CHEMOTHERAPY OF HELMINTHIC INFECTIONS

BY P.J. OKOTH

CLASSIFICATION OF HELMINTHS

Classified into two major phyla:

1. Phylum Platyhelminthes
2. Phylum Nemathelminthes

Platyhelminthes

Derived from Greek:

Platys = broad; helmins = worm

Flat worms

They are classified into:

Cestodes

Trematodes

Platyhelminthes…

Cestodes: tapeworms

1. Taenia saginata (beef tapeworm)
2. Taenia solium (pork tapeworm)
3. Diphyllobothrium latum (fish tapeworm)
4. Ecchinococcus granulosus (hydatid disease)
5. Hymenolepis nana (dwarf tapeworm)

Platyhelminthes…

Trematodes:

Schistosomes:

1. Schistosoma haematobium [urinary schistosomiasis]
2. Schistosoma mansoni [intestinal schistosomiasis]
3. Schistosoma japonicum [intestinal schistosomiasis]

Flukes:

4. Fasciola hepatica – liver flukes
5. Intestinal flukes
6. Lung flukes

Nemathelminthes [Nematodes]

Intestinal nematodes:

Ascaris lumbricoides (roundworm)

Ancylostoma duodenale (hookworm)

Necator americanus (hookworm)

Enterobius vermicularis (thread worm/ pin worm)

Trichuris trichiura (whip worm)

Stronyloides stercoralis

Trichinella spiralis

Nemathelminthes…

Tissue nematodes:

Cutaneous larva migrans

Caused by ancylostoma braziliense and Ancylostoma caninum.

Dracuculus medinensis (Guinea worm)

Trichinella spiralis (trichinellosis)

Toxocara canis and Toxocara cati – cause visceral larva migrans

Nemathelminthes…

Tissue nematodes:…

Filariasis

Wuchereria bancrofti

Brugia malayi

Brugia timori

Loa loa

Onchocerca volvulus – causes onchocerciasis (or river blindness).

Drugs used in the treatment of helminthiasis

P. J. Okoth.

Pharmaceutical classes

Benzimidazoles:

Albendazole – effective against threadworms, roundworms, whipworms, tapeworms, hookworms

Mebendazole – effective against pinworms, roundworms and hookworms

Thiabendazole – effective against roundworms, hookworms

Fenbendazole – effective against gastrointestinal parasites

Triclabendazole – effective against liver flukes

Flubendazole – effective against most intestinal parasites

Niclosamide – effective against tapeworms

Pyrantel pamoate – effective against most nematode infections

Levamisole – effective against nematodes

Diethylcarbamazine – effective against *Wuchereria bancrofti*, *Brugia malayi*, *Brugia timori*, tropical pulmonary eosinophilia, loiasis

Ivermectin – effective against most common intestinal worms (except

Pharmaceutical classes…

Praziquantel – effective against cestodes, some trematodes

Piperazine salts

Oxamniquine

Metrifonate

Suramin

Niclosamide

Yomesan

Mechanism of action

It is a vermicidal drug

It blocks glucose uptake by intestinal tapeworms

It inhibits oxidative phosphorylation in tapeworm mitochondria and interferes with anaerobic generation of ATP by the tapeworm.

The segments of the worm which are voided after use of niclosamide are partially digested by the action of proteolytic enzymes of the small intestine.

Identification of the scolex is thus difficult.

Therapeutic use

Niclosamide is effective against:

Taenia saginata

Taenia solium

Diphylobothrium latum

Hymenolepis nana

Preparations and dosage

Available as 500mg tablets

Dose:

Over 12 yrs: 4 stat. [2gm stat) or 2 stat. then 2 after 1 hour.

6-12 yrs: 1-2 initially followed by 1-2 after 1 hour.

2-6 yrs: 1 stat. then 1 after 1hr

Given on an empty stomach in the morning.

Give a saline purge 2 hrs later to wash off the worms

Preparations and dosage…

For ***H. nana*** the 2gm dose is repeated daily for 5 days.

This is needed because the cysticerci of *H. nana* (which are not affected by niclosamide) develop in the jejunal villi of the same host and worms appear in the intestinal lumen after 4 days.

Praziquantel is the preferred single dose treatment.

Preparations and dosage…

A thorough purge is essential in the case of T. solium so that the segments are passed out and cysticercosis does not occur.

Digestion of the dead segments can be hazardous because the ova released from them may develop into larvae in the intestine, penetrate its wall and cause **visceral cysticercosis**.

Because **praziquantel** does not lead to digestion of the worm and kills encysted larvae as well, it is the drug of choice for T. solium.

Adverse effects

Nausea and vomiting

Abdominal discomfort

Diarrhoea

Dizziness

Headache

Avoid alcohol during treatment

Safe during pregnancy

Levamisole

Ketrax

Tetramisole

Mechanism of action

Levamisole **paralyzes the musculature** of sensitive nematodes which, unable to maintain their anchorage, are expelled by normal peristalsis.

Pharmacokinetics

Levamisole is partly absorbed when given orally and excreted in urine within 6-10 hours.

Indications

It is effective against:

Ascaris lumbricoides

Hookworms

Enterobius vermicularis

Strongyloides stercoralis

Preparations and dosage

Available as 40mg tablets and 40mg/5ml syrup

Dose:

Adults – 120mg stat. [3 tablets / 15mls syrup]

Children 1-4 yrs - 40mg stat. [1 tab or 5ml syrup]

Children 5-15 yrs – 80mg stat. [2 tabs or 10ml syrup]

Given as a single dose after a meal

No purgative is necessary.

Adverse effects

Nausea

Vomiting

Abdominal pain

Diarrhoea

Headache

Dizziness

Drowsiness

Insomnia

Mebendazole

Vermox; Mebex

Is a broad spectrum anthelmintic

It is a benzimidazole derivative

Mechanism of action

Mebendazole blocks glucose uptake by the nematodes and also depletes their glycogen stores.

It kills the worm and also ova of Ascaris.

Hatching of nematode eggs and their larvae are also inhibited.

Pharmacokinetics

Taken orally it is not much absorbed

75-90% of oral dose is passed in the faeces

Indications

It is effective against:

Ascariasis

Hookworms

Enterobiasis [threadworm/ pinworm]

Trichuriasis [whipworm]

Tapeworm

Strongyloidosis

Preparations and dosage

Available as tablets 100mg; 500mg and as suspension 100mg/5ml [30mls]

Dose:

usually 100mg twice daily for 3 days or 500mg stat.

Same dose for adults and children above 2 years.

For enterobiasis, 100mg stat. repet after 10-14 days.

Tapeworm and strongyloidosis 200mg BD x 3 days.

Adverse effects

1. Abdominal pain
2. Nausea
3. Diarrhoea
4. Headache
5. Dizziness

Precautions:

Pregnancy

Children under 2 years [half the dose usually given]

Albendazole

Zentel; Alben

A broad spectrum anthelmintic, similar to mebendazole

A benzimidazole derivative.

Mechanism of action

Blocks glucose uptake by nematodes leading to their death.

Pharmacokinetics

Moderate but inconsistent **absorption**

Fraction absorbed is converted by first pass metabolism to its sulfoxide metabolite which is **active**.

Widely distributed in the body

Albendazole is thus able to exert anthelmintic activity in **tissue** as well.

Indications

Effective against:

- Enterobiasis
- Trichuriasis
- Ascaris lumbricoides
- Hookworm
- Tapeworm

Effective against:

- Strongyloidiasis
- Cysticercosis
- Hydatid disease
- Cutaneous larva migrans
- Visceral larva migrans

Preparations and dosage

Available as

Tablets 200mg [usually in pairs]

Tablets 400mg

Suspension 200mg/5ml [10ml] or 100mg/5ml [20ml]

Dose:

400mg stat.

Indicated for adults and children over 2 yrs.

For strongyloidiasis and taeniasis, **400mg OD x 3 days.**

For **hydatid disease:** 400mg BD x 4 wks, repet after 2 wks for up to 3 courses.

Adverse effects

1. Gastrointestinal discomfort
2. Nausea
3. Dry mouth
4. Headache
5. Diziness
6. Pruritus

Contarindicated in pregnancy: should not be used in pregnancy unless there is no alternative treatment.

Not recommended for children below 2 yrs [can give half the dose for children 1-2 yrs]

Piperazine

Antepar

MOA

Produces flaccid paralysis of the muscles of the worms

The parasites are expelled paralyzed but not dead.

This eliminates the danger of worm migration and absorption of the autolysis products of parasites.

Preparations and dosage

Available as tablets of 500mg and as suspension of 1gm/5ml or 500mg/5ml.

Dose:

For round worms

Adults: 4gm stat. as single dose [8 tablets]

Children: 120mg/kg [max. 4gm] stat. as a single dose

For thread worms [Enterobiasis]:

1-2gm daily in divided doses

Children – 40mg/kg in divided doses.

Ivermectin

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Ivermectin

- Is an extremely potent semisynthetic derivative of the antinematodal principle obtained from Streptomyces avermitilis.
- Ivermectin is the drug of choice for single dose treatment of onchocerciasis and strongyloidiasis.
- It is comparable to diethylcarbazine for bancroftian and brugian filaria.
- It is also highly effective against cutaneous larva migrans and ascariasis.
- It has moderate efficacy against Enterobius and Trichuris.
- It kills insects like scabies and head lice.

Mechanism of action

Nematodes develop **tonic paralysis** when exposed to ivermectin.

It acts through a special type of glutamate gated chloride channel found only in invertebrates.

Such channels are not involved in the motor control of **tapeworms and flukes** which are **unaffected** by ivermectin.

Pharmacokinetics

Ivermectin is well absorbed orally

It is widely distributed in the body, sequestrated in the liver and fat and has a long elimination plasma half-life of 48-60 hours.

Adverse effects

Pruritus

Giddiness

Nausea

Abdominal pain

Constipation

Lethargy

Reactions due to degeneration products of the microfilariae.

Preparations and dosage

A single 10-15mg [0.2mg/kg] oral dose of ivermectin, preferably with 400mg of albendazole, given annually for 5-6 years has been used for filariasis.

For strongyloidiasis: single 0.15-0.2mg/kg dose.

Scabies and pediculosis: ivermectin is the only drug effective orally. Single 0.2mg/kg dose cures most patients.

Available as tablets 3mg; 6mg.

To be taken on an empty stomach.

Drug treatment of

Schistosomiasis is caused by:

- Schistosoma haematobium [causes urinary schistosomiasis]
- Schistosoma mansoni and japonicum [cause intestinal schistosomiasis]

Praziquantel [Biltricide]

Is a **broad spectrum** Schistosomicide active against all the three species of Schistosoma.

Also active against tapeworms, flukes (except Fasciola hepatica)

Mechanism of action:

Praziquantel paralyzes both adult worms and larvae.

Tapeworms lose grip of the intestinal mucosa and are expelled.

Flukes and Schistosomes are also dislodged in tissues and veins.

Praziquantel…

Pharmacokinetics:

It is extensively metabolized following rapid absorption from the intestines.

It crosses the blood-brain barrier and attains therapeutic concentrations in the brain and CSF.

Plasma half-life is 1.5 hours

Metabolites are excreted in urine.

Praziquantel …

Adverse effects:

Nausea

Headache

Dizziness

Drowsiness

Abdominal pain

Reaction to destroyed parasites [schistosomes and flukes]: - itching, fever, urticaria, rashes, body aches.

Praziquantel …

Preparations and dosage:

Available as 600mg tablets

Dose:

40mg/kg stat. or 20mg/kg BD on a single day.

For S. japonicum 60mg/kg in 3 divided doses

Metrifonate

Is an organophosphorous compound effective against Schistosoma haematobium.

Dose:

7.5mg/kg at intervals of 2 weeks for 3 doses.

Available as 100mg tablets.

Oxamniquine

Oxamniquine is an anthelmintic with schistosomicidal activity against *Schistosoma mansoni*, but not against other *Schistosoma* species.

Oxamniquine

Mode of action

Oxamniquine is a semi-synthetic tetrahydroquinoline.

It causes paralysis of the worms and eventual detachment from terminal venules in the mesentery, and death.

Oxamniquine acts mainly on male worms.

The drug causes the male worms to shift from the mesenteric circulation to the liver, where the cellular host response causes its final elimination.

The female worms return to the mesentery, but can no longer release eggs

Oxamniquine

Pharmacokinetics

Peak plasma concentrations are achieved one to three hours after a dose, and the plasma half-life is 1.0 to 2.5 hours.

It is extensively metabolized to inactive metabolites, principally the 6-carboxy derivative, which are excreted in the urine.

About 70% of a dose of oxamniquine is excreted as the 6-carboxy metabolite within 12 hours of a dose.

Oxamniquine

Uses

Oxamniquine is used for treatment of intestinal schistosomiasis.

It is highly effective for treating ***Schistosoma mansoni*** infections.

Oxamniquine

Side effects

It is generally well tolerated.

Dizziness with or without drowsiness is common.

Headache and gastrointestinal effects, such as nausea, vomiting, and diarrhoea, are also common.

Allergic-type reactions, including urticaria, pruritic skin rashes, and fever, may occur.

Epileptiform convulsions, especially in patients with a history of convulsive disorders.

A reddish discoloration of urine, probably due to a metabolite of oxamniquine

Oxamniquine

Preparations and Dosage:

Dosage:

Oral, 15 mg per kg body weight two times a day for one day.

Brand names

Vansil (Pfizer): 250 mg capsules, syrup 250 mg/5 mL

Mansil: 250 mg Tablets

Niridazole [Ambilhar]

Effective against:

Schistosoma mansoni

Schistosoma haematobium

Dose:

25mg/kg per day, orally for 7 days.

Maximum dose is 1.5gm

Available as 500mg tablets.

MOA:

Interferes with gonadal function of worms.

Niridazole is rapidly concentrated in the parasite and inhibits oogenesis and spermatogenesis.

Drug therapy of filariasis

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Diethylcarbamazine [Hetrazan]

Is a piperazine derivative very useful for prevention and cure of filariasis.

Diethylcarbamazine kills both microfilariae and adult worms (Loa loa, W. bancrofti, Brugia malayi)

It is also effective against onchocerciasis and visceral larva migrans.

Diethylcarbamazine [Hetrazan]

Diethylcarbamazine has a **highly selective effect** on microfilariae.

The most important action of the drug appears to be alteration of microfilaria membranes so that they are readily phagocytosed by tissue fixed monocytes, but not by circulating phagocytes.

It also has an effect on the muscular activity of the microfilariae and adult worms due to the piperazine moiety, so that they are dislodged.

Microfilariae present in nodules and transudates are not killed [e.g. in hydrocele]

Diethylcarbamazine [Hetrazan]

Pharmacokinetics:

Rapidly absorbed from the GIT

Peak plasma levels are achieved within 3 hrs

The drug is uniformly distributed in the body with the exception of fat.

Most of the drug is metabolized in the liver and the products are eliminated in urine.

Excretion is faster in acidic urine.

Plasma half-life is 4-12 hours.

Diethylcarbamazine [Hetrazan]

Adverse effects:

- Anorexia
- Nausea
- Vomiting
- Headache
- Dizziness
- Drowsiness

Allergic reactions due to products of destruction of the parasite include:

- Fever
- Tachycardia
- Lymphadenopathy
- Muscular pains
- Skin rashes
- Asthmatic attacks

Diethylcarbamazine…

Preparations and dosage:

Available as diethylcarbamazine citrate tablets 50mg and 100mg.

Also syrup for children 50mg/5ml

Dose: adults and children

1mg/kg daily in three divided doses for the first day;

Increase gradually over 2-3 days to 6mg/kg in 3 divided doses [2mg/kg TDS]

Maintain full dosage for 21 days.

This gradual stepping up of dosage reduces allergic reactions.

The end.

Thank you.

ANTI-AMOEBIC AGENTS

By P. J. Okoth

Introduction

Antiamoebic agents are drugs useful in treating infections caused by the protozoa Entamoeba hitolytica.

Amoebiasis occurs by fecal contamination of food and water.

Amoebic cysts reaching the intestine transform into **trophozoites**.

Introduction

Trophozoites either:-

Live on the surface of colonic mucosa as commensals - form **cysts** that pass into the stools (luminal cycle) and serve to propagate the disease, or

Invade the mucosa – form **amoebic ulcers** and cause acute dysentery (with blood and mucus in stools) or **chronic intestinal amoebiasis** (with vague abdominal symptoms, amoeboma).

Introduction

Occasionally the trophozoites pass into the bloodstream, reach the liver via portal vein and cause amoebic liver abscess.

Such infection is termed extraintestinal amoebiasis, and only trophozoites are present; cyst formation does not occur.

Other organs may rarely be involved: lungs, spleen, brain, and kidneys.

Classification of anti-amoebic drugs

1. **Tissue amoebicides**

b) For both intestinal and extraintestinal amoebiasis:

Nitroimidazoles

Metronidazole
Tinidazole
Secnidazole
Ornidazole
Satranidazole

Alkaloids

Emetine
Dehydroemetine

b) For extraintestinal amoebiasis only

chloroquine

Classification of anti-amoebic drugs

2. **Luminal amoebicides**

a) Amide

Diloxanide furoate

b) 8-Hydroxyquinolines

Quiniodochlor (clioquinol)

Diiodohydroxyquin (iodoquinol)

c) Antibiotics

Tetracyclines

NITROIMIDAZOLES

Antibacterial and anti-protozoal drugs

Metronidazole

Is the prototype nitroimidazole

Metronidazole

Is the prototype nitroimidazole

Spectrum of activity:

It has a broad spectrum cidal activity against protozoa:

Entamoeba histolytica

Trichomonas vaginalis

Giardia lamblia

Many anaerobic bacteria are sensitive to it.

Metronidazole

Mechanism of action:

Metronidazole is selectively toxic to anaerobic microorganisms.

After entering the cell by diffusion, its nitro group is reduced by certain redox proteins operative only in anaerobic microbes, to highly reactive nitro radical, which exerts cytotoxicity by damaging DNA and other critical biomolecules.

Metronidazole

Pharmacokinetics:

Metronidazole is well absorbed from the small intestines

It is widely distributed in the body, attaining therapeutic concentration in the liver, gut wall, pelvic tissues, vaginal secretion, semen, saliva and CSF.

It is metabolized in the liver primarily by oxidation and glucuronide conjugation.

It is excreted in urine partly unchanged and partly as metabolites.

The plasma half-life is 8 hours.

Metronidazole

Adverse effects:

Are relatively frequent but mostly non-serious.

They include:

Nausea

Vomiting

Anorexia

An unpleasant metallic taste in the mouth

Abdominal cramps

Loose stool

Metronidazole

Other **adverse effects** include:

Headache

Glossitis

Dryness of the mouth

Dizziness

Rashes, urticaria and angioedema

Peripheral neuropathy if treatment is prolonged

Epileptiform seizures in very high doses

Metronidazole

Contraindications:

In neurological disease

Blood dyscrasias

First trimester pregnancy

Chronic alcoholism

Metronidazole

Interactions:

A disulfirum-like intolerance to alcohol occurs because metronidazole inhibits alcohol and aldehyde dehydrogenase.

Patients should be told to avoid alcohol

Enzyme inducers (phenobarbitone, rifampicin) may reduce its therapeutic effect.

Cimetidine can reduce metronidazole metabolism. Its dose may need to be decreased.

Metronidazole

Preparations:

Available as:

Tablets 200mg, 400mg

Suspension 200mg/5ml

Intravenous infusion 500mg/100ml

Metronidazole

Uses and dosage:

Metronidazole is active against a wide range of anaerobic bacteria and also protozoa.

Metronidazole: uses and dosage

1. **Amoebiasis (Entamoeba histolytica)**

Metronidazole is a first-line drug for all forms of amoebic infection- both intestinal and extra-intestinal infection.

For invasive dysentery and liver abscess:

800mg TDS for 5-10 days [children 30-50mg/kg/day]

In serious cases of liver abscess:

1g may be infused I.V. slowly, followed by 0.5g every 12 hours till oral therapy is instituted.

For mild intestinal disease:

400mg TDS for 5-7 days.

Metronidazole

Uses and dosage …

2. **Giardiasis** (Giardia lamblia)

   200mg TDS x 7 days or 2g daily for 3 days

3. **Trichomoniasis** (Trichomonas vaginalis) of urogenital tract in both sexes: e.g. trichomonas vaginitis

   400mg TDS X 7days

4. **Anaerobic vaginosis** (Gardnerella vaginalis)

   400mg TDS x 7 days

Metronidazole

Uses and dosage…

5. **Anaerobic bacterial infections:**

Metronidazole is an effective drug for treatment of sepsis due to anaerobic organisms e.g. Bacteroides fragilis, and anaerobic cocci.

Such infections occur mostly after colorectal or pelvic surgery, appendicectomy, etc. leading to:

Intraabdominal infection

Septicaemia

Pelvic infection

Wound infection

Metronidazole

Uses and dosage…

Metronidazole is generally used in combination with gentamicin and cephalosporins.

Dose: for serious infections intravenous administration is recommended:

15mg/kg infused over 1 hour followed by 7.5mg/kg every 6 hours till oral therapy can be instituted with 400-800mg TDS.

Metronidazole

Uses and dosage…

6. **Pseudomembranous enterocolitis** (due to clostridium difficile)

   Usually associated with use of antibiotics

   Oral metronidazole is used at a dose of:

   800mg TDS X 5-7/7

7. **Acute ulcerative gingivitis and dental infections** (Fusobacterium species)

   200-400mg TDS X 5-7/7

   Combine with a penicillin or tetracycline

8. **Helicobacter pylori gastritis/peptic ulcer**

   400mg TDS x 1-2 weeks in combination with Amoxycillin/clarithromycin and a proton pump inhibitor.

Tinidazole

Is similar to metronidazole but has a longer plasma half-life of 12 hours

Has slower metabolism, duration of action is longer and thus more suited for single dose or once daily therapy.

It is better tolerated than metronidazole; the incidence of side effects is lower

Tinidazole

Uses and dosage

Recommended schedules are:

Amoebiasis: 2g OD X 3/7 [children 30-50mg/kg/day]

Trichomoniasis and **Giardiasis**: 2g single dose

Avoid alcohol

Secnidazole

Has the same spectrum of activity and potency as metronidazole

Absorption after oral administration is rapid and complete

Metabolism is slower resulting in a plasma half-life of 17-29 hours

A single dose yields cure rates equal to multiple doses of metronidazole and tinidazole

Side effects profile is similar to metronidazole

Secnidazole

Dosage:

2g single dose (children 30mg/kg) for intestinal amoebiasis, giardiasis, trichomoniasis and non-specific bacterial vaginosis

1.5g/day for 5 days in hepatic amoebiasis.

Available as 500mg and 1g tablets.

Ornidazole

Activity similar to metronidazole, but it is slowly metabolized.

Has longer half-life of 12-14 hours

Dose and duration of regimens for amoebiasis, giardiasis, trichomoniasis, anaerobic infections and bacterial vaginosis resemble those for tinidazole.

Side effect profile is also similar

Available as 500mg tablets and 500mg/100ml vial for I.V. infusion.

Amoebiasis: 2g OD x 3/7

Satranidazole

- Has longer plasma half-life than metronidazole [14 hrs]
- Advantages claimed are:
  - Better tolerability
    - No nausea, vomiting or metallic taste
    - Absence of neurological and disulfirum like reactions
  - It does not produce the acetamide metabolite which is a weak carcinogen
- **Dose**:
  - Amoebiasis 300mg BD for 3-5 days
  - Giardiasis and trichomoniasis 600mg single dose
- Available as 300mg tablet [satrogyl]

Luminal amoebicides

Diloxanide furoate

Diloxanide furoate

Is a highly effective **luminal** amoebicide.

It **directly kills trophozoites** responsible for production of cysts.

The furoate ester is hydrolysed in the intestine and the released diloxanide is largely absorbed, but produces no systemic antiamoebic activity. It is metabolized by glucuronidation and excreted in urine.

Diloxanide is a weaker amoebicide than its furoate ester.

Diloxanide furoate

Diloxanide furoate is less effective in invasive amoebic dysentery, because of poor tissue amoebicidal action.

However, it produces **high cure rates** in **mild** intestinal amoebiasis and in asymptomatic **cyst passers**.

Diloxanide furoate

Dose:

500mg TDS X 5-10 days

Children 20mg/kg/day

Available as 500mg tablets

Combination tablets are available:

Diloxanide furoate 250mg + metronidazole 200mg (e.g. Dirade-M or Entamizole 2 tds x 5-10 days)

Diloxanide furoate 250mg + tinidazole 150mg (e.g. TINIBA-DF 2 TDS X 5 days)

Diloxanide furoate

Diloxanide furoate is very well tolerated; the only side effects are flatulence, occasional nausea, itching and rarely urticaria.

It is the drug of choice for mild intestinal and asymptomatic amoebiasis.

It is given after tissue amoebicide to eradicate cysts.

The end.

Thank you.

ANTIBACTERIAL AGENTS

AMINOGLYCOSIDES

AMINOGLYCOSIDES

- They include:

  Streptomycin

  Neomycin

  Kanamycin

  Amikacin

  Gentamicin

  Tobramycin

  Sisomicin

  netilmicin

INTRODUCTION

- They are used to treat infections caused by **gram negative micro-organisms** such as pseudomonas and proteus species, E.coli and Klebsiella, Enterobacter and serratia species
- They are used most widely **in combination with beta lactam antibiotics** in serious infections with gram negative bacteria, in combination with vancomycin or beta lactam antibiotic for gram positive endocarditis and for treatment of tuberculosis.

PHYSICAL AND CHEMICAL PROPERTIES

- They are water soluble
- Stable in solution
- More active at alkaline than at acid PH

MOA

- Aminoglycosides are **irreversible inhibitors of protein synthesis.** The initial event is passive diffusion through the porin channels across the outer membrane. Drug is then actively transported across the cell membrane into the cytoplasm by an **oxygen dependent process.**
- Transport across cell wall may be **enhanced by cell wall active drugs such as penicillin or vancomycin.** This enhancement is the basis of synergism of these antibiotics with aminoglycosides.

- Inside the cell, aminoglycosides bind to **specific 30S subunit ribosomal proteins.** Protein synthesis is inhibited and this leads to irreversible and lethal cell death
- Aminoglycosides antibiotics are rapidly bactericidal. Bactericidal killing is **conc. Dependent**, the higher the conc, the greater the rate of bacteria killing.

MOA CT'D

- A **post antibiotic effect** i.e. residual bactericidal activity persisting after the serum conc has fallen below the MIC also is a characteristic of aminoglycosides. The duration of effect is also conc dependent.
- These properties probably account for the efficacy of **once-daily dosing regimens** of aminoglycosides

MICROBIAL RESISTANCE

- Bacteria may be resistant to aminoglycosides because of:

  Failure of the antibiotic to penetrate intracellularly

  Low affinity of the drug for the bacterial ribosome

  Inactivation of the drug by microbial enzymes

Clinically **drug inactivation** is the most common mechanism for acquired microbial resistance to aminoglycosides.

- Resistance to **gentamicin** indicates **cross-resistance to tobramycin, amikacin, kanamycin, Paromomycin and netilmicin** because the inactivating enzyme is bifunctional and can modify all these aminoglycosides
- Owing to differences in the chemical structures of streptomycin and other aminoglycosides, this enzyme does not modify streptomycin, which is inactivated by another enzyme; consequently, **gentamicin-resistant strains of enterococci may be susceptible to streptomycin.**

- Transport of aminoglycosides across the cytoplasmic membrane is an **oxygen-dependent active process**. **Strictly anaerobic bacteria** thus are **resistant** to these drugs because they lack the necessary transport system. Similarly, facultative bacteria are resistant when they are grown under anaerobic conditions

ANTIBACTERIAL SPECTRUM

- The antibacterial activity of gentamicin, tobramycin, kanamycin, netilmicin, and amikacin is directed primarily against **aerobic gram-negative bacilli.**
- Aminoglycosides have little activity against anaerobic microorganisms or facultative bacteria under anaerobic conditions. Their action against most gram-positive bacteria is limited, and they should not be used as single agents to treat infections caused by gram-positive bacteria. In combination with a cell wall-active agent, such as a penicillin or vancomycin, an aminoglycoside (streptomycin and gentamicin have been tested most extensively) produces a synergistic bactericidal effect *in vitro* against enterococci, streptococci, and staphylococci.

PHARMACOKINETICS

ABSORPTION

- The aminoglycosides are **highly polar cations** and therefore are **very poorly absorbed from the gastrointestinal tract**. Less than **1%** of a dose is absorbed after either oral or rectal administration.
- The drugs are not inactivated in the intestine and are eliminated quantitatively in the feces. **Absorption** of gentamicin from the **GI** may be **increased** by GI disease (*e.g.*, ulcers or inflammatory bowel disease).
- Intoxication may occur when aminoglycosides are applied topically for long periods to large wounds, burns, or cutaneous ulcers, particularly if there is renal insufficiency.

- All the aminoglycosides are absorbed rapidly from **intramuscular** sites of injection. **Peak concentrations** in plasma occur after **30 to 90 minutes** and are similar to those observed 30 minutes after completion of an intravenous infusion of an equal dose over a 30-minute period. These concentrations typically range from 4 to 12 mg/ml following a 1.5 to 2 mg/kg dose of gentamicin, tobramycin, or netilmicin and from 20 to 35 mg/ml following a 7.5 mg/kg dose of amikacin or kanamycin. In critically ill patients, especially those in shock, absorption of drug may be reduced from intramuscular sites because of poor perfusion.

DISTRIBUTION

- Because of their **polar nature**, the aminoglycosides **do not penetrate into most cells**, CNS, and the eye. Except for streptomycin, there is negligible binding of aminoglycosides to plasma albumin. The apparent volume of distribution of these drugs is **25%** of lean body weight and approximates the volume of extracellular fluid.
- **Concentrations** of aminoglycosides in **secretions and tissues are low**. **High concentrations** are found only in the **renal cortex** and the **endolymph** and **perilymph** of the **inner ear**; the high concentration in these sites likely contribute to the **nephrotoxicity** and **ototoxicity** caused by these drugs.

- Administration of aminoglycosides to **women late in pregnancy** may result in accumulation of drug in fetal plasma and amniotic fluid. Streptomycin and tobramycin can cause **hearing loss in children born to women who receive the drug during pregnancy.**

ELIMINATION

- The aminoglycosides are excreted almost entirely by **glomerular filtration**, and urine concentrations of 50 to 200 mg/ml are achieved. A large fraction of a parenterally administered dose is excreted unchanged during the first 24 hours, with most of this appearing in the first 12 hours. The **half-lives** of the aminoglycosides in plasma are similar and vary between **2 and 3 hours** in patients with normal renal function. Renal clearance of aminoglycosides is approximately two-thirds of the simultaneous creatinine clearance; this observation suggests some **tubular reabsorption** of these drugs.

ADVERSE EFFECTS

- All aminoglycosides have the potential to produce reversible and irreversible **vestibular, cochlear, and renal toxicity.** These side effects complicate the use of these compounds and make their proper administration difficult.

OTOTOXICITY

- Vestibular and auditory dysfunction can follow the administration of any of the aminoglycosides.
- The drug accumulates in the perilymph and endolymph of the inner ear
- Accumulation occurs predominantly when concentrations in plasma are high
- the half-lives of the aminoglycosides are five to six times longer in the otic fluids than in plasma.

- Ototoxicity is **largely irreversible** and results from progressive destruction of vestibular or cochlear sensory cells, which are highly sensitive to damage by aminoglycosides
- The **initial symptoms may be reversible,** its therefore recommended that patients receiving high doses and/or prolonged courses of aminoglycosides be **monitored** carefully for ototoxicity; however, deafness may occur several weeks after therapy is discontinued.

- Although all aminoglycosides are capable of affecting cochlear and vestibular function, some **preferential toxicity** is evident. **Streptomycin** and **gentamicin** produce **predominantly vestibular** effects, whereas **amikacin,kanamycin**, and **neomycin** primarily affect **auditory function**; **tobramycin affects both equally.**
- The incidence of vestibular toxicity is particularly high in patients receiving streptomycin

NEPHROTOXICITY

- Approximately 8% to 26% of patients who receive an aminoglycoside for more than several days will develop mild renal impairment that is **almost always reversible** . The toxicity results from accumulation and retention of aminoglycoside in the proximal tubular cells
- The impairment in renal function is almost always reversible because the **proximal tubular cells have the capacity to regenerate.**
- **Neomycin**, which concentrates to the greatest degree, is **highly nephrotoxic** in human beings and should not be administered systemically. **Streptomycin** does not concentrate in the renal cortex and is the **least nephrotoxic.**

- Other drugs, such as *amphotericin B*, *vancomycin, angiotensin-converting enzyme inhibitors, cisplatin*, and *cyclosporine,* may **potentiate aminoglycoside-induced nephrotoxicity**
- Even though aminoglycosides consistently alter the structure and function of renal proximal tubular cells, these effects usually are reversible. The most important result of this toxicity may be **reduced excretion of the drug**, which, in turn, predisposes to **ototoxicity.**

NEUROMUSCULAR BLOCKADE

- The order of decreasing potency for blockade is neomycin, kanamycin, amikacin, gentamicin, and tobramycin.
- Most episodes occur in **association with anesthesia** or the administration of **other neuromuscular blocking agents.** Patients with **myasthenia gravis** are particularly susceptible to neuromuscular blockade by aminoglycosides
- Aminoglycosides may inhibit prejunctional release of acetylcholine while also reducing postsynaptic sensitivity to the transmitter
- This effect is overcome by administration of intravenous calcium salt or inhibitors of acetylcholinestrase e.g. neostigmine

STREPTOMYCIN

- Streptomycin may be administered by deep intramuscular injection or intravenously.
- Intramuscular injection may be painful, with a hot, tender mass developing at the site of injection.
- The dose of streptomycin is **15 mg/kg per day** for patients with creatinine clearances above 80 ml/min. It typically is administered as a **1000-mg single daily dose**
- The total daily dose should be reduced in direct proportion to the reduction in creatinine clearance for creatinine clearances above 30 ml/min

INDICATIONS

- ***Tularemia-***1 g (15 to 25 mg/kg) streptomycin per day for 7 to 10 days.
- ***Plague-***2 g/day in two divided doses for 7 to 10 days.
- ***Tuberculosis-***in combination with other drugs to which the causative strain is susceptible. The dose for patients with normal renal function is 15 mg/kg per day as a single intramuscular injection for 2 to 3 months

GENTAMICIN

- Gentamicin is an important agent for the treatment of many serious gram-negative bacillary infections. It is the **aminoglycoside of first choice** because of **its low cost and reliable activity** against all but the most resistant gram-negative aerobes.
- Gentamicin preparations are available for **parenteral, ophthalmic, and topical administration.**

DOSAGE

- The **once-daily dose is 5 to 7 mg/kg** given over 30 to 60 minutes for patients with normal renal function (and below this range if renal function is impaired). The upper limit of this dose range may be required to achieve therapeutic levels for trauma or burn patients, those with septic shock, and others in whom drug clearance is more rapid or volume of distribution is larger than normal.
- For **newborns and infants: 3 mg/kg once daily** for preterm newborns younger than 35 weeks' gestation ; 4 mg/kg once daily for newborns older than 35 weeks' gestation; 5 mg/kg daily in two divided doses for neonates with severe infections; and 2 to 2.5 mg/kg every 8 hours for children up to 2 years of age.

INDICATIONS

- ***Urinary Tract Infections-*** a single intramuscular dose of gentamicin (5 mg/kg) has been effective in curing more than 90% of uncomplicated infections of the lower urinary tract
- ***Pneumonia-*** An aminoglycoside in combination with a b-lactam antibiotic may be used for empirical therapy of hospital-acquired pneumonia in which multiple-drug-resistant gram-negative aerobes are a likely causative agent.
- ***Meningitis-*** in adults, 5 mg of a preservative-free formulation of gentamicin (or equivalent dose of another aminoglycoside) is administered directly **intrathecally once daily**

- ***Peritoneal Dialysis-Associated Peritonitis-*** Patients who develop peritonitis as a result of peritoneal dialysis may be treated with aminoglycoside diluted into the dialysis fluid to a concentration of 4 to 8 mg/L for gentamicin, netilmicin, or tobramycin or 6 to 12 mg/L for amikacin

- ***Bacterial Endocarditis-*** low-dose gentamicin (**3 mg/kg per day in combination with a penicillin or vancomycin** has been recommended in certain circumstances for treatment of bacterial endocarditis. There is good evidence that penicillin and gentamicin in combination are effective as a short-course (*i.e.,* 2-week) regimen for **uncomplicated native-valve streptococcal endocarditis**. In cases of enterococcal endocarditis, concomitant administration of penicillin and gentamicin for 4 to 6 weeks has been recommended because of an unacceptably high relapse rate with penicillin alone.

- ***Sepsis-***Included in an empirical regimen used for the febrile patient with granulocytopenia and for infections suspected to be caused by *P. aeruginosa*.
- ***Topical Applications-*** can be used to treat burns Gentamicin is absorbed slowly when it is applied topically in an ointment and somewhat more rapidly when it is applied as a cream.

TOBRAMYCIN

- Tobramycin may be given either intramuscularly or intravenously. Dosages and serum concentrations are identical with those for gentamicin. Tobramycin (TOBREX) also is available in ophthalmic ointments and solutions.
- **Indications** for the use of tobramycin are the **same as those for gentamicin.** The **superior activity** of tobramycin against **P. aeruginosa** makes it the preferred aminoglycoside for treatment of serious infections caused by this organism. It usually should be used concurrently with an antipseudomonal b-lactam antibiotic

AMIKACIN

- The spectrum of antimicrobial activity of amikacin (AMIKIN) is the **broadest of the group**. Because of its **resistance to many of the aminoglycoside-inactivating enzymes**, it has a special role in hospitals where gentamicin- and tobramycin-resistant microorganisms are prevalent.
- The recommended dose of amikacin is **15 mg/kg per day as a single daily dose** or divided into two or three equal portions, which must be reduced for patients with renal failure.

INDICATIONS

- Preferred agent for the initial treatment of serious **nosocomial gram-negative bacillary infections** in hospitals which are resistant to gentamicin and tobramycin.
- Amikacin is active against the vast majority of aerobic gram-negative bacilli in the community and the hospital. This includes most strains of ***Serratia, Proteus, and P. aeruginosa***. It is active against nearly all strains of ***Klebsiella, Enterobacter,*** **and** ***E. coli*** that are resistant to gentamicin and tobramycin.
- It is active against ***M. tuberculosis*** including streptomycin-resistant strains and atypical mycobacteria. It can be used in the treatment of disseminated atypical mycobacterial infection in AIDS patients.

NETILMICIN

- It is similar to gentamicin and tobramycin in its pharmacokinetic properties and dosage.
- Its antibacterial activity is broad against aerobic gram-negative bacilli. Like amikacin, it is not metabolized by the majority of the aminoglycoside-inactivating enzymes, and it therefore may be active against certain bacteria that are resistant to gentamicin.
- Netilmicin is useful for the treatment of serious infections owing to susceptible Enterobacteriaceae and other aerobic gram-negative bacilli. It is effective against certain gentamicin-resistant pathogens, with the exception of enterococci

KANAMYCIN

- Its use has declined markedly because its **spectrum of activity is limited** compared with other aminoglycosides, and it is among the **most toxic.**
- The parenteral dose for adults is **15 mg/kg per day** (two to four equally divided and spaced doses), with a maximum of 1.5 g/day. Children may be given up to 15 mg/kg per day.
- Kanamycin has been employed to treat **tuberculosis** in combination with other effective drugs. It has no therapeutic advantage over streptomycin or amikacin and probably is more toxic; either should be used instead, depending on susceptibility of the isolate.

NEOMYCIN

- *Neomycin sulfate* is available for topical and oral administration. Neomycin and *polymyxin B* have been used for **irrigation of the bladder.** For this purpose, 1 ml of a preparation (NEOSPORIN G.U. IRRIGANT) containing 40 mg neomycin and 200,000 units polymyxin B per milliliter is diluted in 1 L of 0.9% sodium chloride solution and is used for continuous irrigation of the urinary bladder through appropriate catheter systems. The goal is to prevent bacteriuria and bacteremia associated with the use of indwelling catheters. The bladder usually is irrigated at the rate of 1 L every 24 hours.
- Can also be used to sterilise the gut

- Neomycin currently is available in many brands of creams, ointments, and other products alone and in combination with polymyxin, *bacitracin,* other antibiotics and a variety of corticosteroids.
- **Neomycin has been used widely for topical application** in a variety of infections of the skin and mucous membranes caused by microorganisms susceptible to the drug. These include infections associated with burns, wounds, ulcers, and infected dermatoses. However, such treatment does not eradicate bacteria from the lesions.

PAROMOMYCIN

- Has antibacterial activity against pathogenic organisms in the GI tract e.g. E. Histolytica, Diantomoeba fragilis, Tapeworm
- Poorly absorbed after oral administration
- Excreted through the feces 100% as unchanged drug

MACROLIDES

INTRODUCTION

- Include:

  Erythromycin

  Azithromycin

  Clarithromycin

  Telithromycin

  Roxithromycin

MOA

- The macrolides **inhibit bacterial protein synthesis by blocking the aminoacyl translocation reaction and formation of initiation complexes.** Their action may be bactericidal or bacteriostatic, the effect depending on the concentration and on the type of micro-organism.
- The drugs bind to the same 50S subunit of the bacterial ribosome as chloramphenicol and clindamycin, and the three drugs may compete if given concurrently

ANTIMICROBIAL SPECTRUM

- The antimicrobial spectrum of erythromycin is very similar to that of penicillin, and it has proved to be a **safe and effective alternative for penicillin-sensitive patients.**
- Erythromycin is effective **against Gram-positive bacteria and spirochaetes** but not against most Gram-negative organisms, exceptions being *N. gonorrhoeae* and, to a lesser extent, *H. influenzae.*
- ***Mycoplasma pneumoniae, Legionella*** **sp. and some chlamydial organisms** are also susceptible

- **Azithromycin** is less active against Gram-positive bacteria than erythromycin but is considerably **more effective against *H. influenzae* and may be more active against *Legionella*. It has excellent action against *Toxoplasma gondii*, killing the cysts.**
- **Clarithromycin** is as active, and its metabolite is **twice** as active, against ***H. influenzae*** as erythromycin. It is also effective against *Mycobacterium avium-intercellulare* (which can infect immunologically compromised individuals and elderly patients with chronic lung disease), and it may also be useful in leprosy and against ***Helicobacter pylori***
- Both these macrolides are also effective in **Lyme disease**

AVAILABLE DOSAGE FORMS

- Azithromycin- tabs/caps 250&500mg, susp 200mg/5ml, inj 500mg/vial
- Clarithromycin- tabs 250&500mg, syr. 125mg/5ml, inj 500mg/vial
- Erythromycin- tabs 250&500mg, susp. 125mg/5ml,
- Roxithromycin- tabs 150mg, syr 50mg/5ml

INDICATIONS AND DOSES

- Azithromycin- mild to moderate URTIs, uncomplicated skin and soft tissue infections, STIs by susceptible organisms
- Dose: 500mg od for 3 days; child over 6 months 10mg/kg od for 3 days. Alternatively 60mg/kg PO once as a single dose
- Uncomplicated genital chlamydial infections and non-gonococcal urethritis, 1g as a single dose.
- Lyme disease, typhoid, 500mg od for 7-10 days

CLARITHROMYCIN

- Clarithromycin: mild to moderate URTIs and LRTIs, uncomplicated skin and soft tissue infections, adjunct in the treatment of duodenal ulcers for eradication of H. pylori
- Dose: adult-250mg bd for 7 days, increased in pneumonia or severe infections to 500mg bd for upto 14 days(14-21 days in Lyme disease), child-7.5mg/kg twice daily

ERYTHROMYCIN

- Erythromycin: an alternative for penicillin-allergic patients, intestinal amoebiasis, chlamydial, mycoplasmal infections, URTI, LRTI, skin and soft tissue infections, gonococcal male urethritis and female pelvic infections, long term prophylaxis of rheumatic fever, early syphyllis in penicillin allergic patients, tetanus, legionnaires disease
- Dose: adult and child over 8 yrs 250-500mg qid, child below 8yrs 12.5mg/kg for 5-7 days. Duration can go up to 14 days for early syphylis and 21 days for Lyme disease

- Roxithromycin: mild to moderate ENT infections, skin and soft tissues infections, gut infections
- Dose: adults 150mg bd 0r 300mg OD, child, 5mg/kg bd

AZITHROMYCIN

- One of its main advantages is that it is taken up in high amounts by tissues and then slowly released over subsequent days.
- Thus, a 5-day course of oral therapy results in therapeutic drug levels in the blood for 10 days.

TELITHROMYCIN

- Telithromycin is the first commercially available member of a new class of antibiot- ics called *ketolides*.
- Ketolides are structurally related to the macrolides but have an expanded spectrum of activity.
- Telithromycin binds to the same site of the 50S subunit of the bacterial ribosome as the macrolides but has an additional alkyl- aryl extension, which binds to a second distinct site on the ribosome.

TELITHROMYCIN C'TD

- Two sites of contact instead of one result in tighter binding and continued interaction even in the presence of some enzymes that methylate the ribosome and result in resistance to macrolides.
- This tighter binding also limits export of telithro- mycin by macrolide efflux pumps.
- Thus, telithromycin is active against many strains of *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Streptococcus pyogenes* that are re- sistant to macrolides.

PHARMACOKINETICS

- The macrolides are administered orally, azithromycin and clarithromycin being more acid-stable than erythromycin
- Erythromycin can also be given parenterally, although intravenous injections can be followed by local thrombophlebitis
- All three diffuse readily into most tissues but do not cross the blood-brain barrier, and there is poor penetration into synovial fluid.
- The plasma half-life of erythromycin is about 90 minutes; that of clarithromycin is three times longer, and that of azithromycin 8-16 times longer

- Macrolides enter and indeed are concentrated within phagocytes-azithromycin concentrations in phagocyte lysosomes can be 40 times higher than in the blood-and they can enhance intracellular phagocyte killing of bacteria.
- Erythromycin is partly inactivated in the liver; azithromycin is more resistant to inactivation, and clarithromycin is converted to an active metabolite. Their effects on the P450 cytochrome system can affect the bioavailability of other drugs. **The major route of elimination is in the bile.**

INTERACTIONS

- **Presence of food reduces absorption** , should be administered 1hr before or 2 hrs after meals
- Co administration with **antacids reduces absorption**
- Potentiates effects of carbamazepine, corticosteroids, digoxin, theophylline, coumarin anti -coagulants

CONTRA INDICATIONS

- In hepatic disorders
- In patients sensitive to macrolides
- Concommitant administration with vasoconstrictor ergot derivatives for roxithromycin

ADVERSE EFFECTS

- GI disturbances
- Reversible hearing impairment
- Elevated liver transaminases
- Melena
- Pseudomembranous colitis
- Ventricular arrythmias with prolonged QT interval
- Stevens-Johnson and toxic epidermal necrolysis
- Hepatic dysfunctions

TETRACYCLINES & GLYCYLCYCLINES

INTRODUCTION

- Comprises of:

  Tetracycline

  Doxycycline

  Minocycline

  Tigecycline

SPECTRUM OF ACTIVITY

- They have *the favourable effects on*
- *S. pneumoniae*
- *H. influenzae*
- **Rickettsiae,**
- **Mycoplasma,**
- **Chlamydiae**
- **Spirochete.**
- They are *effective against some*

protozoa.

MOA

- Quickly bacteriostatic drugs, but at high dosage they are also bactericidal.
- **They reversibly bind to the 30S ribosomal subunit of bacteria, *blocking the binding of aminoacyl-tRNA to the site A on the mRNA ribosome complex.*** *This prevents addition* of amino acids to the growing peptide, resulting in inhibition of protein synthesis.

MECHANISM OF RESISTANCE

- Bacterial resistance to tetracyclines is mainly due to the following three mechanisms:

  Decreased intracellular accumulation owning to either *impaired influx or increased efflux by an active transport protein pump.*

  Ribosome protection owning to production of proteins that *interfere with tetracycline binding to the target site.*

  Enzymatic inactivation of tetracyclines.

TIGECYCLINE

- Tigecycline is not actually a tetracycline but a member of a structurally related class of antibiotics called the **glycylcyclines,** of which tigecycline is the only commercially available member.
- Tigecycline isn’t recognized by many bacterial efflux pumps and this makes it insensitive to modifications of the 30S ribosomal subunit that confer resistance to tetracyclines.

TIGECYCLINE

- Because these mechanisms account for the bulk of the resistance to tetracyclines, tigecycline has an impressively broad antimi- crobial spectrum.
- It is active against most aerobic gram-negative bacteria, including **multidrug-resistant *Acinetobacter* spp.** However, *P. aeruginosa* and *Proteus* spp., which produce efflux pumps that do recognize this agent, are usually resistant

TIGECYCLINE C'TD

- Most aerobic gram-positive bacteria, including methicillin-resistant staphylococci, vancomycin-resistant enterococci, and penicillin-resistant *S. pneumoniae*, are suscep- tible to tigecycline.
- It also has good activity against anaerobic bacteria, although it is inferior to carbapenems and piperacillin-tazobactam in this regard.
- As would be expected of a tetracycline-related agent, tigecycline appears to have excellent activity against atypical bacteria.

PHARMACOKINETICS

- All tetracylines are administered orally.
- Tetracycline, in particular, is chelated and inactivated by calcium (milk), magnesium, aluminum (antacids) and iron, and should be taken when the stomach is empty.
- Doxycycline is less avidly chelated and can be taken with a meal.

DISTRIBUTION

- Widely distributed in body
- Bind in tissues undergoing calcification (teeth, bones) or tumors with high calcium content (gastric carcinoma)
- All cross placenta and concentrate in fetal bones and teeth
- Minocycline best CSF penetration

  Concentrated in saliva and gingival fluid

EXCRETION

- Concentrate in liver and partially metabolized
- Secreted into bile and excreted in urine
- Doxycycline and minocycline largely excreted in feces

  Use in renal insufficiency

PHARMACODYNAMICS/KINETICS:

-Absorption: ~50% to 80%.

-Protein binding: 41% to 50%

-Metabolism: Hepatic.

-Half-life elimination: 10-17 hours

-Time to peak, serum: 3-6 hours

-Excretion: Urine

INDICATIONS

- First choice for rickettsial infections (typhus), chlamydial infections, and *Mycoplasma pneumonia.*
- They are effective for many spirochetal infections, including relapsing fever (first choice), leptospirosis, Lyme diseases, and syphylis

- They are also effective for treatment of various G+ and G- bacterial infections.

  Brucellosis, cholera, and tularemia can be treated with tetracyclines as the first choice.

- Other uses: *intestinal amebiasis, acne and actinomycosis*

ADVERSE EFFECTS

- **A. Gastrointestinal discomfort**

  • Anorexia, epigastric pain, abdominal distention, nausea, vomiting, diarrhea, sore mouth, perianal irritation

- **B. Hepatic injury (Liver toxicity)**

  Increased during pregnancy

- C. kidney toxicity

  Nephrotoxicity

- **D. Teeth and depression of bone growth**

  • Discoloration enamel and hypoplasia of teeth deposition in fetal and growing bones,

  stunted growth

- **E. Photosensitization**

  Severe sunburn in sun; doxy/demeclocycline

CONTRAINDICATIONS

- Pregnancy
- Children
- Renal insufficiency

  Can use doxycycline

DRUG INTERACTION OF TETRACYCLINES::

antacids containing aluminum, calcium, or magnesium, and iron-containing preparations	Impaire the Absorption of tetracyclines
anticoagulant therapy	Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.
bacteriostatic drugs	interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.

oral contraceptives	Concurrent use of tetracyclines with oral contraceptives may render oral contraceptives less effective.
ergot alkaloids or their derivatives are given with tetracyclines.	Increased risk of ergotism
Bile acid sequestrants	May decrease tetracycline absorption
Iron preparations	May decrease absorption of tetracyclines

Methoxyflurane: Methoxyflurane anesthes	when concurrent with tetracycline) may cause fatal nephrotoxicity; concurrent use is contraindicated.
Methotrexate:	Clearance of methotrexate (high-dose therapy) may be decreased by tetracyclines.

THE 50 S INHIBITORS:

CHLORAMPHENICOL

CLINDAMYCIN/LINCOMYCIN

STREPTOGRAMINS

OXAZOLADINONES

I CHLORAMPHENICOL

BACTERICIDAL – H. INFLUENZAE, N. MENINGITIDES, B. FRAGILIS

BACTERIOSTATIC – S. EPIDERMIDIS, S. AUREUS, , M. PNEUMONIA, L. MONOCYTOGENES, DIPHTHERIA, L. MULTOCIDA, SALMONELLA SP., SHIGELLA SP., E. COLI, RICKETTSIA, ANAEROBES,INEFFECTIVE FOR CHLAMYDIAL INFECTIONS

MECHANISM OF ACTION:

ATTACHES AT P SITES OF 50 S SUBUNIT OF MICROBIAL RIBOSOMES AND INHIBITS FUNCTIONAL ATTACHMENT OF AMINO-ACYL END OF AA-T-RNA TO 50 S SUBUNIT

INHIBITS PEPTIDYL TRANSFERASE STEP

SPECTRUM:

BROAD SPECTRUM ANTIBIOTIC

MORE EFFECTIVE THAN TETRACYCLINES AGAINST TYPHOID FEVER AND OTHER SALMONELLA INFECTIONS

KINETICS:

WELL ABSORBED AFTER ORAL ADMINISTRATION

CHLORAMPHENICOL SUCCINATE USED FOR PARENTERAL ADMINISTRATION IS HIGHLY WATER SOLUBLE

DISTRIBUTED INTO TOTAL BODY WATER

EXCELLENT PENETRATION INTO CSF, OCULAR AND JOINT FLUIDS

RAPIDLY EXCRETED IN URINE, 10% AS CHLORAMPHENICOL; 90% AS GLUCURONIDE CONJUGATE

SYSTEMIC DOSAGE NEED NOT BE ALTERED IN RENAL INSUFFICIENCY BUT MUST BE REDUCED MARKEDLY IN HEPATIC FAILURE

NEWBORNS LESS THAN A WEEK OLD AND PREMATURE INFANTS ALSO CLEAR CHLORAMPHENICOL LESS WELL, DOSAGE SHOULD BE REDUCED AT 25 MG/KG/D

USES: MENINGITIS, RICKETTSIA, SALMONELLA AND ANAEROBIC INFECTIONS

INEFFECTIVE AGAINST CHLAMYDIAL INFECTIONS

OCCASIONALLY USED TOPICALLY IN THE TREATMENT OF EYE INFECTIONS FOR ITS WELL PENETRATION TO OCULAR TISSUES AND THE AQEOUS HUMOR

ADVERSE EFFECTS: GIT, ORAL OR VAGINAL CANDIDIASIS,

IRREVERSIBLE APLASTIC ANEMIA, REVERSIBLE BONE MARROW DEPRESSION, GRAY BABY SYNDROME


Pale or
blue skin
Lethargic
eyes

Gray baby syndrome. Neonates do not have the ability to metabolize chloramphenicol to the acyl glucuronide metabolite. May be exacerbated by preexisting liver failure.

- Symptoms appear in this order: Abdominal distension with or without emesis, progressive pallid cyanosis, vasomotor collapse & irregular respiration, death. Death occurs in 40% of patients within 2 days of initial signs.

- Symptoms first appear after 3-4 days of high dose treatment. (doses above 50mg/kg/d) Drug concentrations are generally 40 g/ml.

Therefore limit dosage to 50mg/kg/d or less (during the first week of life) in full-term infants more than 1 week old and 25 mg/kg/d in premature infants

CLINDAMYCIN/LINCOMYCIN

MECHANISM OF ACTION: ATTACH TO 50 S RIBOSOMAL SUBUNIT, INHIBITS PROTEIN SYNTHESIS BY INTERFERING WITH THE FORMATION OF INITIATION COMPLEXES AND TRANSLOCATION REACTION

SPECTRUM: NARROW GRAM (+) SPECTRUM, EXCELLENT ACTIVITY AGAINST ANAEROBIC BACTERIA; STREP, PNEUMOCOCCI, STAPHYLOCOCCI

RESISTANCE:

MUTATION OF THE RIBOSOMAL RECEPTOR SITE

MODIFICATION OF THE RECEPTOR BY A CONSTITUTIVELY EXPRESSED METHYLASE

ENZYMATIC INACTIVATION

CLINDAMYCIN IS MORE CLINICALLY USED THAN LINCOMYCIN:

- EXCELLENT ABSORPTION
- GIVEN AT 150-300 MG Q 6 HRS – ADULTS; 10-20 MG/KG/D
- FOR CHILDREN
- LOW CONCENTRATION IN CSF
- GOOD BONE PENETRATION
- EXCRETED MAINLY VIA THE LIVER, BILE AND URINE
- HALF LIFE IS 2.5 HOURS NORMALLY AND 6 HOURS IN PATIENTS
- WITH ANURIA
- MORE TOXIC THAN ERYTHROMYCIN
- PROPHYLAXIS OF ENDOCARDITIS IN PATIENTS WITH VALVULAR
- HEART DISEASE FOR DENTAL PROCEDURES

MOST IMPORTANT INDICATION IS THE TREATMENT OF SEVERE ANAEROBIC INFECTION CAUSED BY BACTEROIDES AND OTHER ANAEROBES THAT OFTEN PARTICIPATE IN MIXED INFECTIONS

+ AMINOGLYCOSIDE OR CEPHALOSPORIN USED TO TREAT PENETRATING WOUNDS OF THE ABDOMEN AND THE GUT

SEPTIC ABORTION, PELVIC ABSCESSES, ASPIRATION PNEUMONIA

+ PRIMAQUINE – EFFECTIVE ALTERNATIVE TO TRIMETHOPRIM SULFAMETHOXAZOLE FOR MODERATE TO MODERATELY SEVERE PNEUMOCYSTIS CARINII PNEUMONIA IN AIDS PATIENTS

+ PYRIMETHAMINE FOR AIDS – RELATED TOXOPLASMOSIS OF THE BRAIN

ADVERSE EFFECTS:

DIARRHEA, NAUSEA, SKIN RASHES, IMPAIRED LIVER FUNCTION AND NEUTROPENIA; ANTIBIOTIC ASSOCIATED COLITIS CAUSED BY TOXIGENIC C. DIFFICILE

NEWER AGENTS:

STREPTOGRAMINS:

QUINUPRISITN-DALFOPRISTIN (SYNERCID)

ACTION IS SIMILAR TO MACROLIDES EXCEPT BACTERICIDAL FOR STAPH AND MOST ORGANISMS EXCEPT ENTEROCOCCUS FAECIUM

PROLONGED POSTANTIBIOTIC EFFECT UP TO 10 H FOR STAPH. AUREUS

ADMINISTERED IV AT 7.5 MG/KG Q 8-12 H

ELIMINATED THROUGH FECAL ROUTE, < 20% URINE

INHIBITS CYP 3A4, WHICH METABOLIZES WARFARIN, DIAZEPAM, ASTEMIZOLE, TERFENADINE, CISAPRIDE, NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS AND CYCLOSPORINE.

CLINICAL USES: INFECTIONS CAUSED BY VANCOMYCIN RESISTANT STRAINS OF E FAECIUM BUT NOT E. FAECALIS, BACTEREMIS OR RESPIRATORY TRACT INFECTIONS CAUSED BY METHICILLIN-RESISTANT STAPHYLOCOCCI AND PENICLLIN SUSCEPTIBE AND RESISTANT STRAINS OF S. PHEUMONIA

TOXICITIES: INFUSION RELATED EVENTS, PAIN AT THE INJECTION SITE, ARTHRALGIA, MYALGIA SYND

OXAZOLADINONES: LINEZOLID (ZYVOX)

INHIBITS PROTEIN SYNTHESIS BY PREVENTING FORMATION OF THE RIBOSOME COMPLEX THAT INITIATED PROTEIN SYNTHESIS.

ITS UNIQUE BINDING SITE LOCATED ON 23 S RIBOSOMAL RNA OF THE 50 S SUBUNIT, RESULTS IN NO CROSS RESISTANCE WITH OTHER DRUG CLASSES

HAS HIGH ORAL BIOAVAILABILITY, HALF LIFE OF 4-6 H

USES : STAPH, STREP, ENTEROCOCCI, G(+) ANAEROBIC COCCI, G (+) RODS, CORYNEBACTERIUM, L. MONOCYTOGENES

- TREATMENT OF INFECTIONS CAUSED BY VANCOMYCIN RESISTANT E. FAECIUM AND OTHER INFECTIONS CAUSED BY MULTIPLE DRUG RESISTANT ORGANISMS

QUINOLONES

INTRODUCTION

- The first quinolone, ***nalidixic acid****,* was isolated as a by-product of the synthesis of *chloroquine.* It has been available for the **treatment of urinary tract infections** for many years.
- The introduction of **fluorinated 4-quinolones**, such as *ciprofloxacin* (CIPRO), levofloxacin, *moxifloxacin* (AVELOX), Gemifloxacin and *gatifloxacin* (TEQUIN) represents a particularly important therapeutic advance because these agents have **broad antimicrobial activity** and are effective after oral administration for the treatment of a wide variety of infectious diseases. They have **relatively few side effects**, and **microbial resistance to their action does not develop rapidly**

MOA

- Quinolones **block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV**. Inhibition of DNA gyrase prevents the relaxation of positively supercoiled DNA that is required for normal transcription and replication. Inhibition of topoisomerase IV interferes with separation of replicated chromosomal DNA into the respective daughter cells during cell division.

PHARMACOKINETICS

- The quinolones are well absorbed after oral administration and are distributed widely in body tissues.
- Peak serum levels of the fluoroquinolones are obtained within 1 to 3 hours of an oral dose of 400 mg, with peak levels ranging from 1.1 mg/ml for *sparfloxacin* to 6.4 mg/ml for *levofloxacin.*
- Relatively low serum levels are reached with norfloxacin and limit its usefulness to the treatment of urinary tract infections.
- Food does not impair oral absorption but may delay the time to peak serum concentrations.

- **Bioavailability** ranges from **50% to 95%**
- The **serum half-life** ranges from **3 to 5 hours** for **norfloxacin and ciprofloxacin** to **20 hours** for **sparfloxacin.**
- The volume of distribution of quinolones is high, with concentrations of quinolones in urine, kidney, lung and prostate tissue, stool, bile, and macrophages and neutrophils higher than serum levels.
- Most quinolones are **cleared predominantly by the kidney**, and **dosages must be adjusted for renal failure**. Exceptions are **pefloxacin and moxifloxacin**, which are **metabolized predominantly by the liver** and should not be used in patients with hepatic failure

AVAILABLE DOSAGE FORMS

- **Ciprofloxacin**
- Oral: 250, 500, mg tablets
- Parenteral: 10 mg/mL for IV infusion
- Ophthalmic (Ciloxan): 3 mg/mL solution; 3.3 mg/g ointment
- **Levofloxacin**
- Oral: 250, 500, 750 mg tablets
- Parenteral: 5, 25 mg/mL for IV injection
- Ophthalmic (Quixin): 5 mg/mL solution

- **Moxifloxacin**
- Oral: 400 mg tablets
- Parenteral: 400 mg in IV bag
- **Norfloxacin**
- Oral: 400 mg tablets
- **Ofloxacin**
- Oral: 200, 400 mg tablets
- Parenteral: 200 mg in 50 mL 5% D/W for IV administration; 20, 40 mg/mL for IV injection
- Ophthalmic (Ocuflox): 3 mg/mL solution
- Otic (Floxin Otic): 0.3% solution

CIPROFLOXACIN

- It’s active against aerobic gram-negative bacteria
- It is the most potent of the quinolones against aerobic gram-negative bacteria and is effective against *Pseudomonas aeruginosa*.
- This is balanced by rather weak aerobic gram-positive activity

LEVOFLOXACIN & OFLOXACIN

- *Ofloxacin* is a racemic mixture of an active and an inactive stereoisomer, whereas *levofloxacin* is composed solely of the active stereoisomer.
- Thus, these two agents have the same spectra of activity, but levofloxacin is generally twofold more potent and, as a result, more commonly used.

LEVOFLOXACIN C'TD

- Levofloxacin is not quite as active as ciprofloxacin against aerobic gram-negative bacteria but is still effective against infections caused by most of these bacteria, including *P. aeruginosa*.
- Relative to ciprofloxacin, levofloxacin has enhanced activity against aerobic gram-positive bacteria and is effective in the treatment of severe infec- tions caused by *S. pneumoniae*, including those strains that are penicillin resistant.

MOXIFLOXACIN & GEMIFLOXACIN

- These newer agents, especially gemifloxacin, have enhanced activity against *S. pneumoniae* (including penicillin-resistant strains) and atypical bacteria. This comes at the expense of aerobic gram-negative activity, especially against *P. aeruginosa*. Moxifloxacin contains a methoxy group at R2, which increases potency against anaerobic bacteria.

INDICATIONS

- ***Urinary Tract Infections-*** Nalidixic acid (900mg qid; 12.5mg per kg for children for 7 days) is useful only for urinary tract infections caused by susceptible microorganisms. The fluoroquinolones are significantly more potent and have a much broader spectrum of antimicrobial activity.
- ***Prostatitis-***Norfloxacin, ciprofloxacin, and ofloxacin all have been effective in treatment of prostatitis caused by sensitive bacteria. Fluoroquinolones administered for 4 to 6 weeks appear to be effective in patients not responding to trimethoprim-sulfamethoxazole

- ***Sexually Transmitted Diseases-*** Fluoroquinolones lack activity for *Treponema pallidum* but have activity *in vitro* against *N. gonorrhoeae, C. trachomatis,* and *H. ducreyi.* For chlamydial urethritis/cervicitis, a 7-day course of ofloxacin or sparfloxacin is an alternative to a 7-day treatment with doxycycline or a single dose of azithromycin; Pelvic inflammatory disease has been treated effectively with a 14-day course of ofloxacin combined with an antibiotic with activity against anaerobes (clindamycin or metronidazole) . Chancroid (infection by *H. ducreyi*) can be treated with 3 days of ciprofloxacin.

- ***Gastrointestinal and Abdominal Infections-*** For traveler's diarrhea (frequently caused by enterotoxigenic *E. coli*), the quinolones are equal to trimethoprim-sulfamethoxazole in effectiveness, reducing the duration of loose stools by 1 to 3 days. Norfloxacin, **ciprofloxacin, and ofloxacin** given for 5 days all have been effective in the treatment of patients with **shigellosis**, with even shorter courses effective in many cases . **Norfloxacin** is superior to tetracyclines in decreasing the duration of **diarrhea in cholera. Ciprofloxacin and ofloxacin** treatment cures most patients with enteric fever caused by ***S. typhi***, as well as bacteremic nontyphoidal infections in AIDS patients, and it clears chronic fecal carriage.

- ***Respiratory Tract Infections-***The **major limitation** to the use of quinolones for the treatment of community-acquired pneumonia and bronchitis had been the **poor *in vitro* activity of ciprofloxacin, ofloxacin, and norfloxacin against *S. pneumoniae* and anaerobic bacteria**. However, many of the **newer fluoroquinolones**, including gatifloxacin and moxifloxacin, have **excellent activity against *S. pneumoniae.*** The **fluoroquinolones have *in vitro* activity** against the **rest of the commonly recognized respiratory pathogens**, including *H. influenzae, Moraxella catarrhalis, S. aureus, M. pneumoniae, Chlamydia pneumoniae,* and *Legionella pneumophila.* Either a fluoroquinolone (ciprofloxacin or levofloxacin) or azithromycin is the antibiotic of choice for *L. pneumophila* .

- ***Bone, Joint, and Soft Tissue Infections-*** The fluoroquinolones, may be used appropriately in some cases ; recommended doses are **500 mg every 12 hours or, if severe, 750 mg twice daily for 4 to 6 weeks or more.** Dosage should be reduced for patients with severely impaired renal function. **Ciprofloxacin should not be given to children or pregnant women.** In diabetic foot infections, which are commonly caused by a mixture of bacteria including gram-negative rods, anaerobes, streptococci, and staphylococci, the fluoroquinolones in combination with an agent with antianaerobic activity are a reasonable choice.

- ***Other Infections-*** The quinolones may be used as part of multiple-drug regimens for the treatment of **multidrug-resistant tuberculosis** and for the treatment of atypical mycobacterial infections as well as *M. avium* complex infections in AIDS

ADVERSE EFFECTS

- Quinolones are generally well tolerated, adverse effects include:

  nausea, vomiting, and diarrhea.

  Occasionally, headache, dizziness, insomnia, skin rash, or abnormal liver function tests develop

  Photosensitivity has been reported with lomefloxacin and pefloxacin.

  QT_c prolongation may occur with gatifloxacin, levofloxacin, gemifloxacin, and moxifloxacin.

  Fluoroquinolones may damage growing cartilage and cause an arthropathy. Thus, these drugs are not routinely recommended for patients under 18 years of age.

INTERACTIONS

- Interacts with **divalent** (ca&mg) and **trivalent** (Al&Fe) cations to form **insoluble complexes** thereby decreasing absorption. There should be 2-4 hrs spacing between the two.
- Ciprofloxacin **inhibit metabolism of warfarin** thereby potentiating its effects. It should be substituted by another antibiotic in a patient on warfarin
- Ciproflofloxacin interacts with **theophylline** thru **inhibition of P450** enzymes, which can lead to theophylline toxicity in asthmatics treated with it

RIFAMYCINS

- The rifamycins consist of **rifampin** (also called rifampicin), **rifabutin**, **rifapentine**, and **rifaximin**
- Rifamycins act by inhibiting bacterial RNA polymerase.
- They nestle deep into the DNA/RNA tunnel of this enzyme and, once lodged in this position, sterically block elongation of the nascent mRNA molecule.
- Resistance develops relatively easily and can result from one of several single mutations in the bacterial gene that en- codes RNA polymerase.

RIFAMPICIN

- Rifampin is the oldest and most widely used of the rifamycins. It is also the most po- tent inducer of the cytochrome P-450 system.

RIFABUTIN

- Rifabutin is favored over rifampin in individuals who are simultaneously being treated for tuberculosis and HIV infection because it inhibits the cytochrome P-450 system to a lesser degree than rifampin or rifapentine and thus can be more easily administered along with the many antiretroviral agents that also interact with this system.

RIFAPENTINE

- Rifapentine has a long serum half-life, which has led to its use in once-weekly regi- mens for immunocompetent patients with tuberculosis.

RIFAXIMIN

- Rifaximin is a poorly absorbed rifamycin that is used for the treatment of travelers' diarrhea. Because it is not systemically absorbed, it has limited activity against invasive bacteria, such as *Salmonella* and *Campylobacter* spp.

TOXICITY

- The rifamycins are potent inducers of the cytochrome P-450 system. Thus, they may dramatically affect the levels of other drugs metabolized by this system.
- Rifamycins also commonly cause gastrointestinal complaints such as nausea, vomiting, and di- arrhea and have been associated with hepatitis.
- Skin rashes and hematologic abnor- malities may also occur. Of note, rifampin causes an orange-red discoloration of tears, urine, and other body fluids, which can lead to patient anxiety and the staining of contact lenses.
-

USE

- The rifamycins are used primarily as components of multidrug regimens for mycobacterial infections

METABOLIC INHIBITORS:

SULFONAMIDES

- STRUCTURALLY SIMILAR TO P-AMINOBENZOIC ACID (PABA) THAT COMPETITIVELY INHIBITS DIHYDROPTEROATE SYNTHASE
- INHIBITS GROWTH BY REVERSIBLY BLOCKING FOLIC ACID SYNTHESIS
- MAMMALIAN CELLS DO NOT MAKE FOLIC ACID AND ARE NOT AFFECTED
- CROSS THE PLACENTA AND SECRETED IN BREAST MILK AND SHOULD NOT BE GIVEN TO PREGNANT WOMEN
- HIGHLY BOUND TO PLASMA PROTEINS ESP, ALBUMIN
- PENETRATES CNS WELL

SPECTRUM:

- GRAM (+) & GRAM (-) BACTERIA
- NOCARDIA
- C. TRACHOMATIS
- ENTERIC BACTERIA (E. COLI, KLEBSIELLA, SALMONELLA, SHIGELLA ENTEROBACTER)

RICKETSSIA – SULFONAMIDES DO NOT INHIBIT THESE ORGANISMS BUT STIMULATE ITS GROWTH

RESISTANCE:

- OCCURS AS A RESULT OF MUTATIONS THAT:

1. CAUSE OVERPRODUCTION OF PABA
2. CAUSE PRODUCTION OF A FOLIC ACID SYNTHESIZING ENZYME THAT HAS A LOW AFFINITY FOR SULFONAMIDES
3. CAUSE A LOSS OF PERMEABILITY TO THE SULFONAMIDES

PHARMACOKINETICS:

- 3 MAJOR GROUPS:
  1. ORAL, ABSORBABLE
  2. ORAL, NON-ABSORBABLE
  3. TOPICAL

INTRAVENOUS PREPARATION:

- NA SALTS OF SULFONAMIDES IN D5W

ORAL, ABSORBABLE SULFONAMIDES:

DRUGS	HALF LIFE	ORAL ABS
1.short acting		
Sulfacytine	Short	Prompt (peaks in 1-4h)
Sulfisoxazole	Short (6 h)	Prompt
Sulfamethizole	Short (9 h)	Prompt
2. Medium acting		
Sulfadiazine	Intermediate(10-17h)	Slow (peak in 4-8h)
Sulfamethoxazole	Intermediate (10-12h)	Slow
Sulfapyridine	No data	Slow
Long Acting		
Sulfadoxine	Long (7-9 days)	Intermediate

ABSORBED FROM STOMACH AND SMALL INTESTINE

- DISTRIBUTED WIDELY TO TISSUES AND BODY FLUIDS (CSF), PLACENTA AND FETUS
- PROTEIN BINDING 20% TO OVER 90%
- THERAPEUTIC CONCENTRATION – 40-100 UG/ML OF BLOOD
- PEAK BLOOD LEVELS – 2H TO 6 H AFTER ORAL INGESTION
- METABOLISM: GLUCORONIDATION OR ACETYLATION IN LIVER
- ELIMINATED IN URINE-MAINLY BY GLOMERULAR FILTRATION

CLINICAL USES:

1. URINARY TRACT INFECTION

SULFISOXAZOLE – 1 GM 4X DAILY }COMBINED WITH PHENAZOPYRIDINE

SULFAMETHOXAZOLE – 1 G 2-3 X DAILY } (U.T. ANESTHETIC)

2. RESPIRATORY INFECTIONS
3. SINUSITIS, BRONCHITIS, PNEUMONIA
4. OTITIS MEDIA
5. DYSENTERY
6. ACUTE TOXOPLASMOSIS

SULFADIAZINE + PYRIMETHAMINE – SYNERGISTIC

BLOCK SEQUENTIAL STEPS IN FOLATE SYNTHESIS:

SULFADIZINE- INHIBITS DIHYDROPTEROATE SYNTHASE

PYRIMETHAMINE – INHIBITS DIHYDROFOLATE REDUCTASE

DOSAGE – SULFADIAZINE – 1 G 4X DAILY

SULFADIAZINE + PYRIMETHAMINE – 75 MG LOADING DOSE FFD BY 25 MG OD

FOLINIC ACID – ADMINISTERED TO MINIMIZE BONE MARROW SUPPRESSION

7. MALARIA

- SULFADOXINE + PYRIMETHAMINE – 2ND LINE AGENT IN THE TREATMENT FOR MALARIA

ORAL, NONABSORBABLE AGENTS

SULFASALAZINE (SALICYLAZOSULFAPYRIDINE)

MORE EFFECTIVE THAN SOLUBLE SULFONAMIDES OR OTHER ANTIMICROBIALS TAKEN ORALLY IN INFLAMMATORY BOWEL DISEASE

ULCERATIVE COLITIS

ENTERITIS

OTHER INFLAMMATORY BOWEL DISEASE

SPLIT BY INTESTINAL MICROFLORA TO YIELD:

SULFAPYRIDINE – ABSORBED AND MAY LEAD TO TOXIC SYMPTOMS

IF MORE THAN 4 G OF SULFASALAZINE IS TAKEN PER DAY ESP. IN PERSONS WHO ARE SLOW ACETYLATORS

5-AMINOSALICYLATE (5-ASA) – RELEASED IN THE COLON IN HIGH CONCENTRATIONS AND IS RESPONSIBLE FOR AN ANTI-INFLAMMATORY EFFECT

TOPICAL AGENTS:

SODIUM SULFACETAMIDE OPHTHALMIC SOLUTION OR OINTMENT

- EFFECTIVE FOR BACTERIAL CONJUNCTIVITIS
- ADJUNCT THERAPY FOR TRACHOMA

MAFENIDE ACETATE

- USED TOPICALLY TO PREVENT BACTERIAL COLONIZATION AND INFECTION OF BURN WOUNDS
- INHIBITS ALSO CARBONIC ANHYDRASE – CAUSE METABOLIC ACIDOSIS

SILVER SULFADIAZINE

- LESS TOXIC TOPICAL SULFONAMIDE
- PREFERRED TO MAFENIDE FOR PREVENTION OF INFECTION OF BURN WOUNDS

ADVERSE REACTIONS:

- CROSS ALLERGY WITH THE FFG.
- CARBONIC ANHYDRASE INHIBITORS, THIAZIDES, FUROSEMIDE, BUMETANIDE, FUROSEMIDE, DIAZOXIDE, SULFONYLUREAS, HYPOGLYCEMICS

MOST COMMON ADVERSE EFFECTS:

- FEVER, SKIN RASHES, EXFOLIATIVE DERMATITIS, NAUSEA, VOMITING, URTICARIA, PHOTOSENSITIVITY

URINARY TRACT DISTURBANCES:

SULFAS MAY PPT. IN URINE AT NEUTRAL OR ACID PH-

CRYSTALLURIA – TREATED WITH SOD. BICARBONATE TO ALKALINIZE URINE AND FLUIDS TO MAINTAIN ADEQUATE HYDRATION

HEMATURIA

OBSTRUCTION

IMPLICATED IN NEPHROSIS AND ALLERGIC NEPHRITIS

OTHER SIDE EFFECTS:

STEVENS-JOHNSON SYNDROME – UNCOMMON BUT SERIOUS AND POTENTIALLY FATAL TYPE OF SKIN & MUCOUS MEMBRANE ERUPTIONS

HEMATOPOIETIC DISTURBANCES:

HEMOLYTIC OR APLASTIC ANEMIA, THROMBOCYTOPENIA, GRANULOCYTOPENIA, LEUKEMOID REACTION, PROVOKE HEMOLYTIC REACTIONS IN PATIENTS WITH DEFICIENT RBC GLUCOSE 6 PHOSPHATE DEHYDROGENASE

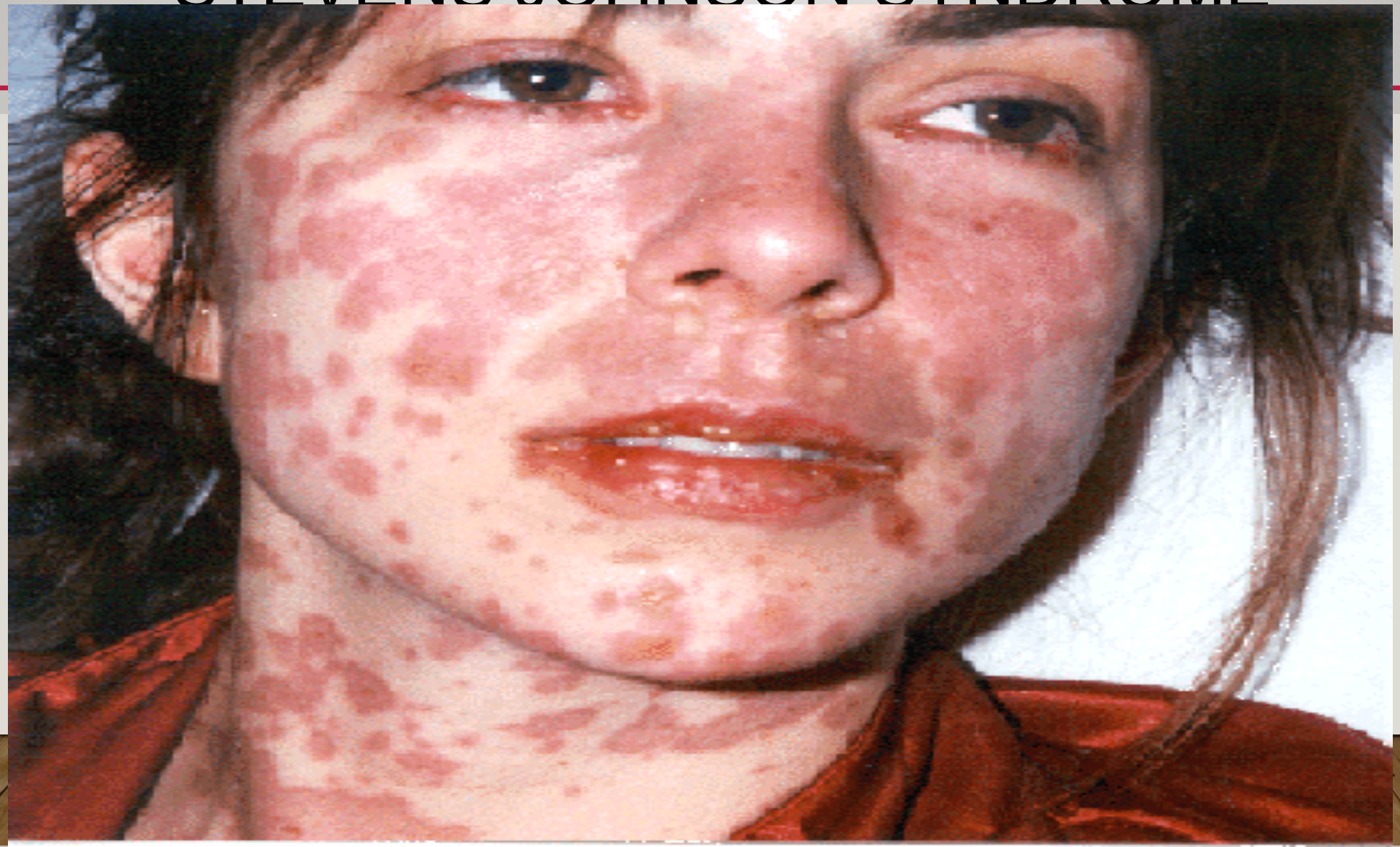
INCREASED RISK OF KERNICTERUS IN NEWBORNS WHEN SULFONAMIDES WERE TAKEN NEAR THE END OF PREGNANCY

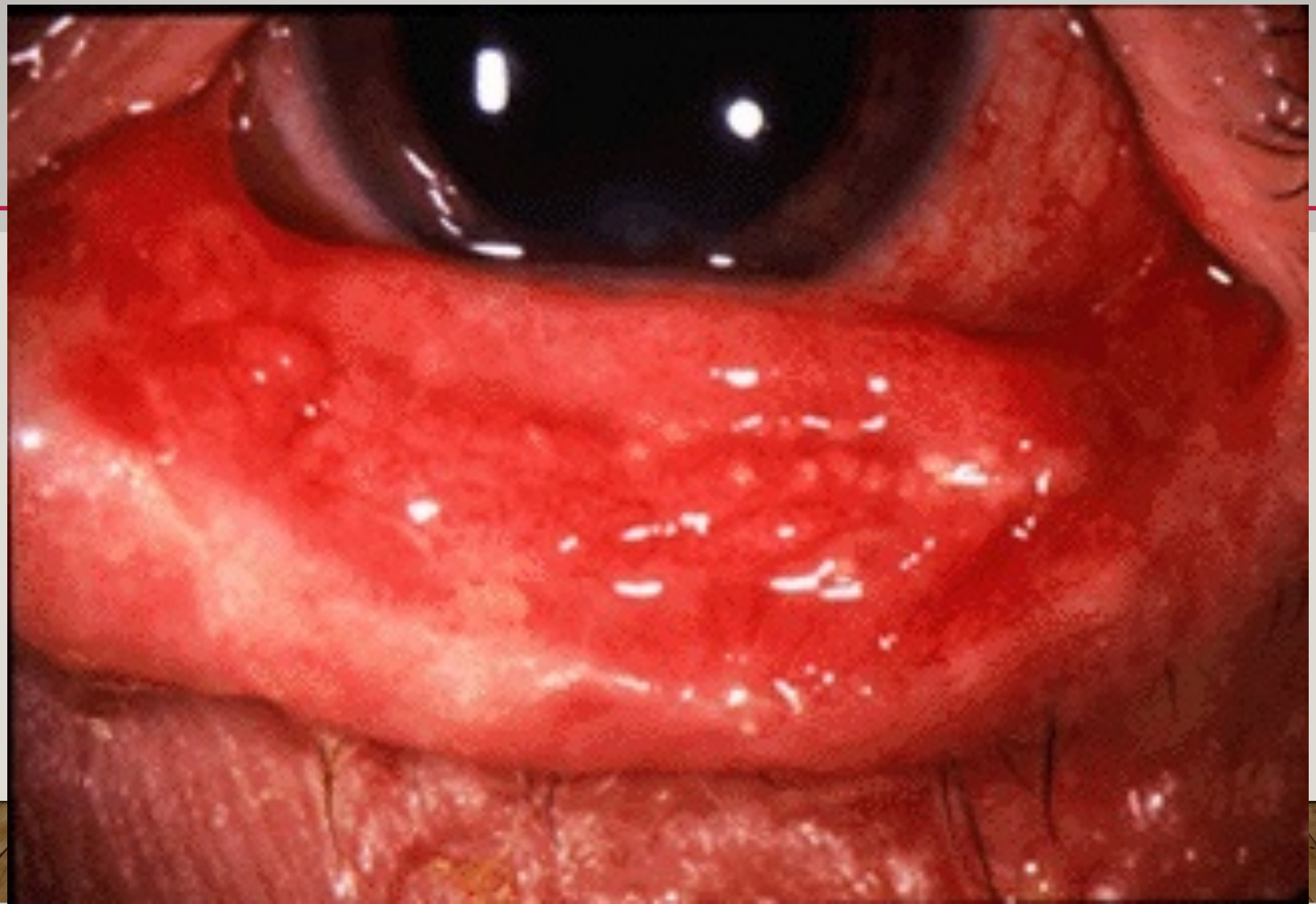
STOMATITIS, CONJUNCTIVITIS, ARTHRITIS, HEPATITIS

POLYARTERITIS NODOSA – RARE

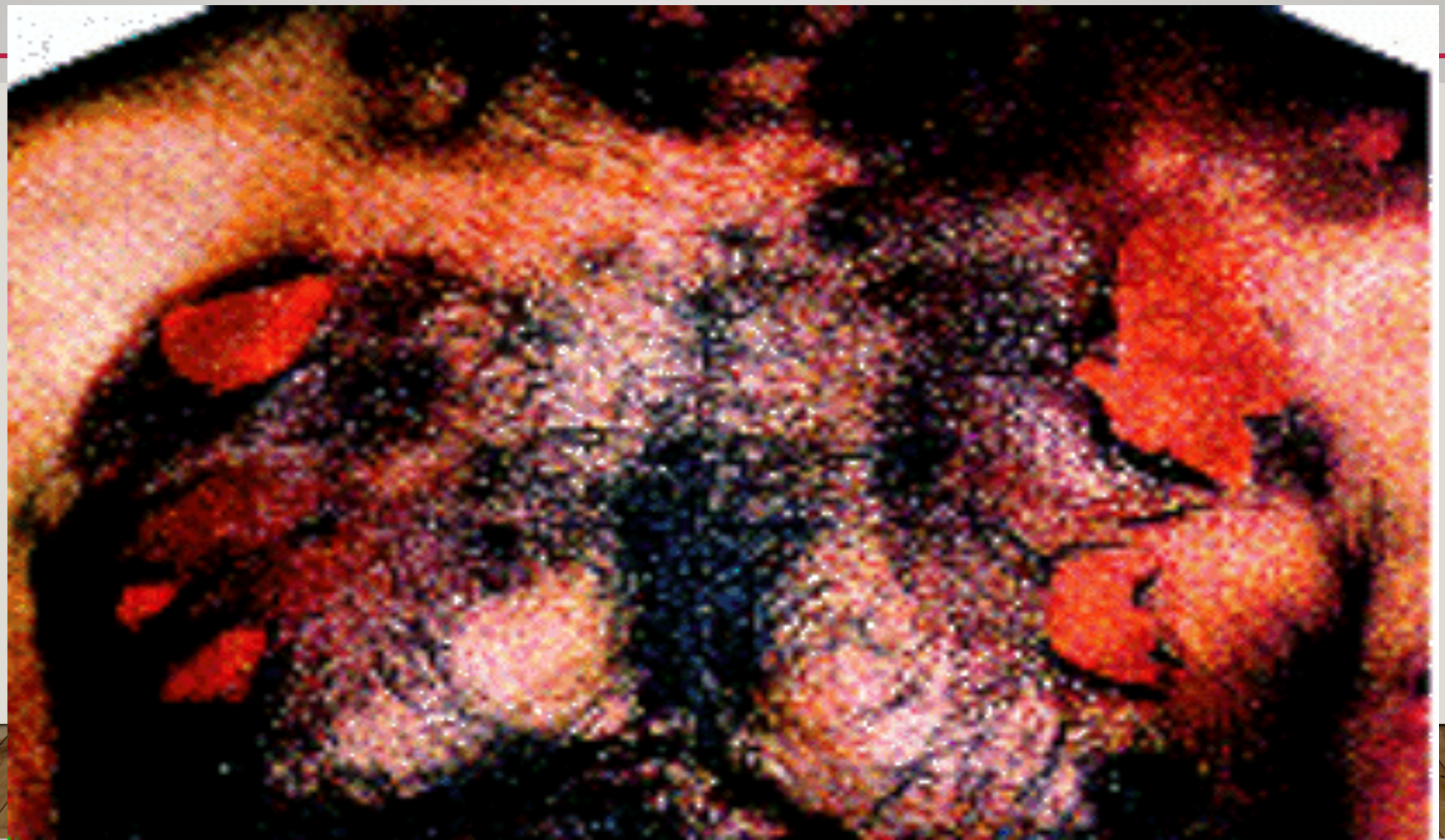
PSYCHOSIS – RARE

STEVENS JOHNSON SYNDROME





TOXIC EPIDERMAL NECROLYSIS



TRIMETHOPRIM

WELL ABSORBED FROM THE GUT

WIDELY DISTRIBUTED IN BODY FLUIDS AND TISSUES INCLDG. CSF

FOUND IN HIGH CONCENTRATIONS IN PROSTATIC & VAGINAL FLUIDS

EVEN IF GIVEN ORALLY ALONE OR IN COMBINATION WITH SULFONAMIDES, IT WILL HAVE THE SAME HALF-LIFE

MORE LIPID SOLUBLE – LARGER VOLUME OF DISTRIBUTION THAN SULFONAMIDES

RESISTANCE TO TM:

DUE TO REDUCED CELL PERMEABILITY

DUE TO OVERPRODUCTION OF DIHYDROFOLATE REDUCTASE

DUE TO PRODUCTION OF AN ALTERED REDUCTASE & REDUCED DRUG BINDING

CLINICAL USES:

ORAL TM:

ACUTE UTI 100 MG BID

COMMUNITY ACQUIRED ORGANISMS – 200 UG TO 600 UG/ML CONCENTRATION OF TM IN URINE

ADVERSE EFFECTS:

MEGALOBLASTIC ANEMIA, LEUCOPENIA, GRANULOCYTOPENIA

PREVENTION OF ADVERSE EFFECTS:

SIMULTANEOUS ADMINISTRATION OF FOLINIC ACID 6 MG-8 MG/DAY

TRIMETHOPRIM-SULFAMETHOXAZOLE (CO-TRIMOXAZOLE)

SYNERGISTICALLY ACTIVE ANTIMICROBIAL AGENT WHICH

BLOCKS TWO SEQUENTIAL STEPS IN THE OBLIGATE ENZYMATIC REACTION IN BACTERIA PREVENTING THE FORMATION OF NUCLEOTIDES:

SULFAMETHOXAZOLE – COMPETITIVELY INHIBITS THE INCORPORATION OF PABA INTO FOLIC ACID

TRIMETHOPRIM INHIBITS DIHYDROFOLATE REDUCTASE PREVENTING THE REDUCTION OF DIHYDROFOLATE TO TETRAHYDROFOLATE

ADVANTAGES OF THE COMBINATION:

- INCREASED POTENCY
- INCREASES SPECTRUM
- DECREASED INCIDENCE OF RESISTANCE
- EXHIBITS SELECTIVE TOXICITY FOR BACTERIA WHICH MUST SYNTHESIZE THEIR OWN FOLIC ACID

TRIMETHOPRIM IS MORE POTENT, MORE LIPID SOLUBLE AND HAS A GREATER VOLUME OF DISTRIBUTION THAN SULFA DRUGS

PENETRATES CSF WELL

- 65-70% OF EACH DRUG IS PROTEIN BOUND
- ELIMINATED IN THE URINE WITHIN 24 H – REDUCE DOSE BY HALF IF CREATININE CLEARANCE IS 15-30 ML/MIN

CLINICAL USES:

ORAL TMP-SMX

- URINARY TRACT INFECTION:

COMPLICATED UTI – 2 DOUBLE STRENGTH TABS (TM-160 MG+SM 800 MG) Q 12 HOURS

RECURRENT UTI PROPHYLAXIS – OF REGULAR SIZE (SINGLE STRENGTH) 3X WEEKLY

PROSTATITIS – 2 DOUBLE STRENGTH TABS (TM 160 MG + SM 800 MG) Q 12 H

SUSCEPTIBLE STRAINS OF SHIGELLA AND SALMONELLA

2 DOUBLE STRENGTH TABS Q 12 H

CHILDREN WITH SHIGELLOSIS, UTI, OTITIS MEDIA-8MG/KG TM AND 40 MG/KG SM Q 12 HOURS

P. CARINII AND OTHER PATHOGENS – ORALLY 15-20 MG/KG

IN IMMUNOSUPPRESSED PATIENTS – ONE DOUBLE STRENGTH TAB DAILY OR 3X WEEKLY

NONTUBERCULOUS MYCOBACTERIAL INFECTION

RESPIRATORY TRACT PATHOGENS – USEFUL ALTERNATIVE TO B LACTAMASE FOR COMMUNITY ACQUIRED BACTERIAL PNEUMONIA

CLINICAL USES:

INRAVENOUS TMP-SMX:

DRUG OF CHOICE FOR MODERATELY SEVERE TO SEVERE PNEUMOCYSTIS PNEUMONIA ESP. PATIENTS WITH AIDS

TM 80 MGS + SM 400MG/5 ML DILUTED IN 125 ML OF D5W

FOLINIC ACID INCREASES MORBIDITY AND TREATMENT FAILURES SO NOT USED

USED FOR GRAM (-) BACTERIAL SEPSIS – INCLDG. THOSE CAUSED BY SOME MULTIPLE DRUG RESISTANT SPECIES SUCH AS ENTEROBACTER AND SERRATIA SHIGELLOSIS, TYPHOID FEVER UTI CAUSED BY SUSCEPTIBLE ORGANISMS IF PATIENT IS UNABLE TO TAKE DRUG ORALLY

DOSAGE- 10-20 MG/KG/DAY OF TM COMPONENT

ORAL PYRIMETHAMINE + SULFADIAZINE= USED IN THE TREATMENT OF LEISHMANIASIS AND TOXOPLASMOSIS

PYRIMETHAMINE + SULFADOXINE = USED IN THE TREATMENT OF FALCIPARUM MALARIA

ADVERSE EFFECTS:

MOSTLY DUE TO UNTOWARD REACTIONS TO SMX

DERMATOLOGICAL EFFECTS

GI EFFECTS: GLOSSITIS, STOMATITIS, NAUSEA AND VOMITING

CNS DISTURBANCES: HEADACHE, DEPRESSION, HALLUCINATIONS

HEMATOLOGIC REACTIONS- APLASTIC, HEMOLYTIC AND MACROCYTIC ANEMIA, COAGULATION DISORDERS

VASCULITIS

RENAL IMPAIRMENT OR DAMAGE

AIDS PATIENTS

MORE SENSITIVE TO INCREASED FREQUENCY OF REACTIONS TOWARD TMP- SMX DRUG:

-RASHES, HEMTOLOGIC EFFECTS-LEUKOPENIA, FEVER, DIARRHEA, ELEVATED HEPATIC AMINOTRANSTERASES, HYPERKALEMIA, HYPONATREMIA

METRONIDAZOLE

- **Metronidazole**, a 5-nitroimidazole, was discovered in the 1950s. It continues to be an important and frequently used antibiotic for the treatment of infections caused by anaerobic bacteria.
- Resistance to metronidazole is rare among obligate anaerobic bacteria. When it does occur, it is thought to result from a decrease in the capacity of the electron transport proteins to reduce the nitro group of metronidazole. The development of resistance in the microaerophilic bacterium *Helicobacter pylori* is more common, although the mechanism remains unclear.

- Metronidazole is effective against nearly all anaerobic gram-negative bacteria, including *Bacteroides fragilis*, and most anaerobic gram-positive bacteria, including *Clostridium* spp.
- It is one of the few antibiotics that has activity against *C. difficile* and is the treatment of choice for infections caused by this organism.
- The microaerophilic (i.e., optimal growth in low levels of oxygen) bacterium *H. pylori* is also frequently susceptible.

- Both oral and IV formulations of metronidazole are available. Oral metronidazole is extremely well absorbed and results in serum levels comparable to those following IV administration.

TOXICITY

- Metronidazole is relatively well tolerated but is associated with some minor toxicities, such as nausea and epigastric discomfort. It can also cause an unpleasant metallic taste and furring of the tongue. Occasionally, metronidazole is associated with neurologic complaints, including headache, dizziness, and peripheral neuropathy.
- Metronidazole can lead to a disulfiram-like reaction; ingestion of alcohol should be avoided while taking this drug.

Shukran

ANTIFUNGAL DRUGS

By P. J. Okoth

Antifungal drugs

These are drugs used for superficial and deep (systemic) fungal infections.

Classification

Antibiotics

Polyenes [disrupt the fungal cell membrane]

Amphotericin B

Nystatin

Hamycin

Natamycin

Heterocyclic benzfuran [inhibits mitosis]

Griseofulvin

Antimetabolite [inhibits DNA synthesis]

Flucytosine

Classification…

Azoles [disrupt the fungal cell membrane]

- **Imidazoles**
  - Topical
    - Clotrimazole
    - Econazole
    - Miconazole
  - Systemic
    - Ketoconazole

Classification…

Azoles…

Triazoles

Systemic

- Fluconazole
- Itraconazole
- Voriconazole
- Posaconazole

Classification…

Allylamine [disrupts fungal cell membrane]

- Terbinafine

Other topical agents

- Tolnaftate
- Undecenoic acid
- Benzoic acid
- Quiniodochlor
- Sodium thiosulphate
- Formaldehyde
- Sulphur

Polyene antibiotics

Mechanism of action:

These act by binding tightly to sterols present in the cell membranes.

The resulting deformity of the membrane allows leakage of intracellular ions and enzymes, causing death.

Polyenes that have useful antifungal activity bind selectively to ergosterol, the most important sterol in fungal (but not mammalian) cells.

Amphotericin

Is obtained from Streptomyces nodosus

Pharmacokinetics:

Has a plasma halflife of 15 days

It is negligibly absorbed from the gut and must be given by intravenous infusion for systemic infection.

It is widely distributed in the body, but CSF penetration is poor.

Amphotericin…

Pharmacokinetics…

Due to its long half-life in plasma, the drug persists in the body for several weeks after stopping treatment.

About 60% is metabolized in the liver.

Very little drug appears in urine. Excretion is slow, both in urine and in bile

Amphotericin..

Adverse reactions:

Adverse reactions are very common since amphotericin is highly toxic

These include:

Acute reaction which occurs with each infusion due to release of cytokines. Lasts 2-5 hours.

- Fever
- Chills
- Pain all over – abdominal, muscle and joint pains
- dyspnoea
- Nausea / vomiting
- Malaise
- Anorexia

Amphotericin…

Adverse reactions: …

Long term toxicity

Nephrotoxicity

- Hypokalaemia
- Inability to concentrate urine
- Renal tubular acidosis
- Reduced glomerular filtration rate
- Azotaemia [uraemia]

Anaemia due to bone marrow depression. Slowly progressing.

Weight loss

Amphotericin…

Acute symptoms may be alleviated by aspirin, an anthistamine (H1) or an antiemetic.

Severe febrile reactions are mitigated by hydrocortisone 25-50mg before each infusion.

Amphotericin…

Drug interactions:

It is additive with other nephrotoxic drugs e.g aminoglycosides

Concurrent digoxin therapy can become toxic if hypokalaemia develops

Flucytosine has supra-additive action with amphotericin in the case of fungi sensitive to both.

Amphotericin…

Antifungal spectrum/ uses:

A drug of choice for most systemic mycoses

Active against:

Cryptococcus neoformans

Candida and other yeasts

Aspergillus

Coccidioides immitis

Histoplasma capsulatum

Amphotericin…

Uses: …

Can be used topically for oral, vaginal and cutaneous candidiasis and otomycosis

It is the most effective drug for various types of systemic mycoses

It is a reserve drug for resistant cases of Kala-azar and mucocutaneous leishmaniasis.

Amphotericin…

Preparations and dosage:

0.25mg/kg, increasing to 1mg/kg by slow infusion in 5% dextrose

The total dose is given over 6-12 hour period.

It is then increased daily by 5-10mg, until a dose of 1mg/kg is reached.

This is continued on alternate days.

Nystatin

p.j.

Nystatin

Named after New York State Laboratory

It is obtained from Streptomyces noursei

Nystatin is too toxic for systemic use

It is also not absorbed from the alimentary canal.

Adverse reactions

Local use has only mild adverse effects

Oral administration may cause bad taste in the mouth, nausea, vomiting, and diarrhoea.

Preparations and dosage

Nystatin tablet: containing 500,000 units of nystatin.

Dose 500,000 units 8hrly in adults and in children over 6 years.

200,000 units BD or TDS for children between 1-5 yrs

100,000 units BD or TID for infants

Nystatin suspension: contains 100,000 units of nystatin per gram.

Oral topical application is made 3 times a day (TID)

Preparations and dosage

Nystatin pessary or **vaginal tablet**: contains 100,000 units of nystatin

The pessary is inserted into the vagina twice or thrice daily [BD or TDS]

Nystatin ointment: contains 100,000 units of nystatin per gram.

Nystatin cream

Nystatin powder

Therapeutic uses

Nystatin is effective in the treatment of localized candidiasis of:

- Vagina (pessaries BD x 2 weeks)
- Mouth (suspension, tablets)
- Skin (cream, ointment, powder)
- Gastrointestinal tract (suspension, tablets)

AZOLES

P.J.

Azoles

Imidazoles

Triazoles

Imidazoles

Comprise of the following drugs:

Ketoconazole

Miconazole

Clotrimazole

Isoconazole

Tioconazole

Econazole

Sulconazole

Imidazoles: mode of action

Imidazoles interfere with fungal oxidative enzymes to cause lethal accumulation of hydrogen peroxide.

They also reduce the formation of ergosterol, an important constituent of the fungal cell wall which thus becomes permeable to intracellular constituents.

Lack of selectivity in these actions result in important adverse effects.

Triazoles

Include:

1. **Fluconazole**
2. **Itraconazole**

Mode of action:

They damage the fungal cell membrane by inhibiting a demethylase enzyme.

They have greater selectivity against fungi, better penetration of the CNS, resistance to degradation and cause less endocrine disturbance than do the imidazoles.

Ketoconazole

The first orally effective broad spectrum antifungal drug useful in both dermatophytosis and deep mycosis.

Pharmacokinetics

Ketoconazole is well absorbed from the gut (poorly where there is gastric hypoacidity)

It is widely distributed in tissues but concentrations in CSF and urine are low

It is metabolized in the liver. Its action is terminated by metabolism.

It is excreted in urine and in faeces

Therapeutic uses

Ketoconazole is a broad spectrum antifungal, useful in dermatophytosis and deep mycosis

It is effective by mouth for systemic mycoses:

Blastomycosis

Coccidioidomycosis

Histoplasmosis

Paracoccidioidomycosis

Ketoconazole is less toxic but less effective than amphotericin.

Therapeutic uses…

Patients with severe illness, meningitis, AIDS or some other causes of immunosuppression should be given amphotericin.

Impairment of steroid synthesis by ketoconazole has been put to other uses: e.g. inhibition of testosterone synthesis lessens bone pain in patients with advanced androgen-dependent prostate cancer.

Preparations and dosage

Ketoconazole is available as:

Tablets [e.g. nizoral]

Dose: 200-400mg orally, daily single dose or 200mg BD.

Cream for fungal skin infections [e.g. nizoral cream; phytoral cream]

Applied BD

Adverse reactions

Nausea and vomiting

Giddiness

Headache

Pruritus

Photophobia

Gynaecomastia and decreased libido and oligozoospermia in men (due to impairment of testosterone synthesis)

Hepatotoxicity

Contraindicated in pregnancy and lactation

Drug interactions

Drugs that lower gastric acidity, e.g. antacids, histamine H2-receptor antagonists, impair the absorption of ketoconazole from the gastrointestinal tract.

Inhibition of drug metabolism by ketoconazole leads to increased effects of oral anticoagulants, phenytoin and cyclosporin, and increases the risk of cardiac dysrhythmias with astemizole and terfenadine.

A disulfirum-like reaction occurs with alcohol

Concurrent use of rifampicin, by enzyme induction, markedly reduces the plasma concentration of ketoconazole.

Clotrimazole

An imidazole compound

It is poorly absorbed following oral administration and is therefore restricted for topical use.

Antifungal Spectrum

Clotrimazole is an effective topical agent for dermatophyte, yeast, and other fungal infections:

- Intertrigo
- Athletes foot
- Ring worm
- Pityriasis versicolor
- Fungal nappy rash
- Oral, cutaneous and vaginal candidiasis
- Otomycosis

Adverse effects

Well tolerated by most patients

Local irritation is stinging and burning sensation

Preparations

Available as:

- Lotion
- Cream
- Powder
- Ear drops (1%) for otitis externa. Applied BD or TDS
- Pessaries/ vaginal tablets:
  - 500mg tablets – stat dose 500mg
  - 200mg tablets – 3 tabs [200mg OD x 3/7]
  - 100mg tablets – 6 tablets [100mg BD x 3/7 or 1 OD x6/7]
- Suspension – for Dandruff, seborrhoeic dermatitis [used as shampoo]
- Mouth paint – for oral thrush

Preparations

Available in several proprietary (brand) names:

- Candid
- Canesten
- Bulkot
- Candistan
- Clozole
- Clotrine
- Labesten
- Medizole
- Micoderm
- Candistat
- Clomzole

Other imidazoles

The other imidazoles – miconazole, econazole, sulconazole – are similar to clotrimazole. They are for topical use.

Tioconazole is used for fungal nail infections and isoconazole for vaginal candidiasis.

Fluconazole and Itraconazole

Are triazoles

Pharmacokinetics

These are well absorbed in the gastrointestinal tract following oral administration.

They are widely distributed in the tissues and obtain adequate CSF levels

Fluconazole is excreted largely unchanged in the urine (eliminated by the kidneys)

Itraconazole is metabolized by the liver

Antifungal spectrum

Fluconazole is effective by mouth for oropharyngeal and oesophageal candidiasis.

Given I.V. fluconazole is effective against systemic candidiasis and cryptococcosis (including cryptococcal meningitis), coccidioidal meningitis and histoplasmosis.

Itraconazole is particularly effective against filamentous fungi e.g. Aspergillus.

Itraconazole is an alternative drug to amphotericin for the treatment of most systemic fungal infections

Dosage

Fluconazole:

100-400mg orally or by I. V. infusion, as daily single dose.

Itraconazole:

100-200mg orally, daily single dose.

Adverse effects

Fluconazole may cause:

Gastrointestinal discomfort

Headaches

Elevation of liver enzymes and

Allergic rash

Contraindicated in pregnancy

Drug interactions

High doses of fluconazole increase the effects of phenytoin, cyclosporin, zidovudine, sulfonylureas and warfarin.

Oral absorption of itraconazole is reduced by antacids, H2 receptor blockers, and proton pump inhibitors.

ALLYLAMINE

p.j.

Terbinafine

A synthetic allylamine derivative

Mechanism of action

Terbinafine exerts its antifungal effect by inhibiting squalene epoxidase in the fungal cell membrane, a key enzyme in sterol biosynthesis in fungi.

This action results in a deficiency in ergosterol and a corresponding low concentration of squalene within the fungal cell causing fungal cell death.

At low concentrations terbinafine is fungicidal against dermatophytes.

The activity against yeasts is fungicidal or fungistatic depending on the species.

Pharmacokinetics

When taken orally, terbinafine is absorbed from the gastrointestinal tract and undergoes extensive metabolism in the liver.

80% is eliminated in urine and 20% in faeces

It is lipophilic, widely distributed, strongly plasma protein bound.

It gets concentrated in sebum, stratum corneum and nail plates.

Uses of terbinafine

It is used topically for dermatophyte infections of the skin

It is used orally for infections of hair and nails where the site (e.g. hair), severity or extent of the infection render topical use inappropriate.

Preparations and dosage

Tablets: 250mg daily in 1-2 doses for Tinea corporis, Tinea cruris and Candida. Duration 2-4 weeks.

Cream is applied 1-2 times daily for 1-2 weeks

Also available as **lotion** applied 1-2 times daily for 1-2 weeks.

Common brand names:

- Lamisil – tablets, cream, lotion.
- Terbisil
- Terbin

Adverse effects

May cause:

Nausea

Diarrhoea

Dyspepsia

Headaches

Cutaneous reactions (allergic) – redness, itchiness, or stinging at the site of application.

Contraindicated in children and lactation.

Griseofulvin

A heterocyclic benzfuran.

Griseofulvin

Was isolated from Penicillium griseofulvium

Was the first chemical compound to cure effectively infections due to the superficial dermatophytes (ring worm), when administered orally.

Mechanism of action

Griseofulvin prevents fungal growth by inhibiting mitosis

It is mainly fungistatic

The therapeutic efficacy of griseofulvin depends on its capacity to bind to keratin as it is being formed in the cells of the nail bed, hair follicles and skin, for dermatophytes especially infect keratinous tissues.

MOA…

Griseofulvin does not kill fungus already established, it merely prevents infection of new keratin.

Therefore, the duration of treatment is governed by the time that it takes for infected keratin to be shed.

On average, hair and skin should be treated for 4-6 weeks while toe nails may need a year or more.

Pharmacokinetics

Absorption is adequate though somewhat irregular due to its low water solubility

Oral administration of a maximum single dose produces peak plasma levels within 4 hours.

Small particles are better absorbed than large particles

Divided oral doses achieve higher blood levels than a single dose.

A diet rich in fat enhances the absorption of griseofulvin

Pharmacokinetics…

Griseofulvin is metabolized in the liver and induces hepatic enzymes

Very small amunts are excreted in urine, while large amounts are eliminated in unchanged form in the faeces.

The drug is deposited in keratin precursor cells and gets firmly incorporated in keratin, making it resistant to fungal invasion.

Adverse reactions

These are usually mild. They include:

Headache – commonset

Gastrointestinal upset [epigastric distress, nausea, vomiting and diarrhoea]

Photosensitivity

Rashes on the skin

Nervous system disturbances [paraesthesiae, peripheral neuritis, vertigo, blurring of vision, lethargy, fatigue, psychomotor incordination]

Contraindications

Pregnancy:

Avoid pregnancy during or within one month of treatment

Men should not father children within six months of treatment.

Drug interactions

Griseofulvin may reduce the anticoagulant effect of warfarin

Simultaneous administration of griseofulvin and phenobarbitone reduces response to the barbiturate

Griseofulvin may cause enhancement of alcoholic effect

Preparations and dosage

Available in tablets of 125mg, 250mg and 500mg.

The **adult** dose is **500mg to 1000mg daily in 2-4 divided doses**.

E.g. 125mg QID; 250mg QID; 500mg BD.

Children are given **10mg/kg/day**, administered as a single dose or in divided doses.

Duration depends on site of infection (turnover rate of keratin)

Indications

Indicated for fungal infections of the skin, hair and nails:

Tinea capitis [ring worm of scalp]. Clinical cure occurs within 4-6 weeks.

Tinea barbae [fungus infection of the beard]

Tinea cruris and Tinea corporis [ringworm of the groin and of the body]. Clinical cure occurs within 3 weeks.

Tinea pedis and Tinea manus [ringworm of feet and hands. Clinical cure 4-6 weeks.

Onychomycosis [fungus infection of the nails]. Treatment more effective for fingernails than for toenails. Duration of tretment: fingernails 4-6 months; toenails 6-12 months.

Griseofulvin is ineffective against:

- Pityriasis versicolor
- Superficial candidiasis
- Systemic mycoses

Flucytosine

5-fluorocytosine

Flucytosine

Flucytosine, or 5-fluorocytosine, a fluorinated pyrimidine analogue, is a synthetic antimycotic drug.

It is structurally related to the cytostatic fluorouracil

It is available in oral and in some countries also in injectable form.

Flucytosine was first synthesized in 1957 but its antifungal properties were discovered in 1964.

Mechanism of action

Flucytosine is metabolized in the fungal cell to 5-fluorouracil which inhibits nucleic acid synthesis.

Pharmacokinetics

Flucytosine is well absorbed from the gut, penetrates effectively into tissues and CSF and almost all is excreted unchanged in the urine.

Precautions

The dose should be reduced for patients with impaired renal function, and the plasma concentration should be monitored.

The drug is well tolerated when renal function is normal.

Indications

It is a drug of choice for:

Systemic candidiasis – in combination with amphotericin

Cryptococcosis – in combination with amphotericin

Chromomycosis

NB:

Candida albicans quickly becomes resistant to flucytosine when used alone. May be combined with amphotericin, or azole antifungals such as fluconazole or itraconazole.

Adverse effects

Due to dose dependent bone marrow depression:

- Leucopenia
- Thrombocytopenia
- Mild anaemia

Enterocolitis

Liver damage

Preparations and Dosage

The drug is dispensed in capsules of 250 mg and 500 mg strength.

The injectable form is diluted in 250 mL saline solution to contain 2.5 g total (10 mg/mL). The solution is physically incompatible with other drugs including amphotericin B.

Dose: 50-150mg/kg body weight, given 6 hourly.

Benzoic acid and salicylic

Whitfield's ointment

Whitfield's ointment

Both benzoic and salicylic acids possess antifungal properties.

Salicylic acid is a comparatively weak antifungal agent but has keratolytic properties

Whitfield's ointment [Benzoic acid compound ointment N.F.] contains 6% of benzoic acid and 3% of salicylic acid in emulsifying ointment, e.g. vaseline.

It is a commonly used preparation.

Indications

1. Tinea versicolor
2. Tinea pedis
3. Ringworm

Whitfield's ointment is applied topically twice daily.

Other antifungals

Undecenoic acid [Mycota – cream, powder]

Indicated in athletes foot, Tinea cruris and other dermatophytoses

Dose: apply BD or TDS until one week after lesions have disappeared.

Formaldehyde

E.g. Futsil solution. For athletes foot.

Sulphur

For Tinea capitis, Tinea corporis, Pityriasis versicolor.

Applied BD.

The end.

Thank you.

BY P.J. OKOTH

ANTIMALARIAL AGENTS

Learning objectives

Describe the life cycle of malaria parasites
Name the four major types of plasmodia that infect man and state the type of malaria each causes
Classify antimalarial drugs
- Based on life cycle
- Based on chemical classification

Discuss individual antimalarial drugs
Discuss the management of uncomplicated and severe malaria.

Life cycle of the malaria parasite

Female mosquito (Anopheles) bites man and infects his blood with **sporozoites**.

Liver cycle:

Sporozoites enter liver cells and develop into **schizonts** which form large numbers of **merozoites**.

The merozoites are released into circulation after 5-16 days.

Tissue schizonticides act during this cycle

Life cycle …

P. vivax, P. ovale, P. malariae have a persistent liver cycle.
They therefore need tissue schizonticides for elimination of the liver cycle so that infections do not recur.
P. falciparum has no persistent liver cycle.

Life cycle …

Erythrocyte cycle:

Merozoites enter RBCs where they develop into schizonts which form more merozoites.

Merozoites are released when the cells burst, causing a clinical attack of malaria.

The merozoites re-enter red blood cells and the cycle is repeated.

Blood schizonticides kill these asexual forms of malaria parasites.

Life cycle…

Sexual forms:

Some merozoites differentiate into male and female **gametocytes** inside the RBCs. They develop further only if ingested by mosquito.

Gametocytocides act on the sexual forms and prevent transmission of the infection. Patient becomes non-infective and parasites fail to develop in the mosquito.

Life cycle…

Mosquito bites infected man and sucks up male and female gametocytes.
Fertilization of gametes occurs and develop into **sporozoites** in the mosquito.
The mosquito then bites another man and infects his blood with sporozoites, and the cycle is repeated.
Since no drugs are effective against sporozoites, infection with the malaria parasite cannot be prevented.

Types of Plasmodia

There are four major types of Plasmodia which infect man:

- Plasmodium falciparum
- Plasmodium vivax
- Plasmodium malariae
- Plasmodium ovale

Types of malaria caused by Plasmodia

P. falciparum causes **malignant tertian malaria**, a fulminating infection, which, if not promptly treated, may result in death.

P. vivax causes **benign tertian malaria** which is mild and has a tendency to relapse.

- In both the above infections, the infected person develops pyrexia with rigors every 3rd day and hence the term "**tertian**".

P. ovale and P. malariae infections are uncommon and usually mild.

- The infected individual develops pyrexia every 4th day and hence, it is described as "**benign quartan**".

Clinical classification of antimalarials

Tissue schizonticides:

Act on the parasites during the hepatic cycle.

Examples: Primaquine, Proguanil, and Tetracyclines

They are used for:

Radical cure i.e. an attack on persisting hepatic forms (hypnocytes) once the parasite has been cleared from the blood. This is best achieved with primaquine.

Clinical classification…

Tissue schizonticides are also used for:

Preventing the initial hepatic cycle, i.e. causal prophylaxis.

Drugs used include: primaquine, doxycycline, and proguanil.

Causal prophylactics prevent the maturation of or destroy the sporozoites within the infected hepatic cells and thus prevent erythrocytic invasion.

Clinical classification…

Erythrocytic or blood schizonticides:

Kill the asexual forms during the erythrocytic cycle.

Examples: chloroquine, quinine, mefloquine, halofantrine, proguanil, pyrimethamine, tetracyclines.

They may be used for:

- Treatment of acute attacks of malaria
- Prevention of attacks by early destruction of erythrocytic forms. This is called suppressive prophylaxis as it does not cure the hepatic cycle.

Clinical classification…

Gametocidal (gametocytocides):

Act on sexual forms and prevent transmission of the infection because the patient becomes non-infective and the parasite fails to develop in the mosquito. Examples: quinine, mefloquine, artesunate, artemether, primaquine.

Chemical classification

Arylaminoalcohols

- Cinchona alkaloids
  - Quinine
- Quinoline-methanol
  - Mefloquine

Sesquiterpenes

- Artemisinin derivatives
  - Artesunate
  - Artemether

Chemical classification

4-Aminoquinolines

Chloroquine

Amodiaquine

8-Aminoquinolines

Primaquine

Phenanthrene methanol

Halofantrine

Chemical classification…

- **Antimetabolites**
  - Biguanide
    - Proguanil
  - Diaminopyrimidine
    - Pyrimethamine
  - Sulfadoxine
  - Dapsone
- **Antibiotics**
  - Tetracycline, doxycycline, minocycline

Quinine

Is obtained from the bark of the South American Cinchona tree. It is a Cinchona alkaloid.

Mechanism of action

Quinine is schizonticidal
It binds to plasmodial DNA to prevent protein synthesis.

Pharmacokinetics

Quinine is well absorbed from the GIT and is almost completely metabolized in the liver.

The plasma half-life is 9-18 hours.

Peak plasma levels are reached within 1-3 hours

Elimination is in urine.

Adverse effects

Cinchonism:

Characterized by:

- Tinnitus
- Diminished auditory acuity (high tone deafness)
- Blurred vision
- Headache
- Nausea and vomiting
- Vertigo
- Postural hypotension

Symptoms usually disappear after withdrawal of the drug.

Adverse effects…

Hypotension

- Associated with excessively rapid I.V. infusion

Hypoglycaemia

- Due to effect of quinine stimulating the cells of the pancreas
- Often significant when quinine is given intravenously and supplementary glucose may be required.

Idiosyncratic reactions

- Pruritus
- Urticaria
- Rashes

Adverse effects…

GIT side effects as a result of local irritation of the gastrointestinal tract.

- Nausea
- Vomiting
- Diarrhoea

Visual disturbances

- Blurred vision
- Distorted colour perception
- Photophobia
- Diplopia
- Night blindness

Adverse effects…

Black water fever

Has been observed in patients with G6PD enzyme deficiency.

It is characterized by:

- Haemolysis
- Haemoglobinuria
- Renal failure

Quinidine-like effects

Hypotension, disturbance of atrioventricular conduction, cardiac arrest.

Formulation

Available as:

Tablets

- 300mg quinine dihydrochloride
- 300mg quinine hydrochloride
- 300mg quinine bisulphate
- 300mg quinine sulphate
- 200mg quinine sulphate

Injectable solutions

- Quinine hydrochloride
- Quinine dihydrochloride
- Quinine sulphate

The ampoules are usually 300mg/ml and come as 600mg (salt)/2ml or 300mg (salt)/ml.

Dosage

Quinine is administered as a seven-day dose of 10mg/kg body weight three times a day (every eight hours)

- Given orally as tablets or reconstituted into syrup for children.

Quinine intramuscular injection

- The dosage of IM quinine injection is a loading dose of 20mg/kg and maintenance of 10mg/kg body weight.

Administration of intramuscular quinine

Quinine MUST be diluted (maximum concentration is 100 mg/ml for adults, and 50mg/ml for children) before intramuscular injection.

A loading dose of 20 mg/kg of quinine (diluted to a maximum 100 mg/ml for adults and 50mg/ml for children) is given by intramuscular injection (preferably the anterior thigh).

A maximum of 3ml should be injected into one site.

If the amount to be injected exceeds 3ml, multiple sites should be used

Dosage …

How to give the intramuscular injection:

E.g. when giving at a strength of 50mg/ml to a child:

Use a 10ml syringe. Draw up 5ml of sterile water for injection, then into the same syringe draw up 300mg (1ml) from an ampoule of quinine.

The syringe now contains 50mg of quinine per ml. Mix the drug by shaking the syringe before injection.

In all situations a maximum of 3ml should be injected into one injection site.

Dosage…

Quinine intravenous infusion:

Is administered in isotonic fluid, either 5% dextrose or normal saline.

Quinine is a **first line treatment** for complicated/severe malaria in the absence of Artesunate.

Quinine administration in adults

Administer quinine as follows:

- A loading dose of quinine **20mg/kg** (maximum 1200mg) diluted in 500ml of isotonic solution (5% dextrose or normal saline) is given intravenously to run **over 4 hours**.
- **8 hours** from commencement of the initial dose of quinine, give **10mg/kg** (maximum 600mg) diluted in isotonic solution to run over 4 hours.
- Repeat **10mg/kg** quinine infusion **every 8 hours** until the patient can take medication orally.

NB: omit loading dose if any quinine has been given in the previous 24 hours or have received mefloquine in the last 7 days.

Quinine administration in adults…

Thereafter a complete course of artemether-lumefantrine (AL) is given

Alternatively oral quinine is continued at 10mg/kg (maximum 600mg) every 8 hours to complete a total of 7 days of treatment.

In children

Put up IV quinine drip 20 mg/kg body weight loading dose in 15mls/kg of 5% dextrose to run over 4 hours.
8 hours from the start of the initial dose of quinine, give 10mg/kg in 10mls/kg of isotonic solution (5% dextrose or normal saline) to run in a way as not to exceed 5 mg salt/kg body weight per hour
Repeat 10mg/kg quinine infusion every 8 hours until the patient can take medication orally.
Thereafter a complete course of artemether-lumefantrine (AL) is given.
Alternatively, oral quinine may be given at 10mg/kg every 8 hours to complete a total (parenteral + oral) of 7 days

NB: omit loading dose if any quinine has been given in the previous 24 hours or have received mefloquine in the last 7 days.

Artemisinin derivatives

Artesunate and Artemether

Artesunate and artemether

Are artemisinin derivatives
They are among the most powerful and efficient drugs for the treatment of malaria.
They have very few side effects
They are derived from the extract of the plant Artemisia annua.

Pharmacodynamics

Both artesunate and artemether and their active metabolite dihydroartemisinin (DHA) are extremely potent antimalarials. They have a broader spectrum of antimalarial activity than any of the other antimalarial drugs.

Mechanism of action

They kill the schizonts, delay the formation of gametocytes, and also kill the gametocytes.

- Activity against liver stages has not been demonstrated
- The drugs do not also prevent the inoculation of sporozoites into the liver following a mosquito bite.

Pharmacokinetics

They follow first-order kinetics when administered orally or intramuscularly.
Absorption of artemether when administered orally is quick, and maximum plasma concentrations are obtained after about two hours.
Artesunate is also quickly absorbed from the gut but hydrolysis, converting it to DHA, is very fast.
Elimination is fast: plasma half-life is 1-2 hours.

Pharmacokinetics…

Artemether is about 90% bound to plasma proteins, whereas DHA is only 50% bound
Artesunate and artemether are converted to the common metabolite DHA in the body.
DHA has nearly the same intrinsic activity against the malaria parasites as the drugs artesunate and artemether.

Preparations and dosage

Available as:

Injectable

Artemether for intramuscular injection (in ampoules)

- For adults: artemether 80mg/ml
- For children: artemether 20mg/ml and 40mg/ml

Artesunate for IM or IV use

- Dispensed as artesunic powder with diluent of 5% sodium bicarbonate to form sodium artesunate solution.
- Administered in 5mls of normal saline or 5% dextrose

Preps and dosage…

Powder for an oral suspension of artemether

Tablets

- Artesunate tablets 100mg for adults and 50mg for children.
- Artemether tablets 50mg

Preparations…

Artemether capsules 40mg
Suppositories for babies and children
Suppogels consisting of soft gelatine capsules containing 4omg artemether dissolved in soya oil.

Dosage

Artemether is administered by the intramuscular route at a loading dose of 3.2 mg/kg IM stat then 1.6 mg/kg/IM daily for 4 consecutive days

Artesunate:

The recommended dose is 3.2 mg/kg on first day followed by 1.6mg/kg daily for 4 consecutive days, or

- 2 tablets of 100mg (200mg) as a single dose on day 1, followed by 1 tablet of 100mg for 4 consecutive days

In-patient management of severe malaria

The current recommended first line treatment of severe malaria in Kenya is **Artesunate** administration [May 2014 protocol]
Quinine is used as a first choice only if artesunate is **not** available.

Artesunate administration

Dissolve artesunic powder with 5% sodium bicarbonate solution (provided with vial)

Dilute resultant solution with 5ml of normal saline or 5% dextrose

For children weighing 20kg and below, administer 3.0mg/kg stat by slow intravenous injection then at 12 hours and at 24 hours until the patient is able to tolerate oral medications.

Artesunate administration…

For patients weighing above 20kg, administer 2.4mg/kg stat by slow intravenous injection then at 12 hours and at 24 hours until the patient is able to tolerate oral medications.
Artesunate can be given IM at the same dosage and intervals.
Thereafter a complete course of artemether-lumefantrine (AL) is given.
Ensure the first 3 doses are completed whether the patient is able to tolerate oral medication or not.

Combination therapies

Combination therapies based on artesunate or artemether are currently recommended for the treatment of malaria.

Combination therapy permits a shorter duration of treatment, which improves compliance.

The theoretical risk of drug resistance is also significantly reduced by using combination therapy.

Combination therapies…

Artemether-Lumefantrine (AL)

Combination consists of artemether 20mg and lumefantrine 120mg per tablet.
It is the recommended first line treatment for **uncomplicated malaria** in Kenya.
It is currently available as a co-formulated regular or child friendly dispersible tablet containing 20 mg of artemether and 120 mg of lumefantrine.

Artemether –Lumefantrine (AL)

Dose:

AL is administered as a six-dose treatment over a three day period.

- 1st dose at time of initial diagnosis (0 hours)
- 2nd dose after 8 hours, then
- Twice a day for the following two days.

E.g. adult dose:

- 4 tabs stat.
- 4 tabs after 8 hours, then
- 4 tabs B.D. x 2/7.

AL …

Weight in kg	Age in yrs	Number of tablets per dose					
		Day 1		Day 2		Day 3	
		1st dose	8hrs	24hrs	36hrs	48hrs	60hrs
5 to <15	5/12 to less than 3 yrs	1	1	1	1	1	1
15 to <25	3-7yrs	2	2	2	2	2	2
25 to <35	8-11 yrs	3	3	3	3	3	3
35 kg and Above	12 yrs and above	4	4	4	4	4	4

AL…

In children below 5 kg, if appropriate weight for age, evaluation of other causes of fever including malaria should be undertaken.
Where malaria is confirmed, the current recommended treatment is **half a tablet of AL** given according to the schedule above under close supervision
For children < 24kg, dispersible tablets should be administered where available.

- Place the tablet in a cup or spoon, add a little water to it, wait a few minutes for tablets to disperse and then administer the resulting suspension to the child.

AL…

Absorption of lumefantrine is increased when the drug is taken with food.
AL is taken with a fatty meal e.g. milk
If vomiting occurs within 30 minutes after drug administration, the dose should be repeated.
Emphasize that all 6 doses must be taken over 3 days even if the patient feels better after a few doses.
Advise patients to return immediately to the nearest health facility if the condition deteriorates at any time or if symptoms have not resolved after 3 days.

AL – Adverse Effects

Dizziness
Fatigue
Lack of appetite
Nausea
Vomiting
Abdominal pain

Palpitations
Muscle pain
Joint pain
Headache
Rash

AL – contraindications

Pregnancy – 1st trimester and lactation.
There is limited data on use in pregnancy
Persons with severe malaria
Persons with known hypersensitivity to either of the components

Artemether -Lumefantrine

LONART – DS

A preparation of artemether and lumefantrine containing artemether 80mg and lumefantrine 480mg per tablet.

Dose:

1 tablet stat. (o hrs),

1 tablet after 8 hours, then

1 tablet B.D. for 2 days.

Other combinations

Amodiaquine plus artesunate

Dose:

Amodiaquine 10mg/kg daily for 3/7

Artesunate 4mg/kg daily for 3/7

Mefloquine + artesunate (Artequin)

Dose:

Artesunate 4mg/kg O.D x 3/7 [200mg O.D x 3/7]

Mefloquine 25mg/kg given as a single dose or split dose. [250mg O.D x3/7]

Combinations…

Artesunate + sulphamethoxypyridazine/pyrimethamine

E.g. CO-ARINATE

Dose:

1 tablet of the combination O.D. for 3 days.

Combinations …

PPQ).

Is the recommended **second line treatment** for uncomplicated malaria in Kenya.

This is currently available as a fixed-dose combination with adult tablets containing **40 mg** of dihydroartemisinin and **320 mg** of piperaquine and paediatric tablets containing **20mg** dihydroartemisinin and **160mg** of piperaquine.

These are administered once daily for three days

Primaquine

An 8-aminoquinolone
Acts at several stages in the development of the plasmodial parasite, possibly by interfering with its mitochondrial function.
Its unique effect is to eliminate the hepatic forms P. vivax and P. ovale after standard antimalarial therapy.

Treatment of uncomplicated vivax malaria

It is vital to have confirmed lab diagnosis of P. vivax malaria before commencing treatment.

P. vivax has both blood and liver stages.

Like falciparum malaria, the recommended treatment for vivax malaria is AL.

However, in order to achieve a radical cure and prevent relapses, **primaquine**, must also be given.

Therapeutic dose of primaquine

Primaquine dose ranges between 0.25 and 0.5mg/kg/day once a day for 14 days.
The usual dose is 15mg O.D. x 14/7
Duration can be extended up to 21 days
It is available as 7.5mg and 15mg tablets.

Primaquine adverse effects

Primaquine causes abdominal discomfort when taken on an empty stomach; it should always be taken with food.
Primaquine may also cause haemolysis in patients with glucose-6-phosphatase dehydrogenase (G6PD) deficiency.
Anorexia
Nausea

Mefloquine

P.J.

Mefloquine

Is similar in several aspects to quinine
It is used for malaria chemoprophylaxis and to treat uncomplicated P. falciparum malaria
Mefloquine is rapidly absorbed from the gastrointestinal tract.
Dose:
20mg/kg [of base] stat. or
10mg/kg stat, then 10mg/kg after 6-8 hours.
Prophylaxis: 1 tablet weekly from 1 week before travelling and for at least 6 weeks after travelling.
Available as 250mg tablets.

Adverse effects of mefloquine

loss of appetite.
Rarely, hallucinations, seizures, psychoses.
Should be avoided in patients taking beta-adrenoceptor and calcium channel antagonists for it causes sinus bradycardia.
Use of mefloquine is contraindicated in those whose activities require fine co-ordination or spatial performance e.g. airline crews.

Halofantrin

A phenanthrene methanol

Halofantrine (Halfan)

Halofantrine is active against the erythrocytic forms of all four Plasmodium species, especially P. falciparum and P. vivax, and at the schizont stage.

Pharmacokinetics:

Absorption from the GIT is variable, incomplete and substantially increased [6-10 times] by taking the drug with food.

It is metabolized to an active metabolite and no unchanged drug is recovered in urine.

Halofantrine

Use:

It is used for the treatment of uncomplicated resistant malaria due to P. falciparum and vivax.

Halofantrine should not be given for prophylaxis.

Adverse effects:

Gastrointestinal symptoms

Pruritis

Prolongation of cardiac QT interval – may predispose to hazardous dysrhythmias.

Halofantrine

Precautions:

The drug should not be taken:

- With food (especially fat)
- With other potentially dysrhythmic drugs e.g. antimalarials, tricyclic antidepressants, antipsychotics, astemizole, terfenadine.
- With drugs causing electrolyte imbalance
- By patients with cardiac disease associated with prolonged QT interval.

Halofantrine

Preparations and dosage:

Available as

250mg tablets

Suspension 100mg/5ml (30 ml bottle)

Dose:

Over 40kg weight, 500mg six-hourly for 3 doses. Total 6 tablets.

Under 40kg weight, 8mg/kg six-hourly for 3 doses. Total 24mg/kg.

Proguanil

An antimetabolite

Proguanil

MOA:

Proguanil inhibits dihydrofolate reductase which converts folic acid to folinic acid, deficiency of which inhibits plasmodial cell division.

Pharmacokinetics:

Proguanil is moderately well absorbed from the gut and is excreted in the urine either unchanged or as an active metabolite.

Proguanil

Preparation and dosage:

Available as 100mg tablets

Dose:

Adults: 200mg (2 tablets) daily

9-14 years: one and a half tablets daily

5-8 years: 1 tab daily

1-4 years: half a tablet daily

< 1 year: a quarter tablet daily.

Proguanil

Use:

Chemoprophylaxis of malaria

Adverse effects:

Allergic reactions

Steven-Johnson syndrome

GI disorders

Sulfadoxine/pyrimethamine combination [SP]

ANTIMETABOLITE

Sulfadoxine/pyrimethamine [SP]

Pyrimethamine acts synergistically with sulfadoxine to inhibit folic acid metabolism.
Sulfadoxine inhibits DHF synthase
Pyrimethamine inhibits plasmodial dihydrofolate reductase, for which it has a high affinity.
This ultimately impairs DNA formation by the parasite.

SP

MOA:

PABA – [DHF synthase]- DHF – [DHF reductase] – THF (Tetrahydric folic acid) – purines – DNA.

SP

Preparations and dosage:

Tablets 500mg sulfadoxine + 25mg pyrimethamine. Also injectable available

Suspension 250mg sulfadoxine + 12.5mg pyrimethamine in 5ml.

Dose:

Over 14 years: 2-3 tablets stat.

9-14 years: 2 tablets stat.

4-8 years: 1 tablet stat.

< 4 years: half tablet stat.

Now mainly used for malaria prophylaxis

SP

Sulphamethoxypyridazine / pyrimethamine combination

Similar to sulfadoxine pyrimethamine in MOA

Contains 500mg sulphamethoxypyridazine and 25mg pyrimethamine.

Dose:

Adult : 2 stat.

The end.

Thanks.

ANTIVIRAL/ANTIRETROVIRAL PHARMACOLOGY

BY

N. KING'ORI

HIV VIRUS

- A retrovirus from the Lentivirus family.
- Genetic material consists of a single-stranded ribonucleic acid (RNA)
- Viral particle is spherical in shape with a diameter of 80-100 nanometers (nm).

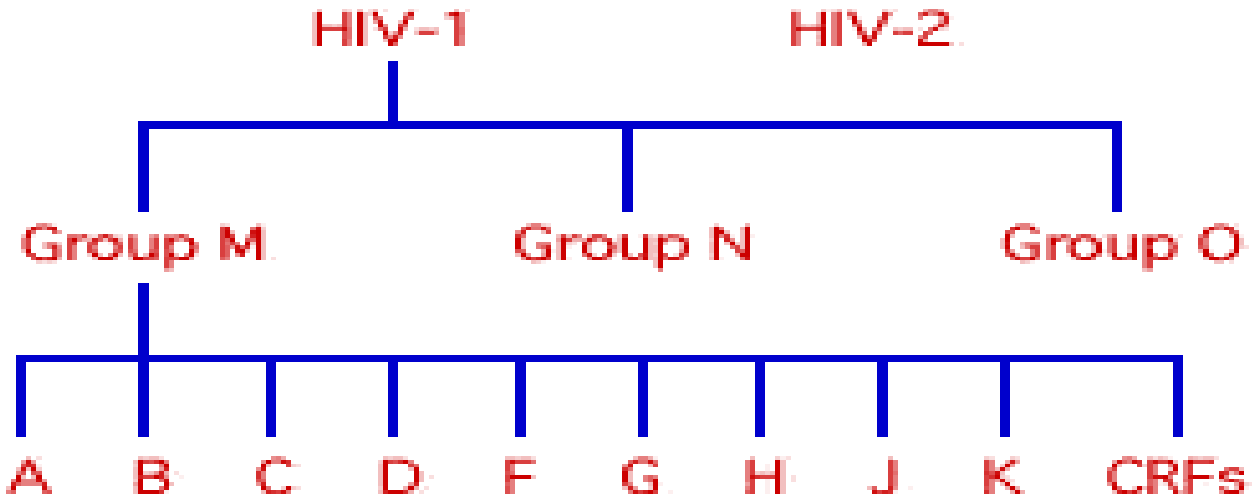
The Biology Of The Human Immunodeficiency Virus

Basic Virology:

There are two types of HIV.

- **HIV – 1**
  - Is found worldwide
  - Is the main cause of the worldwide pandemic
- **HIV – 2**
  - Is mainly found in West Africa, Mozambique and Angola.
  - Causes a similar illness to HIV – 1
  - Less efficiently transmissible rarely causing vertical transmission
  - Less aggressive with slower disease progression

HIV 1 Subtypes



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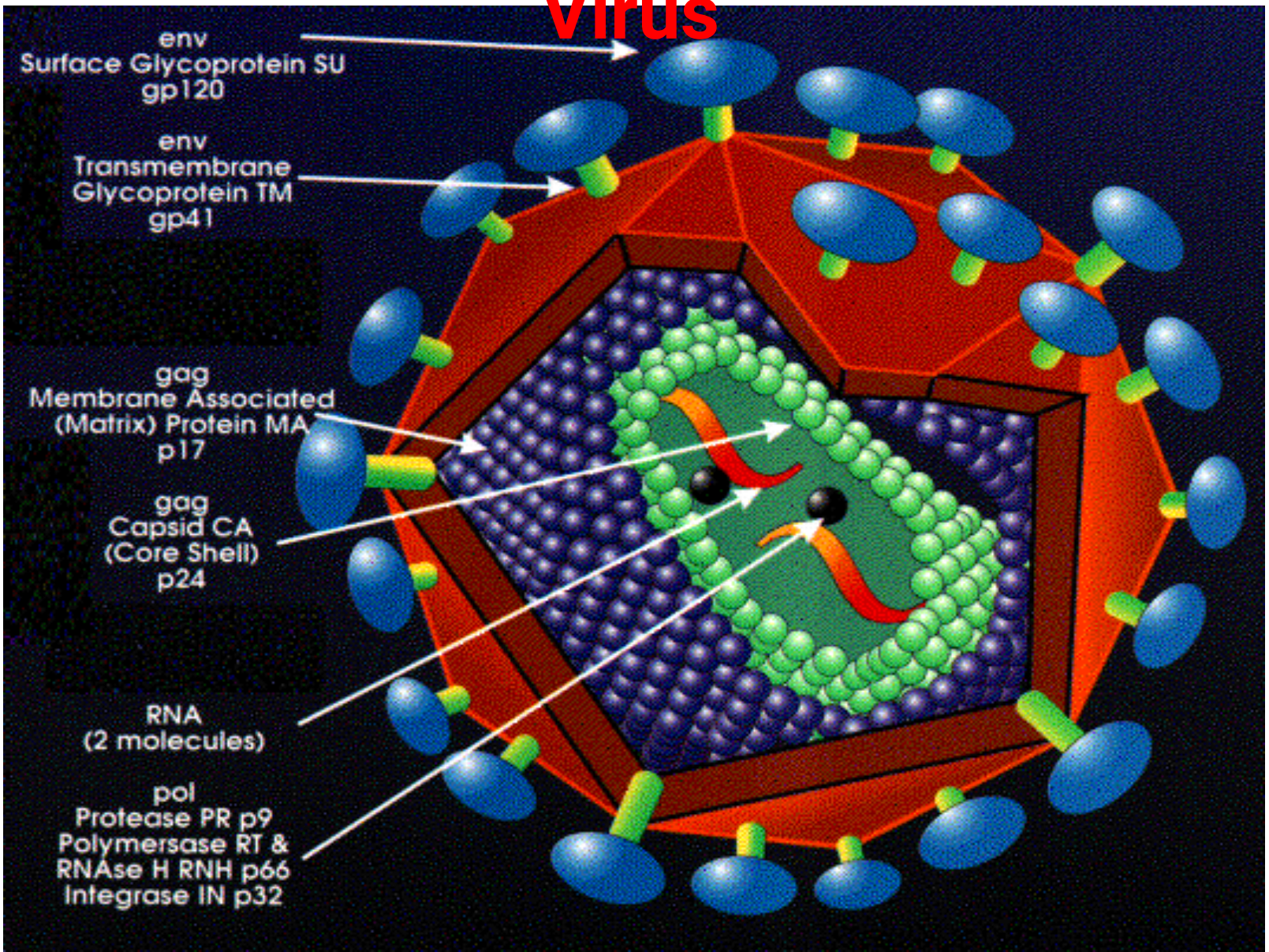
Structure Of Human Immunodeficiency Virus



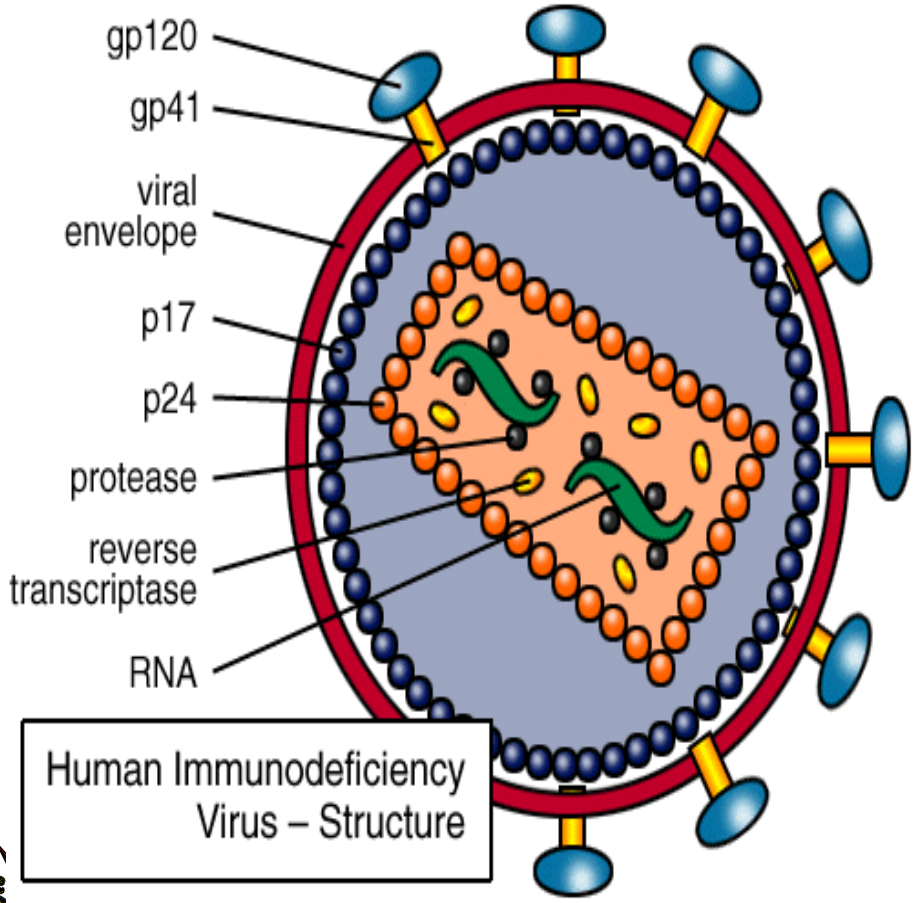
Structure Of Human Immunodeficiency Virus

Has an outer double lipid membrane, (derived from the host membrane).

The lipid membrane is lined by a matrix protein.

The lipid membrane is studded with the surface glycoprotein (gp) 120 and the transmembrane gp 41 protein.

These glycoprotein spikes surround the cone-shaped protein core.



HIV Structure

The core (capsid) is made up of several proteins:-

HIV Glycoproteins

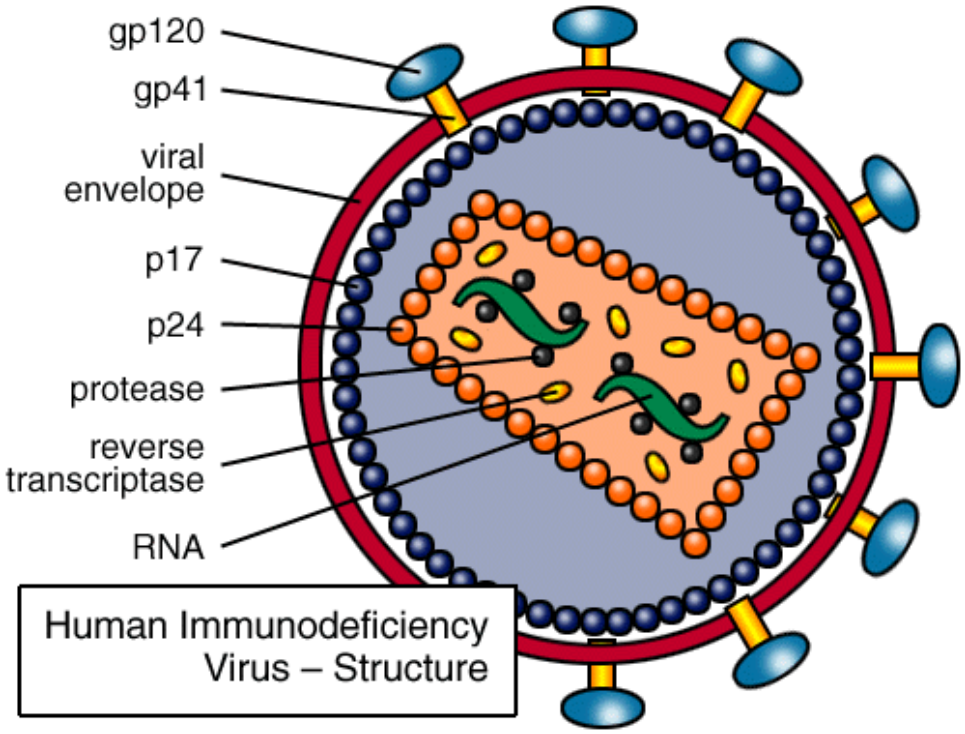
- The gp120 and gp41 mediate the entry of virus into the host cells.

  P_{24} the main protein

  Within the capsid are

  two identical single strands of RNA (the viral genetic material).

  viral enzymes



HIV Structure

Viral Enzymes

- Most important: Reverse Transcriptase (RT), Protease and Integrase.
- RT converts viral single-stranded RNA into a double stranded deoxyribonucleic acid (DNA).
- DNA is incorporated into host nucleus as the proviral DNA.
- Integrase facilitates integration of the DNA into the host's chromosomal DNA.
- Protease enzyme splits generated macro-proteins into smaller viral proteins (core, envelope & regulatory proteins and enzymes) which go into forming new viral particles.

HIV Life Cycle

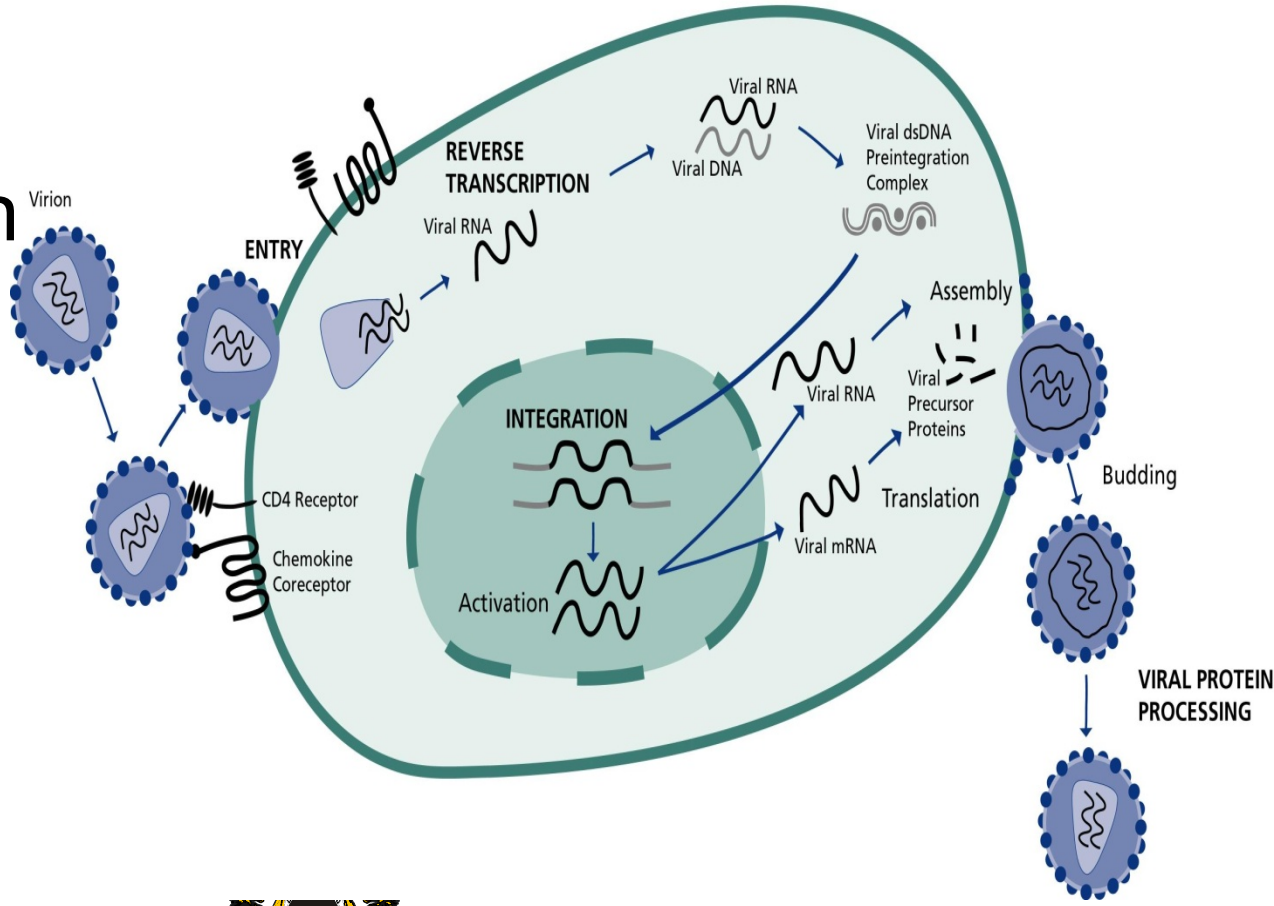
Binding, Fusion and Entry

Transcription

Integration & Replication

Budding

Maturation



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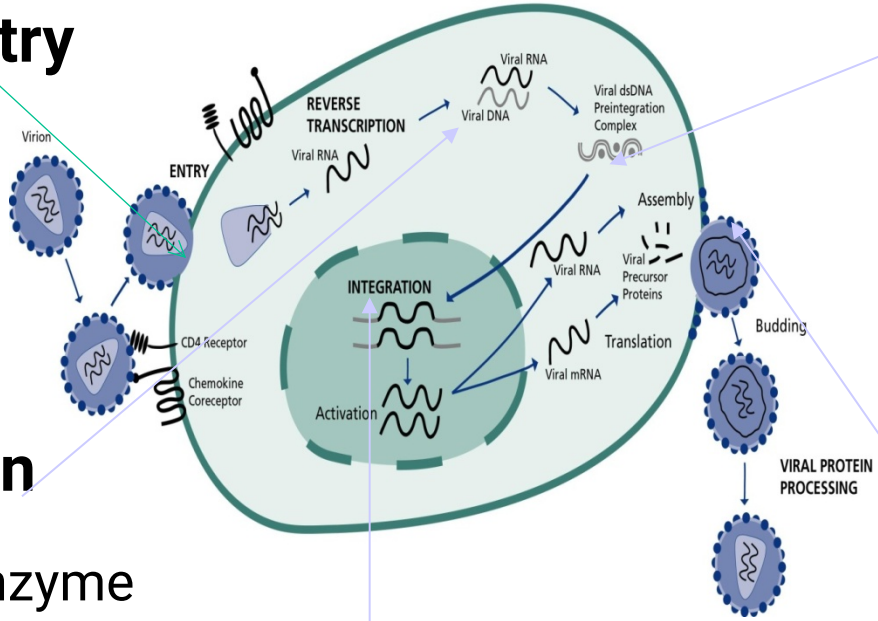
HIV LIFE CYCLE: Enzymes

Fusion & entry



- **Reverse Transcription**
  - The viral enzyme **reverse transcriptase** converts the single stranded viral RNA into double strand DNA

Integration:

The viral enzyme **integrase** inserts the viral DNA (viral genetic material) into the host DNA.

Transcription:

- Activation of host cell results in transcription of viral DNA into mRNA.
- mRNA translated into viral precursor proteins

- **Assembly & Budding**
  - Viral precursor proteins processed by **protease** enzyme into usable forms
    - Proteins assembled with RNA to form viral particles which then bud

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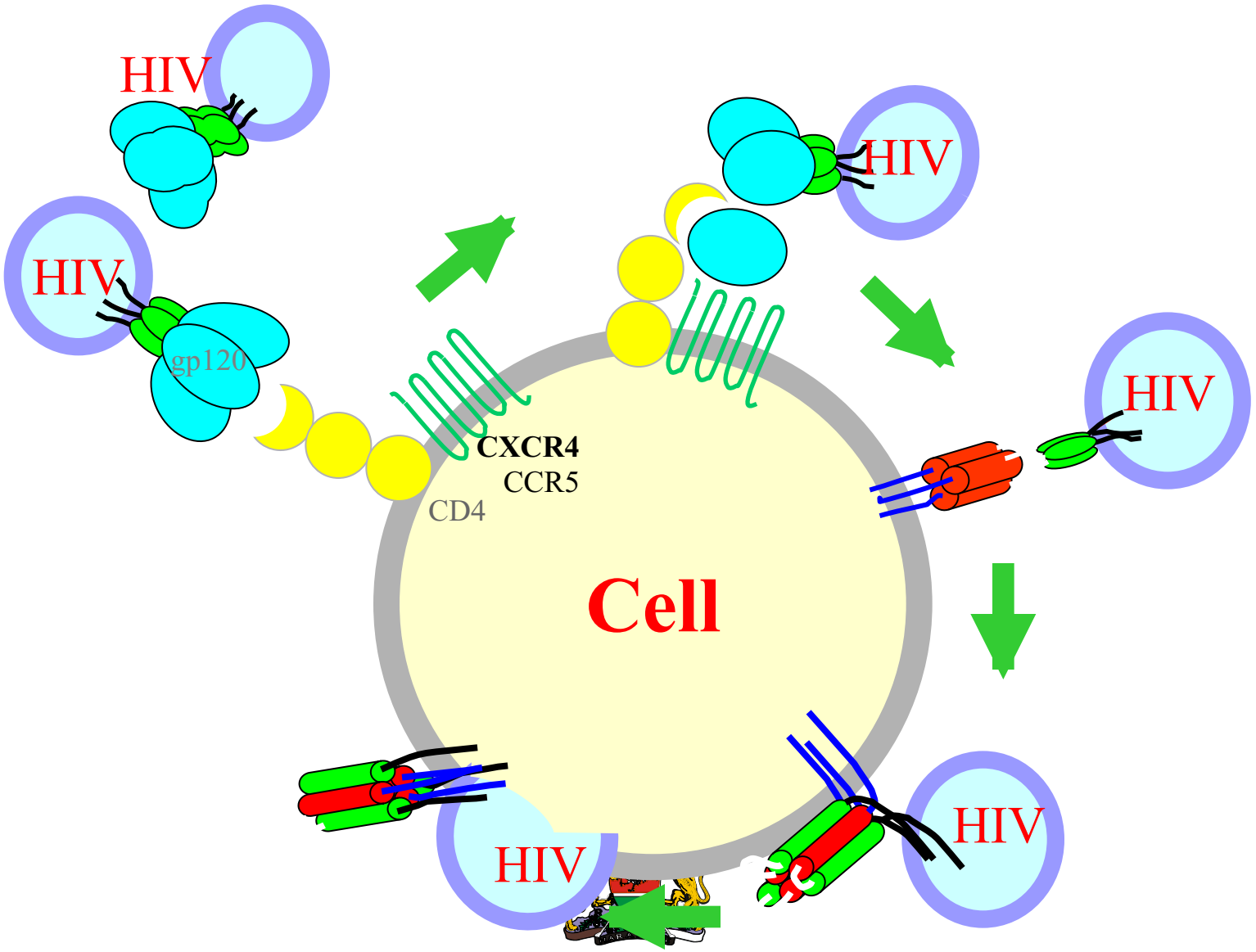
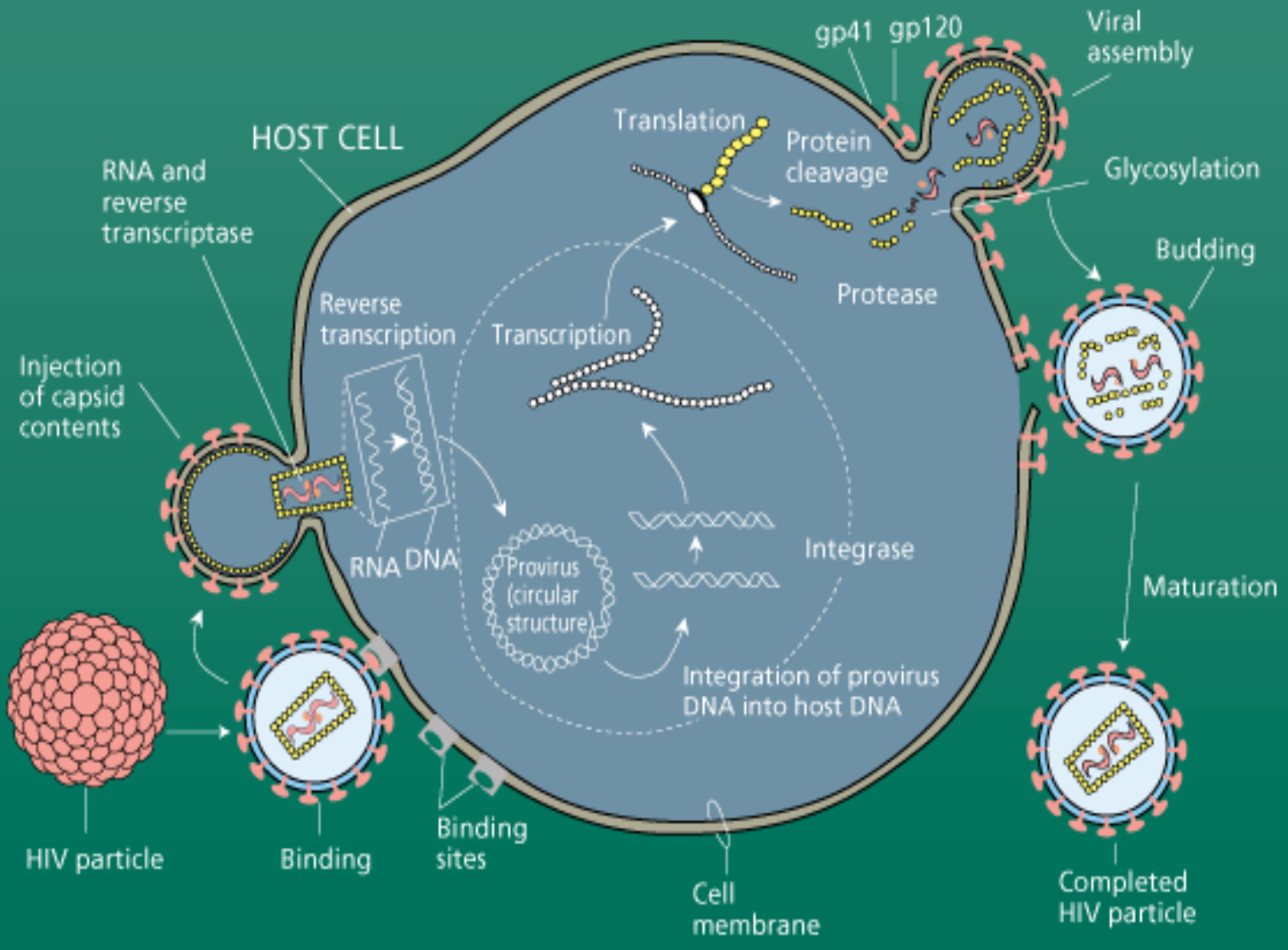
HIV Entry Mechanism

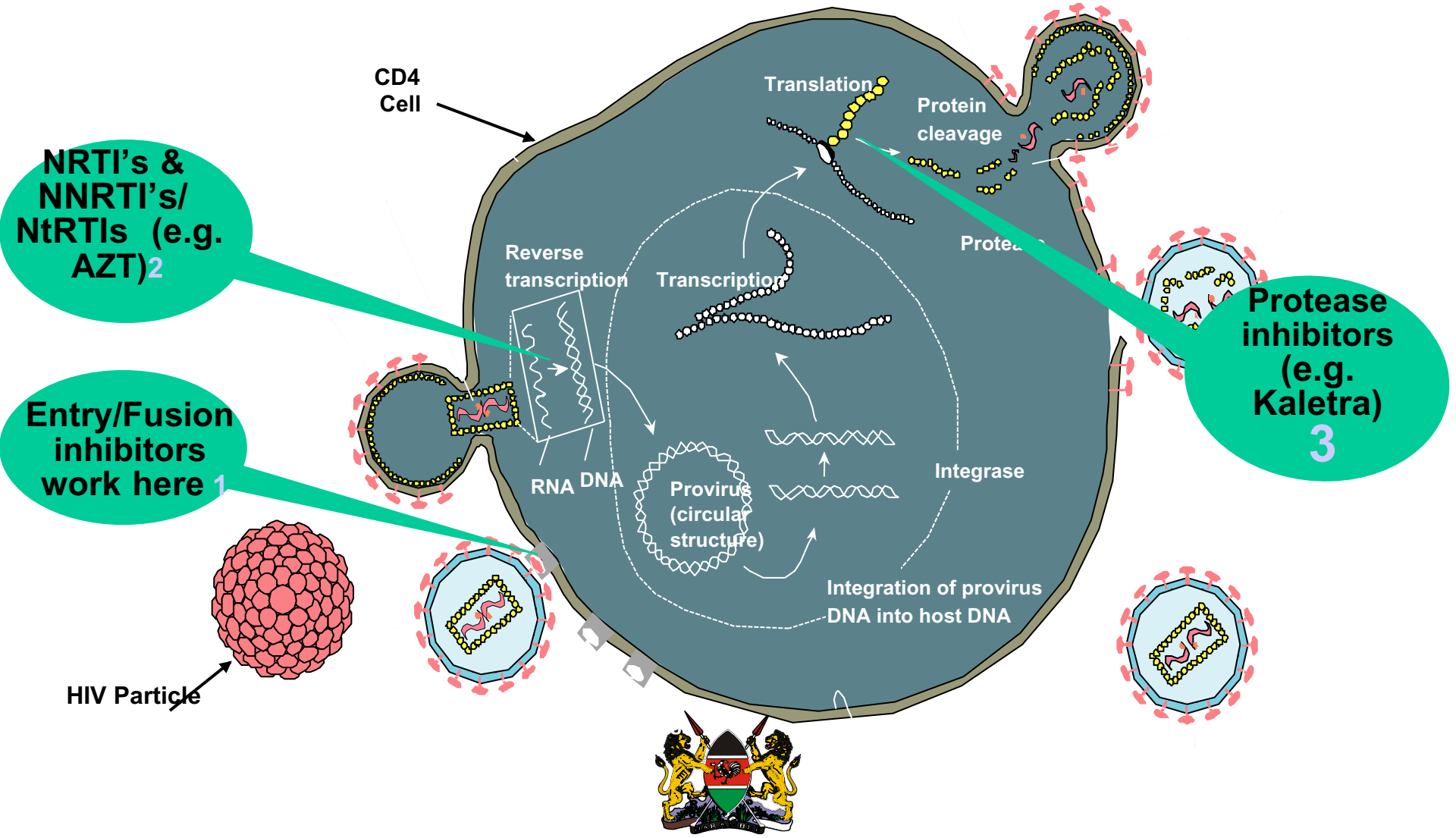


HIV Replication Cycle



Adapted from *HIV/AIDS Handbook*. 3rd ed. Boston: Total Learning Concepts, 1997.

Targets of ARV Drugs



MINISTRY OF HEALTH

Classes of Anti Retro Virals

- Reverse transcriptase (RT) inhibitors
  - Nucleoside RT inhibitors (NRTI)
  - Non-nucleoside RT inhibitors (NNRTI)
  - Nucleotide RT inhibitors (NtNRI)
- Protease inhibitors (PI)
- Entry Inhibitors
  - Attachment inhibitors
  - Chemokine receptor antagonists
  - Fusion inhibitors
- Integrase inhibitors

Antiretroviral Agents

- NRTI Nucleoside Reverse Transcriptase Inhibitor

  - Zidovudine (AZT,ZDV Ritrovir)
  - Didanosine (ddI Videx)
  - Zalcitabine (ddC)
  - Stavudine (d4T Zerit)
  - Lamivudine (3TC Epivir)
  - Abacavir (ABC Ziagen)
  - Emtricitabine (FTC)

- Nucleotide analogues
  - Tenofovir (TDF, Viread)

Antiretroviral Agents

- NNRTI Non-Nucleoside Reverse Transcriptase Inhibitor

  - Nevirapine (NVP- Viramune)
  - Delavirdine (DLV)
  - Efavirenz (EFV- Stocrin, sustiva)

Antiretroviral Agents

- Protease Inhibitors

Protease Inhibitors

- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- Amprenavir (APV)
- Lopinavir/ ritonavir (LPV/r Kaletra, Aluvia)
- Atazanavir (ATZ)
- Darunavir(DRV)

- Fusion inhibitors
  - Enfuvirtide (T-20)

Entry inhibitors

-Maraviroc

Vicroviroc

Integrase inhibitors

Raltegravir

Dalutegravir

Some ARVs as Fixed drug combinations (FDCs)

- AZT + 3TC
- TDF+3TC
- AZT + 3TC + NVP
- TDF+ 3TC + EFV
- TDF + FTC + EFV
- TDF + FTC
- ABC + 3TC
- TDF + 3TC + DTG

Considerations while initiating ART

1. Develop a treatment partnership with your patient.
2. Focus on your patient's concerns and priorities.
3. Use the 5 A's:**A**ssess, **A**dvise, **A**gree, **A**ssist, **A**rrange.
4. Educate patient on disease and support patient self-management.
5. **Or**ganize proactive follow-up.
6. Involve peer educators and support staff in your health facility.
7. Link the patient to community-based resources and support.
8. Use written information—registers, Treatment Plan, treatment cards and written information for patients—to document, monitor, and remind.
9. Work as a clinical team.
10. Assure continuity of care.

Principles of ART

- Antiretroviral treatment is part of the comprehensive care of HIV infection
- Treatment should be planned and started in good time
- Regular follow up and monitoring is essential
- Treatment should be stopped/changed when necessary
- The choice of drugs should take into account
  - Efficacy
  - Tolerability
  - Dose Schedule
  - Affordability and availability

Principles of ART cont'd

- ARV drugs are associated with adverse events and drug-drug interactions
- Adherence is key to successful treatment
- Treatment may fail despite patient's and carer's best efforts
- There should be commitment to continued support of patient (and family)

Characteristics of good HAART

- Potent: should bring down viral load to an undetectable level within 3-4 months of therapy
- Acceptable regimen to maximize adherence
  - simple
  - tolerable side effects
  - patient commitment for life-long therapy
- Reasonable options for future therapy
- Affordable and sustainable

AIM OF ART

Improve symptom free longevity by maximal, sustainable & durable suppression of viral replication
(<50 copies/ml)

Currently HAART does not cure HIV but halts viral replication, thus prevent further disease progression and immune system damage

HISTORY OF ART

1980 - 1987 – No therapy

1987 - 1994 – Mono therapy

1994 - 1999 – Combination therapy (HAART)

1999 - 2002 – Complicated therapy

2002 - 2005 - Simplified therapy

MINISTRY OF HEALTH

Goals of ART

- Improved quality of life/increased longevity
- Reduction of HIV related morbidity and mortality
- Restoration and preservation of immune function
- Maximal suppression of HIV replication

Suppression of HIV Replication

- ARVs must be taken in combination of at least **3 drugs**
- Strict adherence to treatment is of the **utmost importance**
  - <95% adherence allows the rapid development of viral resistance
  - Poor adherers **do badly**
    - **Fail treatment much earlier**

Immune Reconstitution

- ART prevents CD4 destruction by HIV
- CD4 cell count can recover
- Improved function of CD4 cells
- CD4 cells are central to the immune system
  - So there is improved overall function of the immune system
  - It takes from 6 to 8 weeks for this to become evident clinically

Reduction of HIV related morbidity and mortality and Improvement of QOL

- Decreased hospitalizations
- Decreased risk of illnesses
- Increased general well-being
- Reversal of weight loss
- Ability to return to work

HAART INITIATION

- All clients who test positive for HIV should be initiated on HAART irrespective of CD4 count and WHO staging after a successful testing and counselling
- All pregnant mothers who test positive should be initiated on HAART irrespective of CD4 or WHO status

HAART INITIATION(first line) DEC 2020

Age/Weight	Preferred Regimen
• Birth – 4 weeks	AZT + 3TC + RAL or NVP
• < 20 kg (above 4 weeks)	ABC + 3TC + LPV/r
• 20 kg – <35 kg	ABC + 3TC + DTG
• ≥ 35 kg	TDF + 3TC + DTG

HIV EXPOSED INFANT

- AZT/NVP for six weeks
- NVP for six months or up to one week prior to ceasastion of breastfeeding

MINISTRY OF HEALTH

HAART INITIATION

- Infants who initiate ART at less than 4 weeks of age should be initiated on AZT+3TC+RAL. If RAL is not immediately available at the facility, then use NVP instead.
- Once the infant is 4 weeks old, change their regimen to ABC+3TC+ LPV/r 2. DTG 50mg OD to be used for all children ≥20kgs and above. For all the other molecules doses, refer to the dosing chart in the National ART Guidelines 2018

HAART IN SPECIAL CIRCUMSTANCES

POST EXPOSURE PROPHYLAXIS(PEP) PEP should be offered as soon as possible (< 72 hours) after high risk exposure .The recommended ARV agents for PEP are

ADULT >35 kg (TDF/3TC/DTG)

20 - <35kg (ABC/3TC/DTG)

< 20 kg (ABC/3TC/LPV/r)

Pre exposure prophylaxis(PrEP) Oral PrEP should be offered to HIV negative individuals at substantial ongoing risk of HIV infection (including the seronegative partner in a discordant relationship, MSM,FSW, PWID)

- TDF/FTC
- TDF/3TC

PEP/PrEP

- Prep does not eliminate the risk of HIV infection and it does not prevent STIs or unintended pregnancies
- PrEP should only be offered after assessment to establish eligibility, readiness for effective use, required follow-up (including HIV testing every 3 months) and absence of contraindications to TDF and/or FTC

HBV/HIV and HCV/HIV Co-infection

- All HIV positive adolescents and adults should be screened for HBV infection, using serum HBsAg, as part of initial evaluation; children who did not complete routine childhood immunizations should also be screened for HBV
- PLHIV without evidence of hepatitis B infection (HBsAg negative) should be vaccinated against hepatitis B.
- The recommended first-line ART for adults with HIV/HBV co-infection is TDF + 3TC + DTG (superboost DTG 50 mg)
- HCV serology should be offered to individuals at risk of HCV infection
- Direct acting antiviral therapies (DAAs) for treatment of HCV have simplified the management of HIV/HCV co-infection

Interpreting Viral load results and defining treatment failure

- The goal of ART is to achieve sustained viral suppression defined as below **Lower Detection Limit(LDL).**
- **Less than 400** copies/ml are currently considered <LDL(February 2019, VL cut off circular)
- **Persistent low-level viremia (PLLV) is defined as viral load copies between 400-999 copies/ml on two consecutive measures**. These patients are at increased risk of progression to treatment failure, development of ARV resistance and death and therefore require a similar case management approach as patients with VL ≥ 1,000 copies/ml

TREATMENT MONITORING

- Adherence assessment on every visit
- Viral load monitoring every 6 months
- Treatment failure assessment

ADULTS

Clinical failure

- Pt. Deteriorating, new/ recurrent significant stage III / IV O.I or malignancy

Immunological failure

- *CD4 count **NOT** > 100cells/mm^3 after 12 months of effective HAART treatment.
- *CD4 count **drop** > **30%** from peak value while on HAART.
- *CD4 count drop to /below baseline level

Virological confirmation of TF

*viral load **> 1000 copies/ml** 2 results 3 months apart

CHILDREN

Clinical failure

Pt. Deteriorating, new/ recurrent significant **stage III** / **IV** O.I or malignancy

- * Growth failure despite adequate nutrition
- * Delayed, stagnation or regressed developmental milestones
- * Lack of clinical improvement from baseline on presentation to care

Three Main Reasons for Altering a Patient's Regimen

1. Drug Toxicity or Intolerance

- Single drug substitutions appropriate

2. Drug Interactions

- Single drug substitutions appropriate

3. Treatment Failure

- *Entire regimen* must be changed

General Principles for Identification and Management of ADRs

1. At every clinic visit the patient on ART should be monitored clinically for toxicities using appropriate history (history of symptoms that suggest toxicity) and physical examination (relevant signs). Targeted laboratory assessment may be used to confirm specific toxicities.

2. Evaluate concurrent medications and establish whether the toxicity is attributable to an ARV drug (or drugs), or to a non-ARV medication taken at the same time. Consider other disease processes (e.g. concurrent infectious processes or IRIS)

3. 3. All toxicities should be graded. Manage the adverse event according to severity

Drug Toxicity and Intolerance

Two Broad Groups of Side-effects:

1. Common “Mild”

2. Rare and Dangerous

Common mild side effects

- Nausea
- Vomiting
- Lethargy
- Headaches
- Dizzyness
- “Flu” symptoms
- Mild rash

NB

- Patients should “expect” them
- Usually improve within 1-2 months
- Rarely necessary to change/stop regime

MINISTRY OF HEALTH

Rare, potentially serious SE's

- Severe rash/SJ Syndrome
- Hepatotoxicity
- Peripheral Neuropathy
- Haematotoxicity
- Pancreatitis
- Lactic Acidosis

General guide to estimate the severity of grade

Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially life threatening Grade 4
Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care OR medical or operative intervention indicated to prevent permanent impairment, persistent

Management of Adverse Drug Effects

- Try and establish the ARV drug responsible for the adverse effect
- Consider duration of ARV use, other disease processes, other treatments (including self administered)
- If it is necessary to stop ART, discontinue all ARV drugs simultaneously*
- Grade 1 or 2 reactions: continue ART under observation.
  - Single drug substitution may be necessary
- Grade 3 or 4- Stop ART, manage Adverse Event and re-introduce ART.

ARV Drug Class Adverse Effects(summary)

NRTIs

- Peripheral neuropathy
- Pancreatitis
- Lipoatrophy
- Hepatitis
- Lactic acidosis

PIs

- Lipodystrophy
- GI Intolerance
- Hyperglycaemia
- Lipid abnormalities

NNRTIs

- Rash
- Fever
- Nausea
- Diarrhea
- Hepatoxicity

Common Adverse Effects

- Peripheral Neuropathy – d4T,ddI
- Hematotoxicity - AZT
- Hepatotoxicity - NVP
- Diarrhea – NFV
- Skin rash – NVP
- Lipodystrophy – PIs, NRTIs
- CNS disturbance – EFV
- Hypersensitivity – ABC
- Hyperlipidemia-PIs, d4T

Nucleoside Reverse Transcriptase Inhibitors

Mechanism of action

- NRTIs interrupt the HIV replication cycle via competitive inhibition of HIV reverse transcriptase and termination of the DNA chain.
- Reverse transcriptase is an HIV-specific DNA polymerase that allows HIV RNA to be transcribed into single-strand and ultimately double-strand proviral DNA and incorporated into the host-cell genome.
- Proviral DNA chain elongation is necessary before genome incorporation can occur and is accomplished by the addition of purine and pyrimidine nucleosides to the 3’ end of the growing chain.

NRTIs

- NRTIs are structurally similar to the DNA nucleoside bases and become incorporated into the proviral DNA chain, resulting in termination of proviral DNA formation Tenofovir, lamivudine, and emtricitabine exhibit activity against hepatitis B virus (HBV) in addition to HIV and are frequently incorporated into antiretroviral regimens for patients with HIV and HBV coinfection.

Resistance

Resistance to NRTIs occurs by one of two mechanisms: (1) impaired incorporation into the proviral DNA chain or (2) removal from the proviral DNA chain.

Mutations typically occur gradually, with accumulation of several mutations required before clinically significantly resistance develops.

An exception is the M184V mutation, which confers high-level resistance to lamivudine and emtricitabine in a single step. Mutations that selectively impair incorporation into the proviral DNA chain include M184V, Q151M, and K65R.

Pharmacokinetics

- NRTIs are prodrugs and must undergo phosphorylation by intracellular kinases to exert their activity. Collectively, the oral bioavailability of NRTIs ranges from 25%-93%, with tenofovir and didanosine on the lower end of the spectrum. Food does not significantly affect absorption of any of the NRTIs except didanosine, which must be taken on an empty stomach to achieve optimal absorption and drug levels.
- Although serum half-lives of NRTIs are relatively short, intracellular drug levels are the best indicator for drug activity and determine the dose administered for each NRTI.
- Most NRTIs are renally eliminated and require dosage adjustments in patients with renal insufficiency; the exception is abacavir, which is given at the normal dose regardless of creatinine clearance.

- NRTIs are not metabolized by the cytochrome P450 system; therefore, minimal drug-drug interactions occur. Interactions that have been found to be clinically significant involve didanosine.
- When given in combination with tenofovir, didanosine levels are higher than expected, and lower doses must be given to avoid potentially serious adverse effects.
- A similar scenario has been demonstrated when didanosine is combined with ribavirin in the treatment of patients with HIV and hepatitis C virus (HCV) coinfection. This combination should be avoided

Adverse events

- Adverse effects of the NRTI class include mitochondrial toxicities (e.g., lactic acidosis, pancreatitis, peripheral neuropathy, hepatic steatosis, lipoatrophy).
- Mitochondrial toxicities are due to NRTI binding to human mitochondrial DNA polymerase-γ enzyme, impairing cellular respiration.
- Under these conditions, normal aerobic metabolism shifts to an anaerobic process, resulting in the above manifestations.

NRTIs adverse effects

- Peripheral neuropathy
- Pancreatitis
- Lipoatrophy
- Hepatitis
- Lactic acidosis
- Mitochondrial toxicity

Zidovudine(AZT)

- Bone marrow suppression (anaemia, neutropaenia).
- Dose related,synergistic toxicity with other drugs such as TMP-SMX,ganciclovir, etc.
- Headache, nausea,vomiting & myopathy, nail changes

Hepatotoxicity, fever, rash---rare

Stavudine (d4t)

Toxicities:

- Peripheral neuropathy - higher incidence & more severe when used with ddI (Didanosine) or ddC (Zalcitabine)
- Elevated liver enzymes
- Increased incidence of pancreatitis when used with ddI + hydroxyurea & fatal lactic acidosis as described earlier
- Lipodystrophy - some association of fat redistribution syndrome & hyperlipidaemia with d4T

Didanosine (ddI)

Toxicities: Diarrhoea (16%), pancreatitis(4-7%), peripheral neuropathy(9-15%)

- Recent reports of increased incidence of pancreatitis & liver toxicities when used with d4T + hydroxyurea
- 5/1/2001 warning - 3 cases of fatal lactic acidosis +/- pancreatitis in HIV pregnant women receiving ddI + d4T

Drug interactions:

- ddI may interfere absorption of drugs that require gastric acidity (e.g itraconazole, ketoconazole, dapsone)
- Ca++ and Mg++ salts in ddI formulation - may chelate drugs such as tetracyclines & quinolones
- EC formulation - eliminates these drug interactions
- ddI + oral ganciclovir - ddI AUC increased by 100%

Abacavir (ABC)

- Hypersensitivity reaction -Mostly occurring within 6 weeks of initiation of treatment

Signs & Symptoms (At least 2 of the following)

High fever, skin rash, malaise, fatigue, nausea, vomiting, diarrhoea, myalgia, arhralgia, respiratory symptoms

Assessment: can be difficult, but should attempt to rule out concomitant illnesses

NNRTIs

Mechanism of action

- HIV reverse transcriptase is a heterodimer composed of 2 subunits (p66 and p51).
- NNRTIs bind the p66 subunit at a hydrophobic pocket distant from the active site of the enzyme. This noncompetitive binding induces a conformational change in the enzyme that alters the active site and limits its activity.
- Etravirine differs from first-generation NNRTIs in its ability to bind at this site despite the presence of some mutations that limit the efficacy of first-generation agents. It is a highly flexible molecule that is able to rotate within the binding site to allow multiple binding conformations.

Resistance

- Mutations within the reverse transcriptase gene domain alter the ability of the NNRTIs to bind the enzyme.
- First-generation NNRTIs have a low genetic barrier to resistance, whereby a single mutation in the binding site can decrease the ability of the drug to bind, significantly diminishing activity.
- First-generation NNRTI resistance has been associated with mutations at multiple codons; however, the presence of either a K103N or Y181C mutation is sufficient to cause clinical failure of delavirdine, efavirenz, and nevirapine.

Pharmacokinetics

NNRTIs display considerable interindividual variability in their pharmacokinetic properties. All currently approved NNRTIs utilize the cytochrome P450 system for metabolism and exert varying induction and inhibition effects on specific isoenzymes (e.g., CYP3A4, CYP2C9). This results in a significant potential for drug-drug interactions

Adverse events

- Rash, which is the most common adverse effect associated with all NNRTIs, usually develops within the first few weeks of therapy and resolves with continued treatment.
- All NNRTIs except etravirine have the ability to cause some degree of hepatotoxicity. Delavirdine and efavirenz can increase transaminase levels, while nevirapine can cause severe toxicity, including hepatic necrosis in patients with CD4 counts that exceed 250 cells/μL.

Nevirapine (NVP)

- Hepatotoxicity-Increasing reports or serious, even life-threatening hepatic necrosis. 12 fold greater risk in women (CD4 >250, pregnancy)
- 2/3 occurred with 1st 12 weeks of treatment.
- Clinical presentation: fatigue, malaise, anorexia, nausea, with or without elevated transminases.
- Symptoms progressed to jaundice, hepatomegaly, high transaminases leading to hepatic failure in few days.

Efavirenz (EFV)

Averse effects

- Reported in > 50% of patients
- Occurs after 1st few doses
- Usually resolves or stabilizes within first few weeks
- Symptoms: Drowsiness, dizziness, dysphoria, insomnia, somnolence, abnormal dreams, altered concentration & attention span, acute psychosis, depression
- Taking at bedtime may reduce symptoms
- Some evidence of benefit of using drug level to predict CNS toxicities