tetracyclins definitive treatment for mycoplasma*
- Treatment with **marcrolides** is also effective. *azithromycin*



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 meningoencephalitis 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 **gastro-intestinal tract**, where it secretes an **enterotoxin** that produces diarrhea.
- **Treatment** includes **doxycycline**, which reduces the number of intestinal vibrios, and fluid replacement.

Antibiotics Lecture 7

Tetracyclines

(mainly Doxacyclin)

- Their main clinical uses are :

(1) ¹mycoplasma and ²chlamydia infections

(2) A tetracycline—usually in combination with an aminoglycoside—is indicated for ³brucellosis.
→ it's intracellular, so we need a drug with a good penetration: lipophilic tetracycline

(3) They are used in combination regimens to treat gastric and duodenal ulcer disease caused by ⁴*Helicobacter p*

(4) ⁵Acne *Achenae* bacteria

(5) ⁶syphilis

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. *Might cause firing sensation → so take it sitting with 2 cups of water.*
- 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. *C.difficile and pseudomonas are selectively chosen by Tetracyclin. Tetracyclin has a high chance of producing superinfections and diarrhea because of its broad spectrum.*
- They are deposited in growing bones and teeth, causing staining and sometimes dental hypoplasia and bone deformities, *because of calcium-chelating.*
- Phototoxicity: for example, severe sunburn, occurs when the patient receiving a tetracycline is exposed to sun or ultra-violet rays.
- *Excreted in sweat and tears.*
- They shouldn't be given to children, pregnant women or nursing mothers. (may causes hepatotoxicity in pregnant women), *because liver changes in pregnant ladies.*
- *So we must check liver enzymes (ALT,AST) before taking Tetracycline.*

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.

Tigecycline

covers most bacteria except:
P. aeruginosa and *Enterobacter*



Escherichia coli, *Enterococcus faecalis* (vancomycin-susceptible only),
Staphylococcus aureus (MRSA and methicillin-susceptible and resistant isolates),
Streptococcus pyogenes,
Streptococcus anginosus grp,
Streptococcus agalactiae,
or *Bacteroides fragilis*

Lower Respiratory Community

S. pneumoniae
H. influenzae
K. pneumoniae
Legionella pneumophila
Mycoplasma, *Chlamydia*



E. coli,
Enterococcus faecalis (vancomycin-susceptible only),
S. aureus (methicillin-susceptible only),
Citrobacter freundii,
Enterobacter cloacae,
Klebsiella pneumoniae,

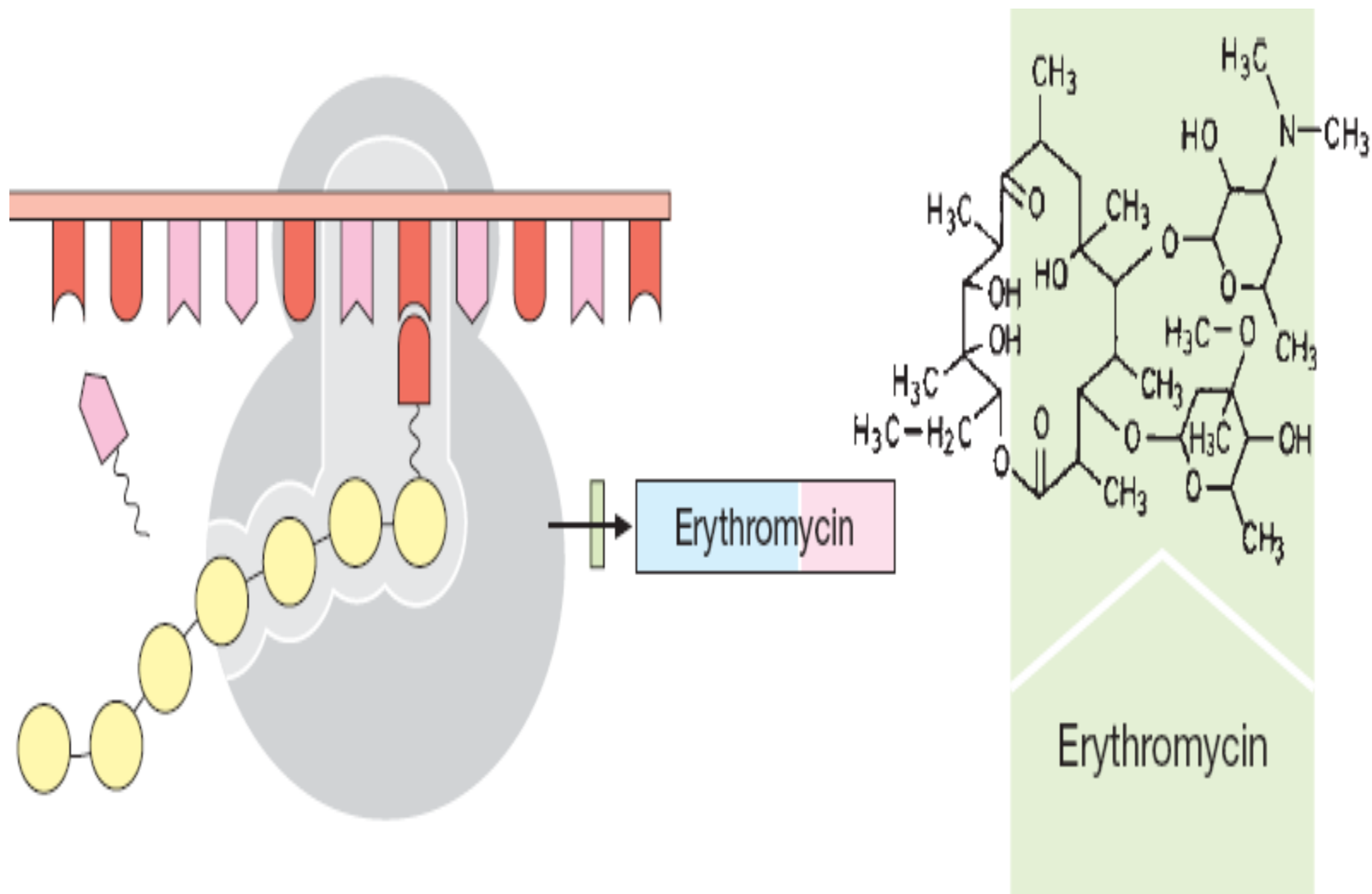


Streptococcus pneumoniae (penicillin-susceptible isolates)
Haemophilus influenzae,
Legionella pneumophila

Tigeciclin is empirically
used to treat community
pneumoniae because it
attacks all the Lower RS
bacteria. Mortality rate
increased slightly due to Tigecycline,
so it is a last drug resort.
(weight benefit-risk).

TACE **Macrolides** orally (inactive against *K. pneumoniae*)

- 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**.



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.

Chlamydia

Chlamydia pneumoniae
Chlamydia psittaci
Chlamydia trachomatis

Mycoplasma

Mycoplasma pneumoniae
Ureaplasma urealyticum

Spirochetes

Treponema pallidum

Gram (+) cocci

Staphylococcus aureus
Streptococcus pyogenes
Streptococcus pneumoniae

Gram (+) bacilli

Corynebacterium diphtheriae

Gram (-) cocci

Moraxella catarrhalis
Neisseria gonorrhoeae

Gram (-) rods

Bordetella pertussis
Campylobacter jejuni
Haemophilus influenzae
Legionella pneumophila

Upper Respiratory

S. pneumoniae
H. influenzae (imperial)
M. catarrhalis
S. pyogenes

Macrolides clinical uses

not imperial against L.R.S

because it's inactive on k.pnem

so we add an antibiotic that kills k.pneumonia like 3rd gen cephalosporins

Lower Respiratory Community
S. pneumoniae
H. influenzae
K. pneumoniae X
Legionella pneumophila
Mycoplasma, Chlamydia

- 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, before using Tigecycline

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. *Can enter neutrophils and be recruited with it to the inflammation site.*
- The drug is slowly released from tissues (tissue half-life of 2–4 days) to produce an elimination half-life approaching 3 days. *Next slide:*

Azithromycin

Why is this special?

Most antibiotics disappear from your body in a few hours, so you have to take them 2 or 3 times a day to keep them working.

Because Azithromycin has such a long half-life (it leaves very slowly), you can stop taking the pills after just 3–5 days, but the medicine stays in your body fighting the bacteria for about 10 days total. (*become reservoir in the patients body*).

In short: You stop swallowing the pills, but the pills haven't stopped working yet.

Macrolides

(Erythromycin)

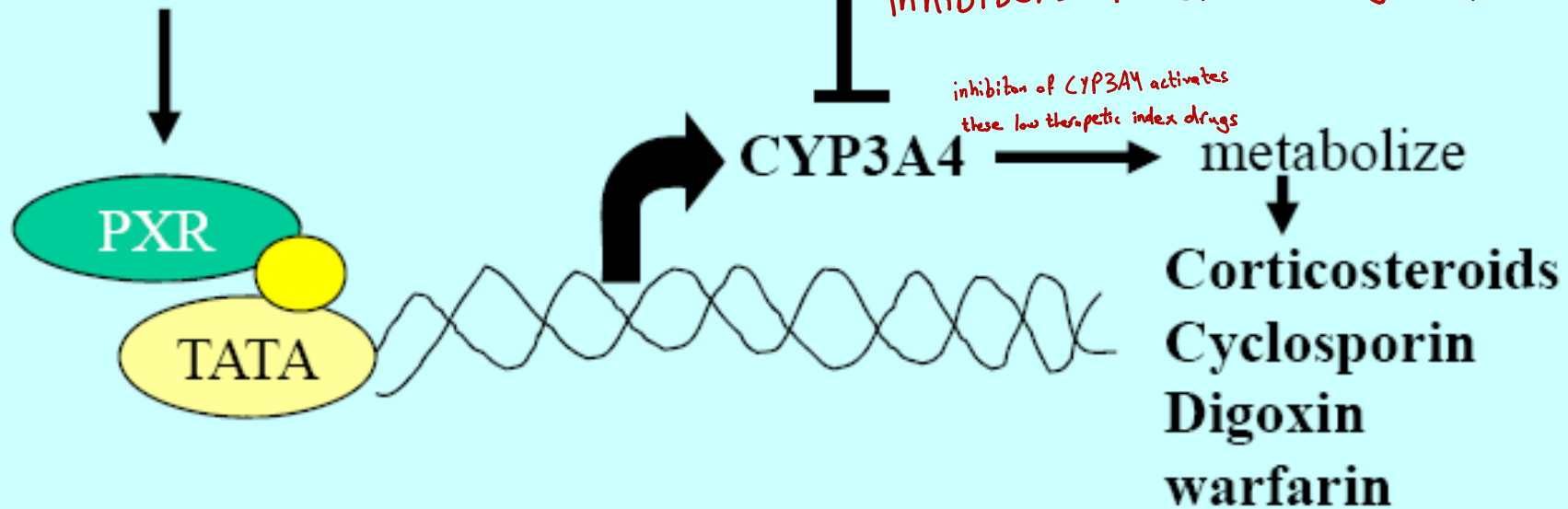
- ¹ **Ototoxicity: Transient deafness** has been associated with erythromycin, especially at high dosages.
- ² **Cholestatic jaundice** especially with the estolate form of erythromycin, *affects the enterohepatic cycle.*

Antibiotics Lecture 8

Drug Interactions of Macrolides

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

Ligand i.e. inducers, subs)



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

Aminoglycosides

TAG

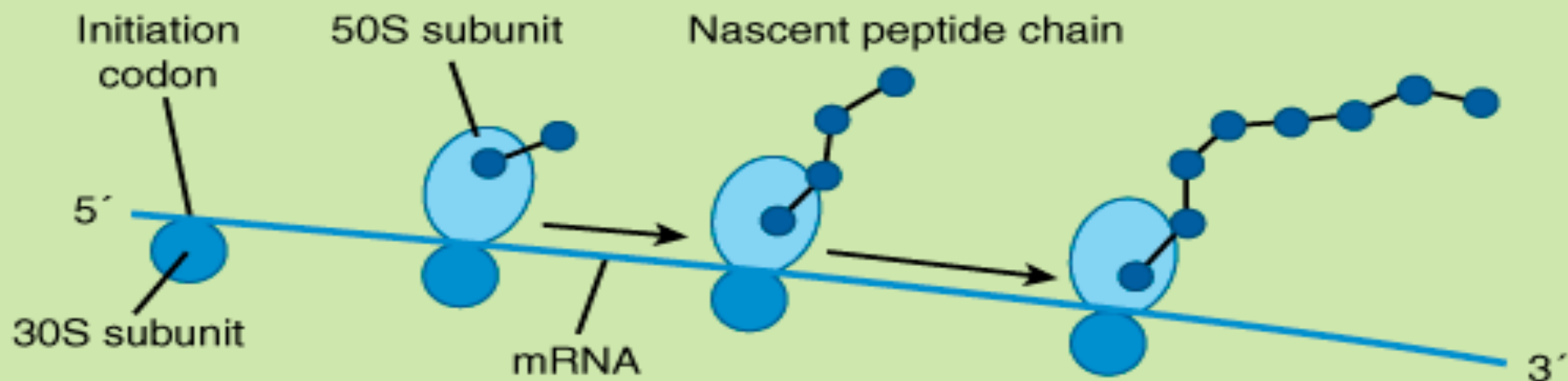
(only bactericidal protein synthesis inhibitor)

- bind to the ribosomal 30S subunit
- inhibit initiation of peptide synthesis and cause misreading of the genetic code. (inhibits translation).
- Streptomycin is the best known member of the group which also includes amikacin, Gentamicin, Tobramycin, Netilmycin, and Neomycin.
synthesized natural natural
↓
best, why? see next slide:
- 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.

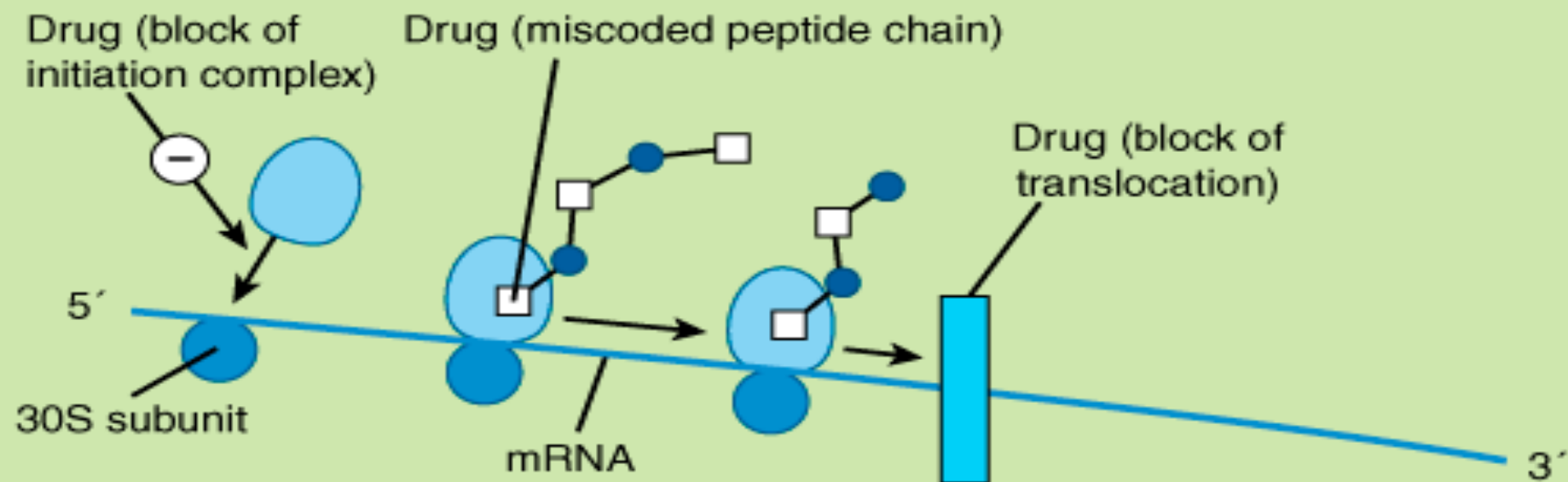
General Properties of Aminoglycosides (Bottom Section)

- **Spectrum of Activity:** Aminoglycosides are active against **all Gram-negative (-)** bacteria but are generally inactive against Gram-positive (+) bacteria.
 - **Effectiveness:** They are considered very good drugs because very few bacterial strains have developed resistance to them. As a result, they remain effective against "superbugs."
 - **Penetration:** These drugs successfully penetrate Gram-negative bacteria by entering through the specific pores that the bacteria use to take in amino acids.
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- **Natural vs. Synthetic:** Among the drugs listed, **Gentamicin** and **Tobramycin** are **natural**, whereas **Amikacin** is **synthetic** and is considered the **best** option in this group.
 - **Mechanism of Resistance:** Bacteria typically develop resistance to aminoglycosides by producing enzymes that add an acetyl group to the drug, rendering it inactive.
 - **Why Amikacin is special:** Amikacin is synthesized specifically to have fewer binding sites for these bacterial enzymes. Because the enzymes cannot bind to it easily (lowering acetylation), the bacteria cannot deactivate it. This is why Amikacin is still used effectively, despite having significant side effects.

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.

2 Ototoxicity

Based on the handwritten blue notes in the image, here is the simplified explanation regarding Ototoxicity (Ear Damage):

- **Dose-Dependent Risk:** While some ear damage is genetic, it can also be dose-dependent. This means the risk increases if the drug accumulates in your body.
- **The "Trough" Level:** To monitor this risk, we check the "trough" level (spelled "truff" in the notes). This is the lowest amount of drug left in your blood just before the next dose. If this level is too high, it means the drug isn't clearing out, increasing the danger.
- **The 1-Week Rule:** If the treatment continues for 1 week or longer, it is standard to monitor both the peak (highest level) and trough (lowest level) to make sure the drug remains safe and effective without causing damage.

1. Nephrotoxicity (Kidney Damage)

- **Dose-Dependent:** This is the main hazard of aminoglycosides. It is strictly related to the amount of drug given—meaning if you increase the dose, you increase the side effects.
- **Why it happens:** Because aminoglycosides are excreted through the urine, increasing the administration of the drug leads to more damage to the kidneys.

2. Ototoxicity (Ear Damage)

- **50% Dose Independence:** Unlike kidney damage, this side effect can be non-dose dependent. This means a patient can suffer from it regardless of the dose amount (it can happen even at low doses), though it can also be dose-related in some contexts.
- **Irreversible:** This damage is permanent; once it happens, the patient may become deaf forever.
- **Specific Risk:** This is linked to genetic "miscoding" in the ear, particularly in people who suffer from a mitochondrial deficiency.

Subclass	Mechanism of Action	Effects	Clinical Applications	Toxicities, Interactions
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Aminoglycosides & Spectinomycin

Gentamicin	Prevents bacterial protein synthesis by binding to the 30S ribosomal subunit	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	Sepsis caused by aerobic gram-negative bacteria synergistic activity in endocarditis caused by streptococci, staphylococci, and enterococci	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
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Tobramycin: Intravenous; more active than gentamicin versus pseudomonas; may also have less nephrotoxicity

Amikacin: Intravenous; resistant to many enzymes that inactivate gentamicin and tobramycin; higher doses and target peaks and troughs than gentamicin and tobramycin

Neomycin: Oral or topical, poor bioavailability; used before bowel surgery to decrease aerobic flora; also used to treat hepatic encephalopathy → Ammonia accumulation → brain damage

Clindomycin

(high penetration)

(clind → anaerobic + gram)

- 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, teeth.
- 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 food entering respiratory tract **aspiration pneumonia**.

Clindamycin and Abdominal Wounds

- Best Use: This drug is considered the best choice for patients who have been stabbed in the abdomen (the note uses the Arabic word "طعن" which means stabbed).
- The Reason: When a stabbing occurs, bacteria that live on the skin (specifically Staph and Strep, which are Gram-positive aerobes) are pushed inside the abdomen, and the anaerobs living in abdomen.
- Action: Clindamycin is used because it effectively treats these specific bacteria that have entered the abdominal cavity from the outside.

- Side-effects generally are limited to GI upsets.

However, a potentially lethal psuedomembranous colitis can occur.

by C. difficile

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

Antibiotics Lecture 9

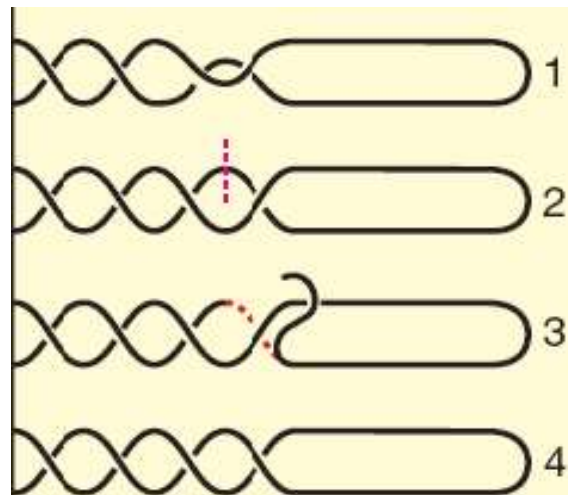
Inhibition of DNA Gyrase

- 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. *recall in Molecular; see next slide:*
- Its a broad spectrum antibiotic active against both Gram-negative and Gram-positive bacteria. It is more active against Gram-negative species.

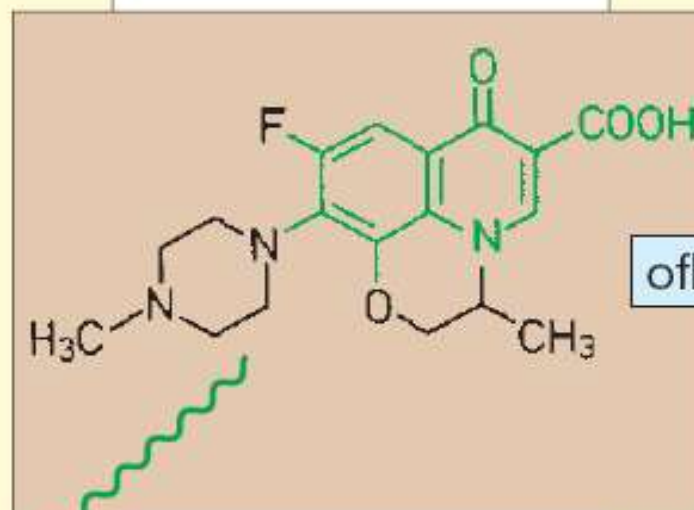
Inhibition of DNA Gyrase

Inhibition of DNA Gyrase (by Fluoroquinolones)

- **The Target:** DNA Gyrase is a bacterial enzyme (Type II Topoisomerase). Its normal job is to cut and relax DNA strands to prevent them from tangling.
- **The Drug:** Fluoroquinolones are antibiotics that specifically block this enzyme.
- **Mechanism:** By trapping DNA gyrase, the drug prevents the DNA from "relaxing." If the DNA remains too tight (supercoiled), the bacteria cannot perform transcription or replication, causing it to die.
- **Spectrum:** It is a **Broad Spectrum** antibiotic. It works on both Gram-positive and Gram-negative bacteria, but is **more active against Gram-negative species**.
- **Selectivity (Handwritten Note):** The drug targets bacteria and not human body cells because the dose given is low enough to be safe for humans while still killing the bacteria (Dose Selection).

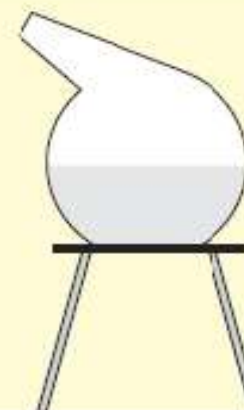
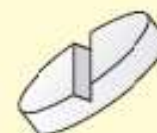


Twisting by
opening, underwinding,
and closure
of DNA strand



Gyrase inhibitors

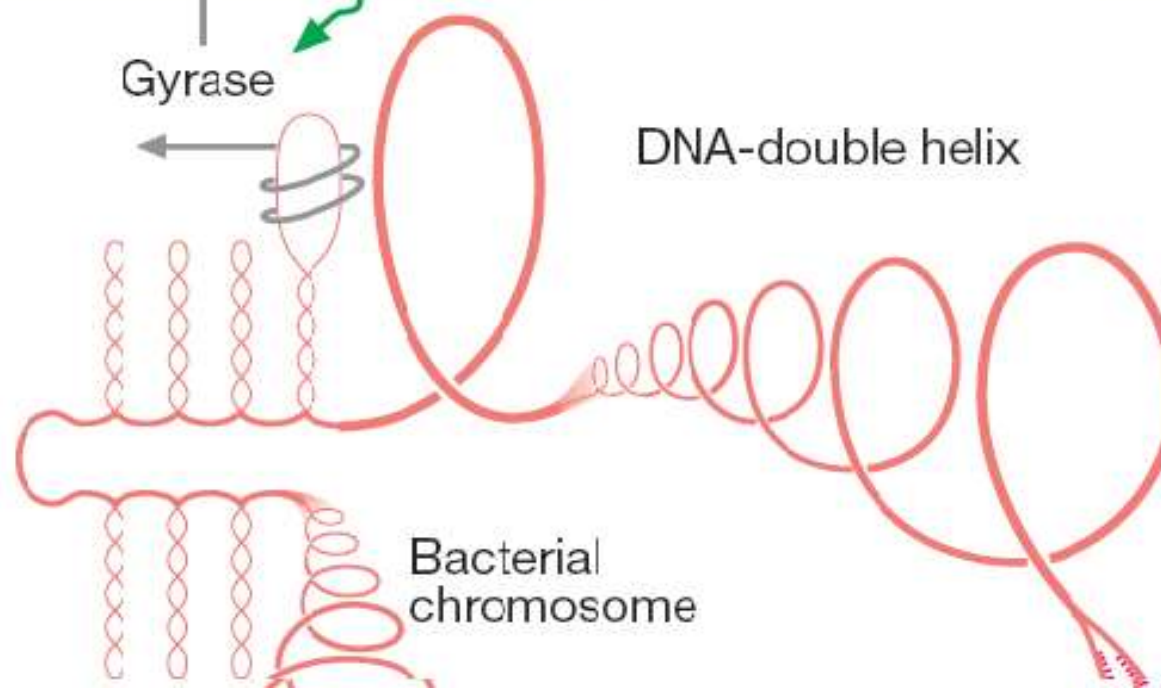
ofloxacin



Gyrase

DNA-double helix

Bacterial
chromosome



GLMC Quinolones (best bacteriocidal)

- 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. *Poor activity against gram(+), such as streptococcus pneumonia.*
- **Levofloxacin, gemifloxacin, and moxifloxacin:** improved activity against **gram-positive** organisms, particularly *S. pneumoniae* and some **staphylococci**.

Ciprofloxacin:
on UTI and GIT

Abdomen (GIT)

E. coli, Proteus ✓
Klebsiella ✓
Enterococcus ✗
Bacteroides sp. ✗

Urinary Tract

E. coli, Proteus ✓
Klebsiella ✓
Enterococcus ✗
Staph saprophyticus ✓

General Note on Cross-Infection:

Enterococcus bacteria from the intestines (feces) can accidentally cause a UTI (Urinary Tract Infection). This often happens during cleaning (like changing a baby) if bacteria are transferred from the feces into the urinary tract.

Quinolone

- Their main uses are:

(1) complicated urinary tract infections, because they're excreted in kidney

(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; High penetration on synovial fluids.

(4) bacterial prostatitis and cervicitis (Levofloxacin penetrate prostate, administration 28 days).

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

- **Moxifloxacin:** It is more effective against **anaerobes** (because it targets topoisomerases 2 and 4), but it is less active against *P. aeruginosa*.
- **Levofloxacin:** It has a very broad spectrum and is active against **almost everything except anaerobes**. It is used as a drug of **last resort** to distinguish it and prevent the development of resistance.

- **Side-effects** are infrequent and usually mild. They consist mainly of **GI disorders** (nausea, vomiting, and diarrhea) and skin rashes. *Not given with calcium.*
- **Arthropathy,** Fluoroquinolones may **damage growing cartilage** and cause an arthropathy. particularly in young individuals.

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

- **Contraindication:** Generally contraindicated in children (under 18), except in special cases such as **cystic fibrosis**.
- **Alternatives:** For children with urinary tract infections (UTIs), use oral Cefixime or Cefdinir instead.

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)

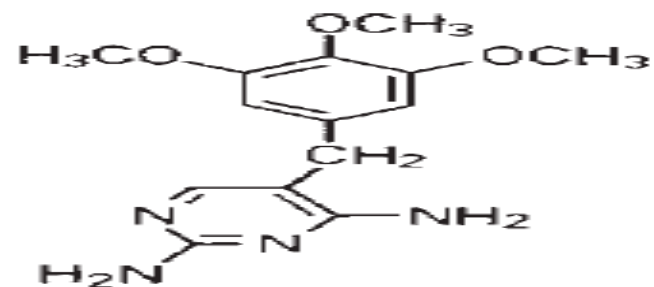
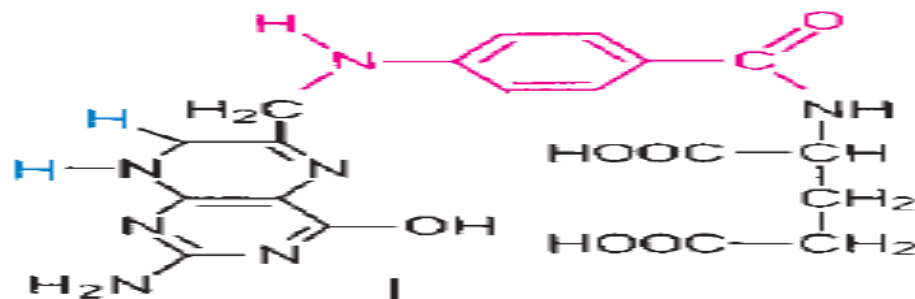
Dihydro-folic acid (DHF)

Sulfonamide inhibits

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) Co-Trimoxazole

- 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. and *E. coli*, for people with Cephalosporins allergy.
- 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*. alternative for vanomycin when the patients have kidney problems.
- **Linezolid** is approved for vancomycin-resistant *E faecium* infections; nosocomial pneumonia (VISA) community-acquired pneumonia; and skin infections, complicated or uncomplicated. It inhibits the initiation of translation (bacteriostatic) side-effect: ↓ platelet-count.
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*. side-effect: deactivates R.S secretion; so not active on pneumonia in R.S

Common Bacteria by Site of Infection

Mouth

Peptococcus

Peptostreptococcus

Actinomyces

Skin/Soft Tissue

S. aureus

S. pyogenes

S. epidermidis

Pasteurella

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

Listeria