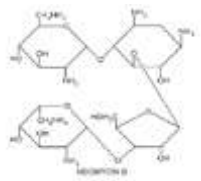
The Aminoglycosides

Active against gram **negative** bacteria.
Hydrophilic compounds, do not cross membranes, do not distribute well.
All given by injection, or locally applied.
Not metabolized.
Excreted by the **kidneys**.
Ototoxic and **nephrotoxic**
→**SAFE ANTIBIOTIC.**



The aminoglycosides consist of two or more amino sugars joined in glycosidic linkage to a hexose nucleus, which usually is in a central position.

glycosidic linkage is a type of covalent bond that joins a **carbohydrate (sugar) molecule to another group**

A hexose is a monosaccharide with six carbon atoms.

The polycationic aminoglycoside chemical structure results in a binding both to the anionic **outer** bacterial membrane and to anionic phospholipids in the cell membranes of mammalian renal proximal tubular cells.

The former contributes to the **bactericidal** effects of these compounds, while the latter binding accounts for their **toxicity**.
Because of their hydrophilicity, the transport of aminoglycosides across the hydrophobic lipid bilayer of eukaryotic cell membranes is **impeded.** يعني ما رح يمر

MECHANISM OF ANTIBACTERIAL ACTION

The antibacterial actions of the aminoglycosides involve
two possibly synergistic effects.

First→ the positively charged aminoglycoside binds to negatively charged sites on the **outer** bacterial membrane, thereby disrupting membrane integrity.
It is likely that the aminoglycoside-induced bacterial outer membrane degradation accounts for the rapid concentration dependent bactericidal effect of these compounds.

MECHANISM…

Second→aminoglycosides bind to various sites on bacterial **30S** ribosomal subunits, disrupting the initiation of protein synthesis and inducing errors in the translation of messenger RNA to peptides.
They also bind to sites on bacterial **50S** ribosomal subunits, although the significance of this binding is uncertain.
In addition, they have a post antibiotic effect→ that is, they continue to suppress bacterial regrowth even after removal of the antibiotic from the bacterial microenvironment.
It is likely that ribosome disruption accounts for this postantibiotic activity

The **postantibiotic effect** is characterized by prolonged suppression of bacterial regrowth after the initially high aminoglycoside concentration has fallen to a subinhibitory level.
Perhaps **resumption** of bacterial ribosomal function requires the time-consuming synthesis of new ribosomes after their disruption by aminoglycosides.
The **postantibiotic** effect explains why aminoglycosides can be given in single daily doses despite their short half-life.

MECHANISM…

Penetration of aminoglycosides through the **outer** bacterial membrane occurs both by outer membrane disruption and by diffusion through outer membrane porins.

Penetration through the **inner** bacterial membrane occurs in **two phases.**

The first→ requires that the **cytosol** have a negative electron potential and therefore be inhibited by the presence of a low pH.

The second phase→ depends on aerobic bacterial metabolism and therefore will be inhibited by low oxygen tension.

The latter two observations are of considerable clinical relevance, since both a low pH and a low oxygen tension frequently occur in bacterial abscesses.

Administration of **B-lactam antibiotics** will reverse the negative effects of both low pH and low oxygen tension on the ability of aminoglycosides to penetrate into bacteria, this ability accounts in part for the synergism that occurs between **aminoglycoside and B-lactam antibiotic** drugs.

The Aminoglycosides…

Used to treat infections caused by aerobic **gram-negative bacteria** and rapidly **bactericidal.**

They inhibit protein synthesis by binding to the **30S** ribosomal subunit and alter protein synthesis.[**bacteriostatic]**

Streptomycin→Used only in TB.

- Gentamicin.
- Tobramycin.
- Amikacin.
- Netilmicin
- Neomycin

Gentamicin:

Widely used in hospitals.

Good for Staphylococcus and Gram-negative organisms.

Short T1/2.

Toxic, blood level monitoring is required.

Incompatible with other drugs, so given separately.

Neomycin:

Very toxic, not given systemically.

Given to sterilize the bowel before surgery.

Also **locally** as drops or **ointment** in ear, nose, eye, or skin infections.

Tetracyclines

Wide spectrum of activity (Gram positive and negative bacteria), but resistance develops very rapidly.

Bacteriostatic, only stop bacterial growth, do not kill bacteria. So, we depend on the presence of a good patient's immune system.

Disrupt function of **30S or 50S ribosomal** subunits to reversibly inhibit protein synthesis.

Orally absorbed, but absorption **affected by food,** and dairy products.

Widely distributed in the body.

Rarely used nowadays, EXCEPT:

Doxycycline: given once daily for acne.

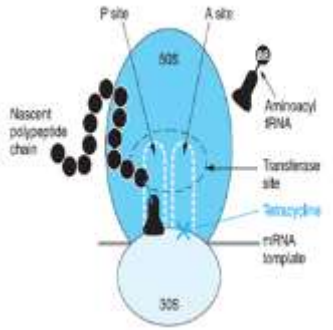
Adverse Effects:

Nausea, vomiting, diarrhea.

Changes in normal flora leading to diarrhea and candida infection.

Bone deposits in children, appears on teeth.

A transfer RNA is an adaptor molecule composed of RNA, typically 76 to 90 nucleotides in length that serves as the physical link between the mRNA and the amino acid sequence of proteins.

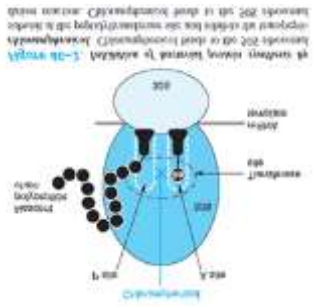


Tetracyclines inhibit bacterial protein synthesis by binding to the 30S subunit and blocking tRNA binding to the A site.

Chloramphenicol

Broad spectrum against G- & G+
Very widely distributed.
Very effective, no resistance.
Very toxic. **(the gray-baby syndrome)**
Disrupt function of **50S** ribosomal subunits to reversibly inhibit protein synthesis.
Gray baby syndrome is a **rare** but serious side effect that occurs in newborn infants (especially premature babies) following the accumulation of antibiotic chloramphenicol.
Was the drug of choice for→
1-Salmonella(Typhoid Fever), but replaced by safer drugs.
2-Still used for meningitis caused by H. influenzea.
3-Aplastic anemia:
-Incidence is common 1/40,000.
-Delayed for a few months after intake.
-Fatal.

→transpeptidation reaction:
A reaction involving the transfer of one or more amino acids from one peptide chain to another



Mechanism of Action

Chloramphenicol (Chloromycetin) is a **nitrobenzene** derivative that affects protein synthesis by binding to the **50S** ribosomal subunit preventing **peptide bond formation**.
It prevents the attachment of the amino acid end of **aminoacyl-tRNA to the A site**, hence the association of **peptidyltransferase** with the amino acid substrate.
Resistance due to changes in the ribosome binding site results in a **decreased affinity** for the drug, **decreased permeability**, and plasmids that code for enzymes that degrade the antibiotic.
The drug-induced inhibition of mitochondrial protein synthesis is probably responsible for the associated toxicity.

Antibacterial Spectrum

Chloramphenicol is a broad-spectrum antibiotic that is effective **against gram-positive and gram-negative bacteria**, including Rickettsia, Mycoplasma, and Chlamydia spp.
Chloramphenicol is also effective against most anaerobic bacteria, including Bacteroides fragilis.

Absorption, Distribution, Metabolism, and Excretion

Chloramphenicol is rapidly and completely absorbed from the gastrointestinal tract and is not affected by food ingestion[unlike tetracyclins] or metal ions.
→**Parenteral administration** is generally reserved for situations in which **oral therapy** is contraindicated, as in the treatment of meningitis and septicemia or when vomiting prohibits oral administration.
The biological **half-life of chloramphenicol is 1.5 to 3.5 hours[short]**. Although up to 60% of the drug is bound to serum albumin, it penetrates the **brain** and **CSF** and **crosses** the **placental barrier**.
Chloramphenicol is inactivated in the **liver** by **glucuronosyltransferase** and is rapidly **excreted (80–90% of dose) in the urine.**

Clinical Uses

The potentially fatal nature of chloramphenicol **induced bone marrow suppression restricts** its use to a few life-threatening infections in which the benefits outweigh the risks. There is no justification for its use in treating minor infections.

Chloramphenicol is no longer recognized as the treatment of choice for any bacterial infection. In almost all instances, other effective antimicrobial agents are available.

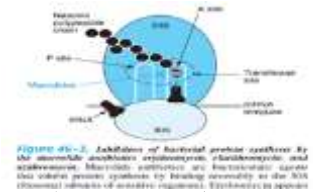
Since **effective CSF** levels are obtained, it used to be a choice for treatment of specific bacterial causes
of **meningitis**, **Haemophilus influenzae**, **Neisseria meningitidis**, **and S. pneumoniae**
Additionally, it was effective **against H. influenzae–related arthritis, osteomyelitis, and epiglottitis.**
The development of **B-lactamase-producing** strains of H. influenzae increased the use of chloramphenicol.
However, with the advent of **third-generation cephalosporins** such as ceftriaxone and cefotaxime, chloramphenicol use has significantly decreased.
If the patient is **hypersensitive to B-lactams**, chloramphenicol administration is appropriate therapy for **meningitis** caused by **N. meningitidis and S. pneumoniae.**

Chloramphenicol remains a **major** treatment of **typhoid and paratyphoid fever** in developing countries. However, with increasing resistance to ampicillin, trimethoprim- sulfamethoxazole and, to some extent, chloramphenicol, fluoroquinolones and some third-generation cephalosporins (e.g., ceftriaxone) have become the drugs of choice.

Chloramphenicol also is widely used for the **topical treatment of eye infections.**
It is a **very effective** agent because of its extremely broad spectrum of activity and its ability to penetrate ocular tissue.
The availability of safer, less irritating instilled ophthalmic antibiotics and the increase in fatal aplastic anemia associated with the use of this dosage form suggest that this agent might best be withdrawn.
Chloramphenicol is an alternative to tetracycline for rickettsial diseases, especially in children younger than 8 years, alone or in combination with other antibiotics.
it has been used to **treat vancomycin-resistant enterococci.**
Another indication for chloramphenicol is in the **treatment** of serious **anaerobic infections** caused by penicillin-resistant bacteria, such as **B. fragilis**

Erythromycins(Macrolides)

Same spectrum of penicillin, so substitutes in penicillin allergic patients.
Widely distributed in the body, even the prostate gland.
Safe drugs for children:
Can be given orally.



بديل منيح بحالة اذا كان المريض عنده حساسية من البنسلين
Can cause **nausea**, **vomiting**, **and diarrhea**.
Rarely can cause jaundice.
-EX: -Clarithromycin
-Azithromycin
→Long acting, short courses.
Used to eradicate Helicobacter pylori.

Lincomycin and Clindamycin

Effective against **Gram positive** bacteria, like penicillins.
Clindamycin binds exclusively to the 50S subunit of bacterial ribosomes and suppresses protein synthesis.
So **misused** by doctors in the treatment of simple sore throat or URTI.
Should be reserved for deep seated infections like bone infection.

Lincomycin and Clindamycin…

Overuse of lincomycin caused many cases of Pseudomembraneous colitis caused by **overgrowth** of resistant intestinal flora (Clostridium difficilli).

Vancomycin

Very toxic agent: **ototoxic and nephrotoxic**.
Reserved for severe Staphylococcal infection, given by slow IV infusion.
Given orally for **Pseudomembraneous colitis.**
Vancomycin inhibits the synthesis of the cell wall in sensitive bacteria by binding with high affinity to the D-alanyl-D-alanine terminus of cell wall .
drug is **bactericidal** for dividing microorganisms .
D-alanyl-D-alanine A dipeptide comprising D-alanine with a D-alanyl residue attached to the α-nitrogen. It is a component of bacterial peptidoglycan and forms an important target for development of antibacterial drugs .

Tuberculosis

The most important communicable disease in the world.
Caused by **Mycobacterium tuberculosis**
The ability of the tubercle bacillus to remain dormant but viable and capable of causing disease is a major therapeutic challenge.

Groups at high risk for tuberculosis infection

HIV-infected persons, **immigrants** from countries with high rates of tuberculosis, the **homeless**, **health care** professionals, **intravenous** drug users, persons taking **immunosuppressive** agents.
The three basic concepts in tuberculosis treatment→
(1) Regimens must contain multiple drugs to which the organism is susceptible.
عشان تخف الRESISTEANCE
(2) Drugs must be taken regularly.
(3) Drug therapy must continue for a sufficient time.
first-line drugs
isoniazid ,rifampin, pyrazinamide Ethambutol,streptomycin
زيد و رزان وبتول اشتروا ستربلس
الخامس احفظوه بعينكم الله

Antituberculous Drugs

Isoniazid(INH)
primary action of isoniazid is to inhibit the biosynthesis of mycolic acids—**long**, **branched lipids** that are attached to polysaccharide, to form part of the mycobacterial cell wall.
-First line drug.
-Rapidly absorbed after **oral** administration.
-Widely distributed and excreted by the kidneys.
-Diffuses widely in the body, enters infected cells.
-Metabolized in the liver:
Fast metabolizers.
Slow metabolizers.
Causes neuropathy, especially in slow metabolizers. Can be corrected by Vitamin B6.
If a drug is metabolized too quickly, it may decrease the drug's efficacy while if the drug is metabolized too slowly, toxicity may result.
drugs that are metabolized by CYP2D6, certain individuals will eliminate these drugs quickly (ultrarapid metabolizers) while others slowly

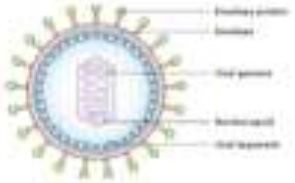
Rifampin
Another first line drug.
Broad spectrum antibiotic, so misused by doctors.
Use in Jordan is restricted for TB and prophylaxis of meningitis contacts.
-Can cause **red discoloration** of secretions: tears, urine etc.
-inhibits RNA polymerase of mycobacteria and other microorganisms by forming a stable drug–enzyme complex, leading to suppression of initiation of chain formation in RNA synthesis. RNA polymerase also known as DNA-dependent RNA polymerase, is an enzyme that produces primary transcript RNA.

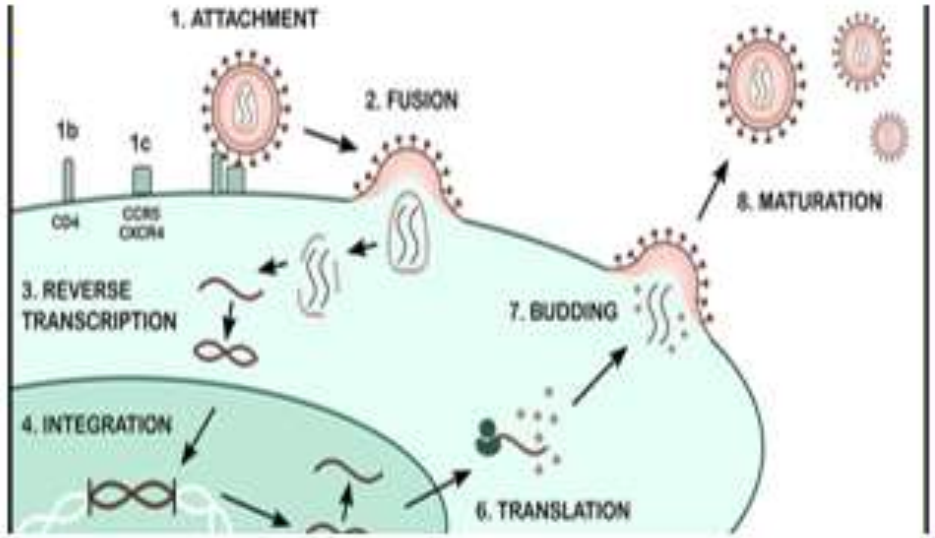
Streptomycin
An aminoglycoside, 1947.
Was the first effective antituberculous drug.
-Should be given by injection, resulted in noncompliance of the patients.
-Ototoxic.
-Resistance developed very rapidly.
-Replaced by isoniazid.
-Still used in some cases.

#هاي السلايدة بتقدروا تعتبروها زي مراجعة لمعلومات بتعرفها بحالة كنتوا دارسين فايرو

Antiviral Agents

- Viruses are obligate intracellular microbes
- use many of the host cell's biochemical mechanisms and products to sustain their viability
- A mature virus(virion) can exist outside a host cell and still retain its infective properties.
- the virus must enter the host cell, take over the host cell's mechanisms for nucleic acid and protein synthesis, and direct the host cell to make new viral particles.
- Viruses are composed of one or more strands of a nucleic acid (core) enclosed by a protein coat (capsid).
- Many viruses possess an outer envelope of protein or lipoprotein.
- Viral cores can contain either DNA or RNA.
- viruses may be classified as DNA viruses or RNA viruses.
- Further classification is usually based on morphology, cellular site of viral multiplication, or other characteristics.





1)The virus attaches to the host cell via specific proteins present on the surface of the cell.
2) It fuses with the cell membrane and enters the cell.
3) (Recall that we have two types of viruses, those are DNA and RNA viruses), RNA viruses would undergo reverse transcription to synthesize DNA out of RNA.
4) The synthesized DNA would fuse with the host's DNA (it becomes integrated with it).
5) Transcription of the integrated DNA occurs.
6) Translation of RNA produces host cell proteins AND viral proteins.
7) Budding.
8) Maturation.

DNA viruses

adenoviruses (colds, conjunctivitis)
hepadnaviruses (hepatitis B);
herpesviruses (cytomegalovirus chickenpox)
papillomaviruses (warts)

RNA viruses

arborviruses (yellow fever)
arenaviruses (meningitis);
orthomyxoviruses(influenza);
paramyxoviruses (measles, mumps)
picornaviruses (meningitis, colds);
rubella virus (German measles)
retroviruses (AIDS).

Antiviral Agents

Viruses live intracellular,
so **drugs should be able to enter the human cells**.
#Used primarily in the treatment of herpesviruses: -
Acyclovir
1-Wide spectrum antiviral agent.
2-Herpes virus.
3-Available as oral tablets, IV injections, eye drops and **ointmen**t, or as a **cream.**
4-used In Varicella= Chicken Pox, use is restricted to immunocompromized patients.
5-Side Effects: N, V, Skin rashes استفراغ وغثيان

ANTIINFLUENZA AGENTS

1-**Amantadine**
2-**Rimantadine**
3-**Oseltamivir**
4-**Zanamivir.**

-**Amantadine** (Symmetrel) is a synthetic tricyclic amine,
-rimantadine (Flumadine) is its -methyl derivative.
-Their **mechanism** of action involves inhibition of the viral M2 protein, an integral membrane protein that acts as a H channel.
Blockade of the **M2 protein** prevents the acid-mediated dissociation of the ribonucleoprotein complex
-the pH changes that result from M2 inhibition inhibit viral assembly.
Ribonucleoprotein an association that combines a RNA and an RNA-binding protein together.
During the replication of many viruses, hundreds to thousands of proteins assemble around the viral nucleic acid to form a protein shell called a capsid.

other antiviral agent…

Used in the treatment of HBV hepatitis C virus (HCV) ,respiratory syncytial virus (RSV) ,some human papilloma virus (HPV) HIV infection.

ANTI HIV AGENT:

1-Zidovudine→

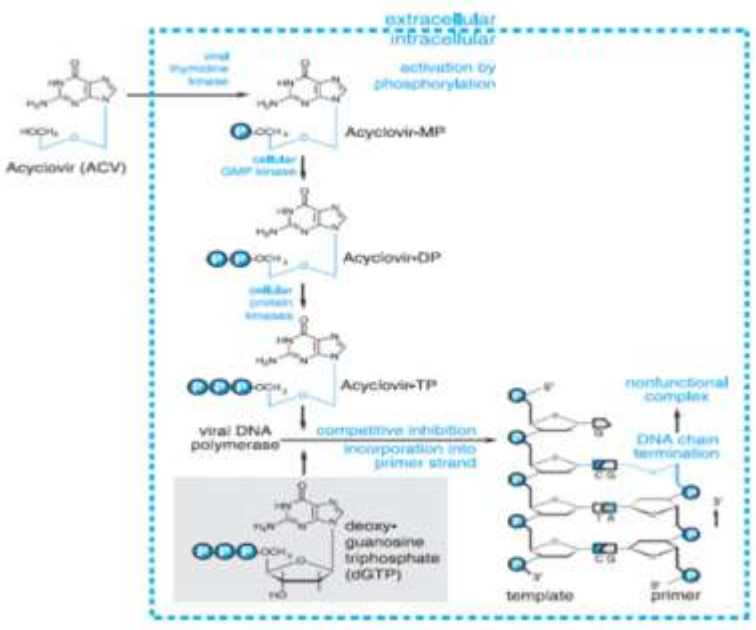
- Inhibits viral DNA production.
- Expensive. (its disadvantage)
- Causes nausea, vomiting,, muscle pain, and bone marrow suppression (decreasing the immunity of an already immunocompromised patient).

2-Indinavir→

-Protease inhibitor.

- block the part of HIV called protease. HIV-1 protease is an enzyme required for the proteolytic cleavage of the viral polyprotein precursors into the individual functional proteins found in infectious HIV-1.
- **Indinavir** binds to the protease active site and inhibits the activity of the enzyme preventing the production of functional proteins Expensive. (most HIV agents are, and they have lots of bad effects) n Causes Nausea, Vomiting, Diarrhea, Renal stone formation.
- **indinavir** wears off quickly after dosing, so requires very precise dosing every eight hours to prevent HIV from forming drug-resistant mutations, including resistances to other protease inhibitors

Acyclovir mimics a specific nucleic acid called dGTP (deoxy-guanosine triphosphate),
First, acyclovir gets incorporated into the host cell .
Then, it gets converted into Acyclovir-MP by viral thymidine kinase. After that it's converted into Acyclovir-DP using cellular kinases.
Then it's converted into Acyclovir-TP which is specifically the molecule that mimics dGTP but affect the virus negatively.
So this Acyclovir-TP gets incorporated in the viral DNA making it dysfunctional and affecting the production of viral proteins.

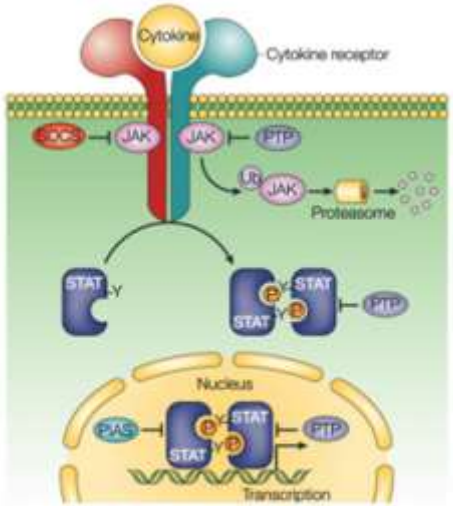


Interferons

• Interferons (IFNs) are **potent cytokines** that possess antiviral,immunomodulating (so that the body would recognize the virus and respond to it), and anti-proliferative activities. • ***Natural*** substances produced by virally infected cells. (Artificial drugs which mimic the effect of these naturally produced substances have been made).
• Viral infection ***gives immunity*** for variable duration.
• ***Modify*** the immune response to increase resistance to viral infection, and control growth of the virus using anti-proliferative activity.

- Obtained in small amounts from donor's WBCs. (the donor should be a patient who had got infected and then treated from it.)
- Nowadays, obtained commercially by recombinant DNA technology.
- Used in Hepatitis C, and some leukemias.
- Can cause nausea, fever, and malaise (flu-like symptoms)

Mechanisms of Action…
Following binding to specific cellular receptors, IFNs activate the JAK-STAT signal transduction pathway. This, in turn, leads to synthesis of over two dozen proteins that contribute to viral resistance mediated at different stages of viral penetration. (remember how viruses enter host cells by binding to certain proteins at the surface of these host cells).



Nature Reviews | Immunology

بحالة وصلتوا لهاي الصفحة لا تنسونا من دعواتكم
وخلي ببالكم هالدعاء
"اللهم ارني عجائب قدرتك في تيسيره"

LECTURES 6-9
Dr.Manar
Ghada Alzoubi