# Chemptherapy3

## Chloramphenicol

- efficient against gram positive and gram negative and anaerobic bacteria
  - Rickettsia, Mycoplasma, and Chlamydia spp
  - Serious Anaerobic infections—Bacteroides fragilis — B.fragilis is a penicillin-resistant bacteria
- Short half-life
- 60% is bound to serum albumin
- Penetrates the brain and CSF and crosses the placental barrier
- Inactivated by the liver by glucuronosyltransferase and excreted in the urine
- Widely distributed
- Absorped very well(from GI tract) and rapid and it is not affected by food ingestion or metal ions — It is taken orally but sometimes it is taken parenterally –when you can't take it orally– — Treatment for meningitis&septicemia
- Effective with no resistance — Resistance may happen due to changes in the ribosomal binding sites
- Very toxic — That is why we only use it in a few life-threatening infections in which the benefits outweigh the risks — The grey baby syndrome
- Bacteristatic — Disrupts the function of 50s ribosomal subunits —> inhibits protein synthesis — Binds to the 50s ribosomal subunit preventing peptide bond formation — It prevents the attachment of tRNA to the A site — Chloramphenicol binds to peptidyltransferase and prevents natural binding of the amino acid therefore inhibiting protein sythesis
- Was used against salmonella(typhoid fever) but now we replaced it by a safer drugs
- Still used for meningitis caused by H. influenzea & Neisseria meningitidis & S. pneumoniae
  - Because effective CSF levels are obtained
  - it was effective against H. influenzae–related arthritis, osteomyelitis, epiglottitis
    - The development of B–lactamase–producing strains of H. influenzae increased the use of chloramphenicol
    - But with the advent of third–generation cephalosporins, chloramphenicol usage has significantly decreased
    - But if the patient is hypersensitive to B–lactams, chloramphenicol administration is appropriate therapy
- Causes aplastic anemia
  - The effect is not instantly after the intake
  - Fatal
- decreased permeability (can no longer enter the site of action)and plasmids that code for enzymes that degrade the antibiotic
- It may cause toxicity by the induced inhibition of mitochondrial protein synthesis –in human cells–
- Used for the topical treatment of eye infections — It is very effective because of its ability to penetrate ocular tissue — But the drug is still dangerous and there's a safer antibiotics so this agent might best be withdrawn
- Alternative to tetracyclin for rickettsial diseases, especially in children younger than 8 years
  alone or in combination
- Used to treat vancomycin–resistant enterococci

## Erythromycins(Macrolides)

- Same spectrum of penicillin — so substitutes in penicillin allergic patients
- Widely distributed — Even the prostate gland
- Safe drug for children
  - Can be taken orally
  - Can cause nausea, vomiting, and diarrhea
  - Can cause jaundice but rarely
- Short courses —–>long acting
- Used to eradicate Helicobacter pylori
- Examples
  - Clarithromycin
  - Azithromycin

## Lincomycin and Clindamycin

- Effective against +ve bacteria –like penicillin–
- Binds to the 50s ribosomal subunits and suppresses protein synthesis
- misused by doctors in the treatment of simple sore throat or URTI
- Should be reserved for deep seated infections like bone infection
- The overuse causes Pseudomembraneous colitis caused by the overgrowth of resistant intestinal flora

## Vancomycin

- Very toxic — ototoxic and nephrotoxic
- Reserved for severe Staphylococcal infection — given by slow IV infusion — Given orally for Pseudomembraneous colitis
- inhibits the synthesis of the cell wall – prevents peptidoglycan formation in cell wall– — by binding with high affinity to the D–alanyl–D–alanine terminus of cell wall

## Tuberculosis

- Caused by Mycobacterium tuberculosis
- It can remain dormant but viable and capable of causing disease
- 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
- three basic concepts in tuberculosis treatment
  - Regimens must contain multiple drugs to which the organism is susceptible — To reduce resistance and side effects
  - Drugs must be taken regularly
  - Drug therapy must continue for a sufficient time
- first–line drugs
  - Isoniazid(INH)
    - inhibit the biosynthesis of mycolic acids(cell wall)
    - Rapidly absorbed after oral administration
    - Widely distributed and excreted by the kidneys
    - Metabolized in the liver
      - Fast metabolizers — May decrease the efficacy
      - Slow metabolizers — May result in toxicity
    - Diffuses widely in the body
    - Causes neuropathy, especially in slow metabolizers — Can be corrected by Vitamin B6
  - Rifampin
    - Broad spectrum antibiotic
    - Use in Jordan is restricted for TB and prophylaxis of meningitis contacts
    - Can cause red discoloration of secretions
    - Inhibits RNA synthesis by the inhibition of RNA polymerase of mycobacteria by forming a stable drug–enzyme complex
  - Streptomycin
    - aminoglycoside
    - the first effective antituberculous drug
    - given by injection
    - Ototoxic
    - Resistance developed very rapidly
    - Replaced by isoniazid
    - Still used in some cases
  - pyrazinamide
  - ethambutol

## Antiviral Agents

- ANTIHERPESVIRUS AGENTS — Acyclovir
  - Wide spectrum antiviral agent — specifically efficient against the herpes virus
  - commonly used as an ointment or as a cream
  - Its use is restricted to immunocompromized patients in varicella – chickenpox
  - Side effects
    - Nausea
    - Vomiting
    - Skin rashes
  - Mimics the effect of dGTP — First, it is incorporated into the host cell that contains the virus — then converted into acyclovir monophosphate by viral thymidine kinase — Then acyclovir monophosphate is converted into acyclovir diphosphate and then acyclovir triphosphate using cellular protein kinases — this is the form of the drug that resembles the dGTP in structure — It tricks the viral DNA polymerase
- ANTIINFLUENZA AGENTS
  - Amantadine (Symmetrel) — synthetic tricyclic amine
  - Rimantadine (Flumadine) — The methyl derivative of this tricyclic amine
  - Both mechanism of action is similar and involves inhibition of the viral M2 protein — M2 protein: integral membrane protein that acts as a H channel — leads to a decrease in the pH — any process that requires an acidic environment cannot go further
  - The blockade od M2 protein prevents the acid–mediated dissociation of the ribonucleoprotein complex
  - Also the ph change inhibits viral assembly
  - Another examples
    - Oseltamivir
    - Zanamivir
- OTHER ANTIVIRAL AGENTS
  - Used in the treatment of:–
    - HBV — Anti–HIV agents
      - Zidovudine
        - Inhibits viral DNA production
        - Expensive; the main problem
        - Causes N, V, muscle pain, and bone marrow suppression — The bone marrow suppression will reduce the function of the immune system
      - Indinavir
        - Protease inhibitor –by binding to its active site – — Blocks HIV–1 protease which is an enzyme required for the proteolytic cleavage of the viral polyprotein precursors into the individual functional proteins found in infectious HIV–1
        - Causes N, V, Diarrhea, Renal stone formation
        - wears off quickly after dosing — requires very precise dosing every eight hours — to prevent HIV from forming drug–resistant mutations
        - Expensive
      - Most HIV drugs are very expensive and have very bad side effects
    - Hepatitis C virus
    - Respiratory syncytial virus
    - Human papilloma virus
    - HIV infection
  - Interferones
    - potent cytokines that possess antiviral, immunomodulating, and antiproliferative activities
      - This will inhibit the production of more viruses
      - Immunomodulating: the body recognizes the virus in other infections and can attack it
    - Natural substance — Produced by virally infected cells
    - Modify the immune response to increase resistance to viral infection
    - The mechanism:– — After the binding to its specific cellular receptors , IFNs will activate JAK–STAT — Will synthesis proteins that contribute to viral resistance