Chemotherapy / Antimicrobials

Antibiotics

1/ Sulfonamides

- almost obsolete because of:
  1) bacteriostatic 2) bacterial resistance
  3) Toxicity: a/ nausea
     b/ Rashes
     c/ Blood dyscrasia: presence of abnormal material + WBC > 10^6 ← confirmation
     d/ Crystallization or precipitation in urinary tract & stone formation

→ imp. chemical Features:
benzene ring directly linked to sulfur & NH_2 group is important too

Cotrimoxazole – Trimethoprim combination (Bactrim/Septrin/Balakatrin): * one of the few still used sulfa drugs
* very effective fixed combination "no resistance"
* useful in UTI & RTI & Salmonella & pneumocystis pneumonia" an opportunistic infection of AIDS patients

Mechanism: Structural analogs & competitive antagonists of PABA, Para-aminobenzoic acid; inhibits normal bacterial utilization of PABA for the synthesis of folic acid.

PABA —(dihydropteroate synthase)→ Dihydrofolic acid —(Dihydrophalate Reductase)→ Tetrahydrofolic acid

Sulfonamides compete with PABA (−)

Trimethoprim (−) Synergism of ____

2/ Quinolones

* interfere with cell division of bacteria

1. Nalidixic acid very old urinary antiseptic
2. Norfloxacin used only for UTI, 3 day course

chemical Feature: contain a carboxylic acid moiety at carbon 3 of the primary ring structure

Mechanism: Fluoroquinolones bind & nuclear enzymes & inhibit DNA synthesis ① Topoisomerase IV ② DNA gyrase introduces negative supercoils into DNA

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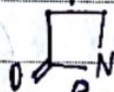
Fluorinated 4 Quinolones : such as ciprofloxacin CIPRU
moxifloxacin AVELOX ~~gatifloxacin~~ TEQUIN
→ Wide range of action even Clostridium botulinum bacteria which produces botulinum toxin
→ Expensive
→ Prophylaxis for meningitis
→ Can cause upset g.i & epilepsy

3) Beta lactam antibiotics



• contain β lactam ring → active functional group where antibiotic activity resides
• inhibit cell wall synthesis
• resistant bacteria produces a lactamase which breaks this ring
• penicillin G is the prototype for all antibiotics & β-lactam antibiotics
• oldest antibiotics but new agents are still being discovered & added

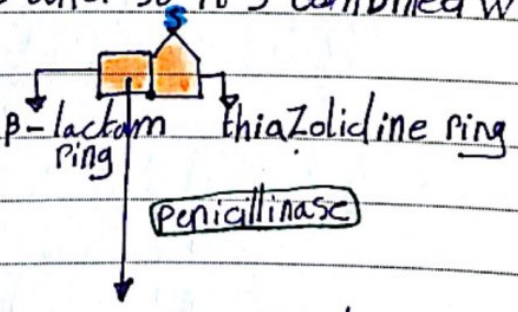
The penicillins 1) most widely used antibiotics
2) effective against gram+ bacteria like Staph., Strept., Pneumococcus & many others

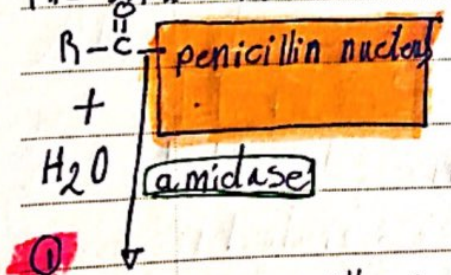
* Can be synthetic or semisynthetic (modified natural),

penicillinase: produced by resistant bacteria inactivates penicillins by breaking the β-lactam ring.

Clavulanic acid inhibits this enzyme and so it's combined with ampicillin to give Augmentin

the structure of penicillin has two rings: β-lactam ring, thiazolidine ring





① 6-aminopenicillanic acid

+ ② R-CH "carboxylate"

penicillin + H_2O —amidase→ ① + ② semisynthetic

peptidoglycans provide rigid mechanical stability → cell walls of bacteria are essential for their growth & development → last step in peptidoglycan synthesis is inhibited by β-lactam antibiotics

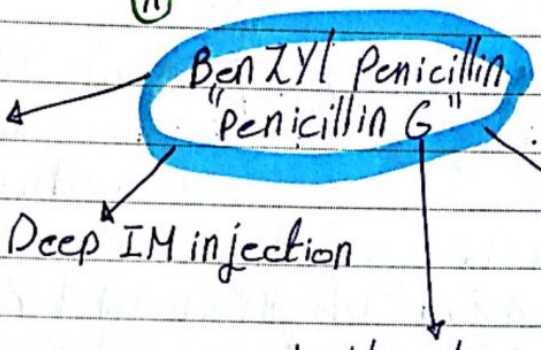
No.

↳ mechanism

cell wall is 50 to 100 molecules thick in Gram + and 1 – 2 molecules thick in Gram –

Sulbactam & Tazobactam are similar in function to clavulanic acid

(A)



(B) Procain benzylpenicillin : painless – prolonged action injection

(C) phenoxymethyl penicillin : oral but not destroyed by gastric juic

(D) eloxacillin, dicloxacillin & Fluclocillin : penicillinase resistant "for staphylococcus.

(E) Ampicillin : 1) broad spectrum penicillin can cause diarrhea due to overgrowth of normal flora & incomplete absorption
2) normally administrated with β-lactamase inhibitor.

(F) Amoxicillin : 1) same but more completely absorped than ampicillin
2) so less diarrhea & longer acting than ampicillin

(G) AZlocillin / Pipercillin / Ticarcillin : have extended spectrum (proteus, pseudomonas, Klebsiella) and other Gram ⊖ microorganisms

Adverse Effects of Penicillins (relatively very safe drugs except):
pain of injection / abscess formation / Allergic reactions:
skin rash / urticaria / Anaphylaxis / rash, fever, bronchospasm / dermatitis & stevens – Johnson syndrome

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Penicillinase resistant Penicillins (antistaphylococcal)

- includes: Nafcillin, Oxacillin, cloxacillin, ~~dicloxacillin~~ more resistant to bacterial β-lactamases than penicillin G. No.

effective against MRSA & MRSE

methicillin is another penicillinase resistant antibiotic similar to nafcillin & oxacillin.

parenteral therapy of nafcillin & oxacillin offers comparable efficacy & antimicrobial spectra of activity.

used for severe staphylococcal infections like: empyema, Pneumonia, endocarditis, cellulitis, osteomyelitis, septic arthritis & toxic shock syndrome.

β-lactamase inhibitor combinations

β-lactam antibiotic + β-lactamase inhibitor

ampicillin – Sulbactam Unasyn

ticarcillin – Clavulanic acid Timentin

piperacillin – tazobactam Zosyn

amoxicillin – Clavulanic acid Augmentin

all except for the last one are parenteral formulations

⇒ elemination of the combination drugs occurs primarily by renal sare

⇒ require dose adjustments in patients with renal insufficiency.

- the addition of β-lactamase inhibitor boardens the antibacterial activit against β-lactamase-producing organisms. spectrum of

used in treating infections with known or suspected mixed bacterial flora such as: biliary infections / diabetic foot ulcers / endomyometritis & peritonitis

H/ Cephalosporins

- came 1 decade after penicillins
- rarely the drugs of choice for any infection
- mainly used for surgical prophylaxis 1st
- expensive, especially for the newer generations
- same toxicity as penicillins / cross allergic with the activity differs among the generations penicillins

Cephim nucleus → generations differ in modifications in the R1 & R2 groups

penicillins الى β-lactam

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① 1st generation: good activity against gram + bacteria and relatively modest activity against gram − bacteria
Cephalothin, Cefazolin

② 2nd generation: increased activity against gram − bacteria
Cefamandole, cefoxitine

③ 3rd generation: increased activity / more active against Entero bacteriaceae, including β-lactamase producing strains
Cefoperazone, Cefotaxime, Ceftriaxone

④ 4th generation: extended spectrum of activity & stability from hydrolysis
Cefepime

4| Nitrofurans (Nitrofurantoin) ~> chemistry & mechanism of action

* a number of 5-nitro-2-furaldehyde derivatives, called nitrofurans,
* used in treatment or prophylaxis of microbial infections, primarily in the urinary tract.
* modify various bacterial macromolecules that affect a variety of biochemichal processes (e.g DNA, RNA & protein synthesis).
* slower reduction in mamalian cells prevents high serum concentrations.
* Nitrofurantoin is primarily active against Gram − bacteria E. Coli & P. mirabilis & some Gram + like S. aureus & Enterococcus Faecalis
* no resistance because they modify various bacterial macromolecules
* nitrofuratoin is the treatment for Long-term prophylaxis of lower UTI caused by susceptible bacteria
* not used as a bacterial supressant
* used prophylactically post intercourse in women with chronic UTI
* a urinary concentration greater than 100 µg/mL ensures bactericidal activity
* Nausea & Vomiting are the most commonly observed adverse effects

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6) **Methenamine**: hexamethylenetetramine is an aromatic acid
* hydrolyzed at an acid PH (less than 6) to liberate 1) ammonia 2) the active alkylating agent (formaldehyde)
* Formaldehyde denatures protein & is bactericidal.
* usually administered as salt.
* this salt is either Mandelic (mandelamine) or Hippuric (Hiprex, Urex) acid.
* these acids acidify the urine, which is necessary to generate formaldehyde.
* also, the resulting low urine PH by itself is bacteriostatic for some organisms
* Methenamine is administrated orally & is well absorbed from the intestinal tract
* 10-30% decomposes in the stomach unless the tablets are protected by an enteric coating
* The inactive form of methenamine (ammonia) is virtually distributed to every body fluid
* almost all of the methenamine moiety is excreted into the urine by 24 hours
* It's not a primary drug for therapy of acute infections, but is primarily used for long-term prophylactic or supressive therapy of recurring UTIS
* should be used to maintain sterile urine after appropriate antimicrobial agents have been employed to eradicate the infection

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6) Aminoglycosides

- active against gram (−) 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 & nephrotoxic

consist of 2 or more aminosugars joined in glycosidic linkage to a hexose nucleus, which is usually in a central position

Polycataionic binds to negatively charged sites on bacterial membrane & disrupts membrane integrity also has a postantibiotic effect due to its binding to ribosomes 30s & 50s.

given in single daily doses despite their short half life.

Penetration through the outer bacterial membrane occurs by:
1) outer membrane disruption 2) diffusion through outer membrane porins

Penetration through inner bacterial membrane occurs in 2 phases:
1) The first requires that the cytosol has a negative electron potential "inhibited by the presence of low PH"
2) The second depends on aerobic bacterial metabolism "inhibited by low oxygen tension" but both a low PH & low O_2 occur in bacterial abscesses to overcome this administration of β-lactam antibiotics will reverse the negative effects of both low PH & low oxygen tension on the ability of aminoglycosides to penetrate into bacteria

↳ synergism between

treats infections caused by Gram − / bactericidal / inhibit protein synthesis by binding to the 30s ribosomal subunit or alter

Streptomycin 1947 → used only in TB

Gentamicin Tobramycin Amikacin Netilmicin Neomycin

Gentamicin: 1) widely used in hospitals / short T1/2 / toxic; so blood level monitoring is required
2) good for Staph. & Gram −
3) Incompatible with other drugs, so given seperately

1) very toxic, not given systemically
2) given to sterilize the bowel before surgery
3) locally as drops of ointments in small for (nose) eye / or skin infections

7) Tetracyclines
- Wide spectrum Gram+ & Gram− but resistance develops very rapidly
- bacteriostatic so depends on the presence of a good immune system
- disrupts function of 30S or 50S ribosomal subunits to reversibly inhibit protein synthesis
- orally absorbed, but absorption depends / affected by food & diary products
- Widely distributed in the body

※ they bind to the 30S subunit & inhibit tRNA binding to the A site thus inhibit bacterial protein synthesis

Barely used nowadays, Except: Doxycycline, given once daily for acne

Adverse Effects: 1) Nausea 2) vomiting 3) diarrhea
2) changes in normal flora leading to diarrhea & Candida infection
3) Bone deposits in children, appears on teeth

8) Chloramphenicol
1) very widely distributed, 2) broad spectrum, 3) very effective, 4) no resistance, 5) very toxic "the gray-baby Syndrome", 6) reversibly inhibits proteins synthesis by disrupting the function of 50S ribosome

a rare but serious side effect that occurs in new born infants (especially premature babies) following the accumulation of chloramphenicol.

* the drug of choice for Salmonella (Typhoid Fever) "WAS", but was replaced by safer drugs
* Still used for meningitis caused by H. influenzae
⇒ causes Aplastic Anemia, incedence is common 1/40,000, delayed for a few months after intake, Fatal
. binds to the peptidyl transferase site (50S subunit) and inhibits the transpeptidation reaction, → transfering one aa or more from one peptide chain to another

chloramphenicol/chloromycetin is a nitrobenzene derivative binds to the 50S subunit preventing peptide bond formation
prevents attachment of aa end of aminoacyl-tRNA to the A site, hence the association of peptidyl transferase with the substrate

➡ resistance due to changes in the ribosome binding sites results in

- decreased affinity for the drug & decreased permeability & plasmids that encode for enzymes that degrade the antibiotic
- the drug induced inhibition of mitochondrial protein synthesis is probably responsible for the associated toxicity
- broad-spectrum against Gram + & Gram − ● including Rickettsia, Mycoplasma, & chlamydia
- effective against most anaerobic bacteria, including Bacteroids fragilis
- completely absorbed from GIT, not affected by food ingestion or metal ions
- Parenteral administration is reserved for when oral therapy is contraindicated as in the treatment of meningitis, septicemia or when vomiting prohibits oral administration
- biological half-life is 1.5 to 3.5 hours (remember gray baby)
- although up to 60% of the drug is bound to serum albumin, it penetrates the brain & CSF and crosses the placental barrier
- chloramphenicol is inactivated in the liver by glucuronosyltransferase and is rapidly excreted (80-90%) of the dose in the urine.

Clinical use: the potentially fatal nature of chloramphenicol induced bone marrow suppression "remember Aplastic anemia :)" restricts its use to a few life threatning infections in which the benefits outweigh the risks. There's no justification for its use in treating minor infections.

- 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:

1) Haemophilus influenzae / Neisseria Meningitidis / and 3) S. pneumoniae
→ was effective too against H. influenzae-related arthritis, osteomyelitis & epiglottitis

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→ development of β-lactamase producing strains of H. influenzae increased the use of chloramphenicol.
However with the advent of 3rd generation cephalosporins such as ceftriaxone & cefotaxime, chloramphenicol use has significantly decreased.

If the patient is hypersensitive to β-lactams, chloramphenicol administration is appropriate therapy for meningitis caused by N. meningitidis & S. pneumoniae
- chloramphenicol remains a major treatment of typhoid & paratyphoid fever in developing countries

However with increased resistance to ampicillin/trimethoprim-Sulfamethoxazole and to some extent chloramphenicol, fluoroquinolones & some 3rd generation cephalosporins (e.g. ceftriaxone) have become the drugs of choice
- Widely used for topical treatment of eye infections.
- very effective because of its broad spectrum of activity & ability to penetrate ocular tissue
- The availability of safer, less irritating instilled opthalmic antibiotics and 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 tetracyclin for rickettsial diseases, espicially 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

9) Erythromycin (Macrolides):

- Same spectrum of penicillin, so ~~can be an alternative for~~ penicillin-allergic patients
- Widely distributed in the body, even the prostate gland
- Safe drugs for children:

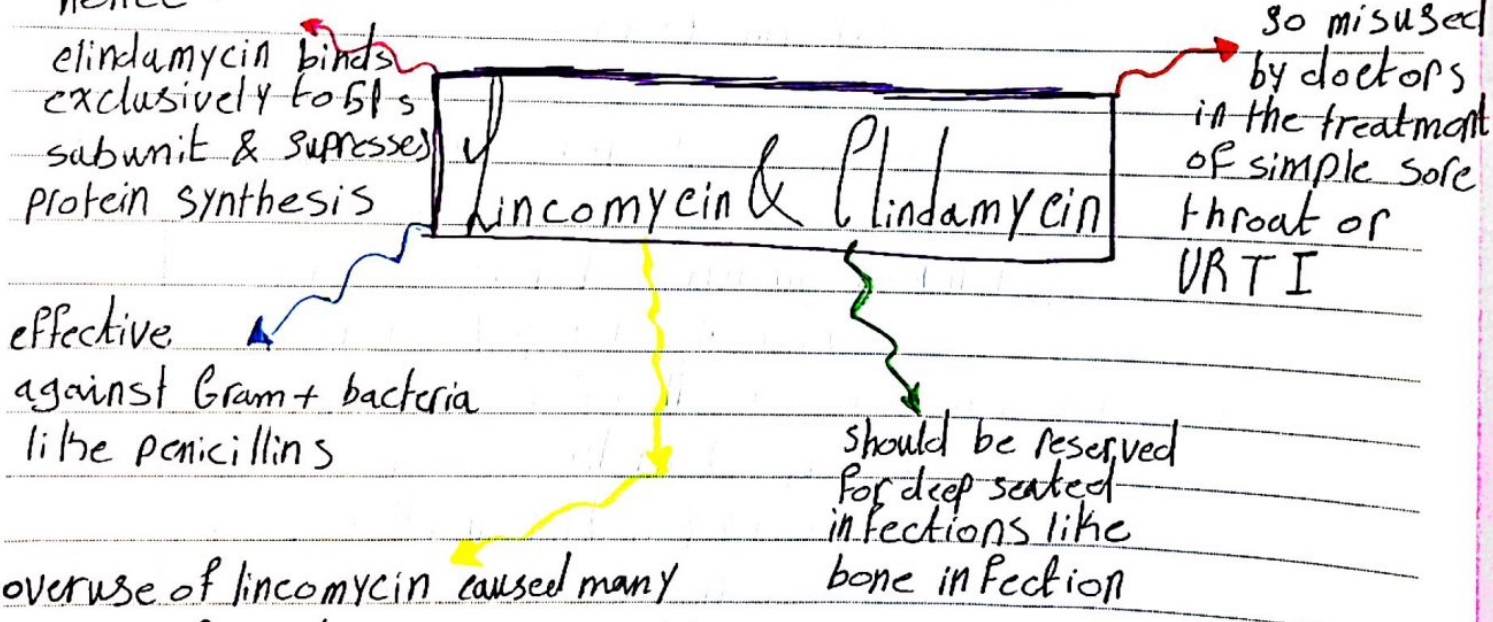
can be given orally / can cause nausea, vomiting & diarrhea / rarely can cause jaundice

Clarithromycin

Azithromycin

- Long acting / short courses
- used to eradicate Helicobacter pylori

- all 3 macrolide antibiotics inhibit protein synthesis by reversibly binding to the 50s ribosomal subunit of sensitive organisms & they are "bacteriostatic agents", hence



overuse of lincomycin caused many cases of pseudomembraneous colitis caused by overgrowth of resistant intestinal flora "Clostridium difficilli"

10) Vancomycin

* Very toxic agent: ototoxic & 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
* Bactericidal for dividing microorganisms

it's dipeptide attached to the α-nitrogen of bacterial peptidoglycan and a 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 the disease is a major therapeutic challenge

Groups at risk:

HIV patients
the homeless
healthcare professionals
intravenous drug users
people taking immunosupressive agents
immigrants from countries with high rates of tuberculosis

3 Basic concepts in TB treatment:

1) Regimens must contain Mutiple drugs to which the organism is susceptible
2) Drug must be taken regularly
3) Drug therapy must continue for a sufficient time

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Firs Line Drugs :

Rifampin

Isoniazid :) remember pipe from micro

Pyrazinamide

Ethambutol

Streptomycin remember from aminoglycosides

Isoniazid (INH) inhibits the biosynthesis of mycolic acids → which are long branched lipids that are attached to polysaccharides, to form part of the mycobacterial cell wall.

- First line drug
- rapidly absorbed after oral administration
- widely distributed & excreted by the kidneys
- diffuses widely in the body, enters infected cells
- Metabolized in the liver — the drug's efficacy

- Fast metabolizers → if the drug is metabolized too quickly it may decrease
- slow metabolizers → if too slowly toxicity may result causing neuropathy, can be corrected by vitamin B6

drugs that are metabolized by CYP2D6, certain individuals will eliminate the quickly "ultrarapid metabolizers" while others slowly

Rifampin → another 1st line drug
- broad spectrum antibiotic, so misused by doctors
- use in Jordan is restricted for TB and prophylaxis for meningitis contacts
- can cause Red discoloration of secretions: tears/urine etc. reversible

*inhibits RNA polymerase of mycobacteria & other microorganisms by forming a stable drug-enzyme complex, leading to Supression of initiation of chain formation in RNA synthesis

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Streptomycin

- an aminoglycoside, 1947
- 1st effective antituberculosis drug
- Should be given by injection, which results in noncompliance of the patients
- ototoxic . resistance developed very rapidly
- replaced by isoniazid
- still used in some cases

Antiviral Agents

- viruses are obligate intra cellular microbes.
- use many of the host cell's biochemical mechanisms & products to sustain their viability.
- a mature virus "virion" can exist outside a host cell & still retain its infective properties.
- viruses take over the host cell's mechanisms for nucleic acid & protein synthesis, and direct the host cell to make new viral particles.

Classification of viruses

- 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 either contain DNA or RNA, and viruses can be classified accordingly.
- Further classification is usually based on: 1 morphology, 2 cellular site of viral multiplication

DNA viruses:
1. adenoviruses (colds, conjunctivitis)
2. hepadnaviruses (hepatitis B)
3. herpesviruses (cytomegalovirus + chickenpox)
4. Papillomaviruses (warts)

RNA viruses:
1. rubella virus "German measels"
2. Retroviruses "AIDS"
3. arboviruses ↓ Yellow fever
4. arenaviruses ↓ meningitis
5. picornaviruses ↓ meningitis / colds viruses
6. orthomyxoviruses (influenza)
7. Paramyxoviruses (measles, mumps)

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• Keep in mind ⊘ that viruses live intracellularly and so antiviral drugs should be able to enter the human cells.

No.

Antiherpesvirus Agents used primarily in the treatment of herpesviruses.

#1 Acyclovir: • wide spectrum antiviral agent / herpes virus

• Available as oral tablets, IV injections, eye drops, ointments or creams

• In Varicella = chicken Pox, use is restricted to immunocompromised patients

• Side Effects: N, V, Skin rashes

The idea is that Acyclovir is converted to Acyclovir monophosphate (Acyclovir - MP) by a thymidine kinase then phosphorylated further by cellular enzymes to acyclovir - DP (then) & acyclovir - TP, uninfected cells convert very little or no drug to the phosphorylated derivatives; thus acyclovir is selectively activated in cells infected with herpesviruses that encode for appropriate thymidine kinase Now Acyclovir competes with deoxy-guanosine triphosphate (dGTP) and is incorporated into the primer strand during viral DNA replication leading to chain termination and formation of an inactive complex with the viral DNA Polymerase. (competitive inhibition)

Anti Influenza Agents Amantadine, Rimantadine, Oseltamivir, 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 an 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 RNA & 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

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Other Antiviral drugs:

* used in the treatment of ~~HBV, HCV, HPV, HIV infection~~ & respiratory syncytial virus (RSV)

Zidovudine . Inhibits viral DNA production/Expensive
. causes: N, V, muscle pain, and bone marrow suppression
↳ Anti HIV agent

Indinavir . Expensive + . protease inhibitor
blocks the part of HIV called protease. HIV-1 protease is an enzyme required for the proteolytic cleavage of the viral poly protein precursors into the individual functional proteins found in infectious HIV-1, so Indinavir binds to the protease active site and inhibits the activity of the enzyme.
. causes: N, V, 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 resistance to other protease inhibitors.
↳ Anti HIV agent

Interferones (IFNs): potent cytokines that possess antiviral, immunomodulating and antiproliferative activities, natural substances produced by virally infected cells; viral infection gives immunity for variable duration, modifies the immune response to increase resistance to viral infection, and control growth of the virus.

Obtained in small amounts from donor WBC	Nowadays obtained commercially by recombinant DNA technology
Used in Hepatitis C & some leukemias	Can cause nausea, fever & malaise (flu-like symptoms)

Mechanism of Action "Last one"

* Following binding to specific cellular receptors, IFNs activate the JAK-STAT signal transduction pathway, this in turn leads to synthesis of over 2 dozen proteins that contribute to viral resistance mediated at different stages of viral penetration.