

# INTRODUCTION TO ANTI-MICROBIAL AGENTS

Anti-microbial agents are among the most advanced ~~that are~~

Some diseases that are mostly considered incurable & lethal can now be treated with new drugs.

The powerful and specific activity of this agent are targeted at bacterial and fungal cell wall-synthesizing enzymes, the bacterial ribosomes. The enzymes required for nucleotide and DNA synthesis as well as the machinery of viral replication are also inhibited.

## Definition of Terms

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## BACTERICIDAL

They are agents that destroys bacteria that cause infections. They act through different mechanisms particularly, the destruction of the bacterial cell wall.

Examples are:- Penicillins, Cephalosporins, Isomiazid, Aminoglycosides.

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## BACTEROSTATICS

### Antimicrobial

These are agents that prevents the growth of organisms causing infection. They do not necessarily kill the bacteria but they rather inhibit the growth.

→ The effectiveness of the bacteriostatic agent depend on the immune system of the host. Some examples of bacteriostatic agents are Sulphonamide, Tetracycline and Chlorophenicol.

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### (iii) ANTIMICROBIAL SPECTRUM

Anti microbial agents vary in the degree of their effectiveness against different micro-organisms.

Some selectively inhibit some specialized metabolic processes in the organism such as their effectiveness is limited relatively to few micro-organism and are called NARROW SPECTRUM AGENTS, e.g. Antifungal, antibiotics.

On the other hand, some antibiotics or antimicrobial agent will interfere with chemical reaction common to many micro-organisms (both the gram positive and gram negative).

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They are also effective in non-bacterial microbes.

Such as Rickettsial, these agents are called BROAD SPECTRUM ANTIMICROBIAL AGENT. Antimicrobial agents that <sup>treats</sup> infections by suppressing or destroying the causative micro-organisms be it bacteria, fungi, protozoa or viruses and are derived from natural substances are called ANTIBIOTICS.

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NOTE → All antibiotics are antimicrobial agents but not all antimicrobial agents are antibiotics.

Pre-antimicrobial therapy tests:

- Gram Staining
- Microbiological culture
- Susceptibility / Sensitivity test

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i) Gram Stain - A gram stain helps to immediately identify the cause of infection, by identifying the causative agent in gram positive or gram negative. The test allows better choice of drug therapy especially when an anti-microbial drugs regimen must begin without delay.

ii) Microbiology Culture - This test is to identify specific causative agent and it involves microbiology cultures of specimen, or body fluid, and infected tissues. These specimens are collected and cultured for analysis.

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iii) Susceptibility Test - This helps to determine microbial sensitivity to a given drug and can be used to predict whether the drug will be effective on a particular microbes.

### Types of Susceptibility Test

iv) Broth dilution Sensitivity test - For this test, tools of nutrients. Broth containing specified concentration of antimicrobial agents are

inoculated with known number of micro-organisms  
test tubes are incubated for 16-24 hrs at  
 $37^{\circ}\text{C}$ . EMMANUEL ELIYAHU

After incubation, the fool that has or contains  
the lowest concentration of antimicrobial  
agents that inhibited bacterial growth in the  
tube are defined as minimum inhibiting concent-  
ration (MIC)

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1) Disc Sensitivity Test: This measures microbial  
sensitivity or antimicrobial sensitivity of  
the agent (drug). For this, the antimicrobial  
agents are impregnated on the paper disc, and  
this place in colony of microbial growth which  
is inoculated on the surface of an agar plate.

This test is standardized for the testing of  
Bacteria that can be easily grown on the  
surface.

NOTE: Antimicrobial agents should be used  
when significant infection has been diagnosed  
Abx Nigeria strongly suspected.  
Peflix HOT 40 is established indication for

Emprophylactic therapy (i.e. for prevention)  
to reduce - disease transmission

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christened to RANTU NOT SAWO NO INFECTION

### EMPIRICAL THERAPY

This is recommended in clinical situations where the severity of infection is life-threatening and also in a situation whereby further delay in treatment may worsen or aggravate disease process, therefore a life-threatening disease condition, therapy must begin before infectious organism is identified.

In such cases, the choice of specific drug therapy is ~~advised~~ based on the clinical experience

suggesting that a particular therapeutic agent would be effective in a given condition and would not be effective in the other.

Generally, a broad spectrum anti-microbial agent is the most appropriate choice until the specific organism is identified in all cases. However, Specimen for Culture must be taken from the patient before therapy begins.

## Duration of Anti-microbial therapy

To achieve the therapeutic goal, anti-microbial agent must be continued in a specific duration usually 5 - 10 days, with full dosage therapy for acute or uncomplicated cases, or infections.

The treatment should be continued until the patient has shown sign of recovery and there is no sign of infection after at 72 hours (3 days) for chronic treatments of ~~infective~~ infections ~~for~~ example - Treatment of Endo-carditis, ~~noturni~~ ~~desmodermitis~~, require longer duration, lasting 4 - 6 weeks. ~~INFLAMMATION - INFLAMMATION~~

After the sixth week of treatment, there should be a follow up culture analysis to ascertain the therapeutic effectiveness.

Drug is changed if there is still sign of infection.

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## MICROBIAL RESISTANCE

An appreciation of microbial resistance is useful for understanding of their antimicrobial activity. Over used or under used of antimicrobial agent may lead to the development of resistance. The mechanisms of resistance includes :-

① Selection - This is a chromosome mediated process whereby a natural resistance bacteria may exist especially in the Hospital, the bacteria becomes sensitive to some anti-microbial agent and to others.

② Mutation - This is also a chromosome mediated mechanism whereby within bacterial or viral population, mutant strain of the organism resist to resist antimicrobial therapy.

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③ Transferred resistance - This maybe as a result of resistance transferred from one bacteria to another by exchange of genes. Such genes may be contained within bacteriophages like in case of viruses, which infect bacteria and transferred within the plasmids, the so-called r-factor ( $r = \text{resistant}$ ) (i.e. resistant factor) plasmid Confering or Containing the r-factor are transferred to other bacteria by Conjugation, an actual passage of the DNA material from one bacterium to a new DNA in another bacterium.

④ Enzyme Inactivation of antimicrobial agent -  
some of the bacteria can develop enzyme system  
that can destroy antimicrobial agent e.g. *Staphylococcus*  
may develop penicillinase which destroys Penicillin.  
) Altered Metabolic Pathway : For this type of  
mechanism, the usual pathway is altered by the  
bacterial, so that the alternative pathway may  
develop e.g. resistance to ~~benzene~~ <sup>bacterium</sup> bacterium  
and other Sulphonamides is due to the development  
of ~~alternating~~ alternative pathway for the  
synthesis of folic acid by the bacteria. The bac-  
terial no longer use para-amino benzoic Acid (PABA)  
(PABA) and therefore cannot be destroyed by the  
Sulphonamides.

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Specific Toxicity that are associated with anti-microbial agents/therapy.

### 1) Sulphonamides

They are insoluble in water and may precipitate in urinary tract that may cause formation of Crystals in the urine known as Crystal Urea, Bl. May occur in some individuals who has certain genetic enzyme deficiency e.g. Lack of Glucose 6 phospho dehydrogenase G-6-P-D

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### 2) Penicillin

They are among the most safe anti-microbial agent known, however, it can cause hypersensitivity reaction leading to anaphylactic condition. Some times this can be very serious, leading to death. Penicillin can also cause convulsion if given in high doses.

Among other drugs which can cause hypersensitivity reaction is Cephalosporin

### 3) Aminoglycosides

- Streptomycin - This causes ~~can~~ cranial nerve VII damage leading to hearing disturbance

and (non-acoustic) in the vestibular apparatus  
Vestibular apparatus is responsible for maintaining balanced movement and it is found in the ear.

Gentamycin - This also causes damage to renal tubules. They are very serious when given to people with renal impairment. It depends on renal excretion, and therefore should not be given to patient with renal impairment.

Tetracycline - They form complexes with calcium. It incorporates with calcium. Any tissue that have calcium will be incorporated e.g. the teeth and the bones, hence, tetracycline can cause decoloration of teeth if given during the time when permanent teeth are not developed.

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## SULPHONAMIDE SIDE EFFECTS

Sulphonamides ~~belong~~ belong to the group of anti-aminobenzoic acids (PABA).

Sulphonamides were discovered during the search for major bullet by Gerhard Domagk who was looking for the drug that will selectively harm

The bacteria but no adverse effect to the host.  
It was discovered that ~~penicill~~ was able to

prevent mice from dying after injected with Staphylococcus

~~Further work~~ Further work shows that Pronostac is not effective in-vitro but effective when given in-vivo. This led to the discovery that Pronostac is broken enzymatically in the body to produce Sulphonamide drug. Sulphonamide are effective against a wide range of organisms usually gram positive and gram negative cocci and bacila. It is effective against virus and fungi. It is effective against virus and fungi. It is important to NOTE that Sulphonamides are not antibiotics and they are bacteriostatic and ~~not~~ not bactericidal.  
~~It is important to note that~~

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## MECHANISM OF ACTION

Human beings and other animals do not synthesize folic acid but rather depends on ~~the~~ ~~for~~ exogenous or dietary intake of folic acid.

Para-amino benzoic acid is a precursor of folic acid synthesis and has ~~for~~ structural similarity with Sulphonamide.

Sulphonamide antagonizes and competes PABA from being incorporated to synthesis of folic acid. Sulphonamides are narrow spectrum - and sometimes can be combined with trimethoprim to form bacterium and Septin and this might be toxic to human.

i.e; Sulphonamide + Trimethoprim  $\Rightarrow$  Seplin & Bactrim  
This is because ~~of~~ ~~that~~ ~~is~~ inhibited by Trimethoprim ~~is~~ in human ~~of~~ animals.

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folic acid is used for the synthesis of purin and pyrimidine.

The pathway inhibited by Sulphonamide is not in human beings but the pathway inhibited by Trimethoprim is in both bacteria and human and as a result Trimethoprim is toxic in humans.

Trimethoprim inhibits Dihydrofolic acid reductase  
enzyme responsible for conversion of dihydrofolic acid  
to tetrahydrofolic acid.

Tetrahydrofolic acid is a building block for the synthesis  
of purine and pyrimidine and ultimately the synthesis  
of DNA

### INHIBITORS OF SULPHONAMIDES

(1) Para - amino Benzoic Acid (PABA) — It Competes with Sulphonamides to antagonize its action.

(i) Procaine — It's also a competitive antagonist of Sulphonamides action because of its structural similarity and same as PABA. Procaine is an ester of PABA, Pulse contains PABA, also bacteria requirement for folic acid is reduced in a medium containing purine.

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### CLASSES OF SULPHONAMIDES

(1) Short-acting Sulphonamide — This is general and Standard Sulpha-drug with which other Sulphonamides are compared : These are rapidly absorbed and rapidly excreted. It rapidly enters the cerebrospinal fluid (CSF) than others. Its half life is  $2\frac{1}{2}$  hours

Examples are :-

= Sulpha diazine

Sulphamerazine  
Sulphamethazine

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⇒ Intermediate Acting Sulphonamide : This has a half-life of 7 - 12 hours. They are rapidly absorbed, widely distributed, protein bound and hepatocally.

Examples include:-  
Sulphamerazine

⇒ Long-acting Sulphonamide : They are rapidly absorbed but excreted slowly. The half-life is 35 hours. E.g. includes :-

- Sulphamethoxypyridazine
- Pyrimethamin
- Bactrim
- Septrim

Adverse Reactions to Sulphonamides - This is

Partly due to allergy and partly due to toxicity.

The commonest side effects are of

- Fever

- Skin rash

- Photo sensitivity (MENT 3-4 NATURAL)

- Nausea & vomiting

- Diarrhoea

Others include:-

- Hepatitis ANYAMELE EMMANUEL

- Conjunctivitis

- ~~Hemos~~ Hematopoietic disturbance

- Agranulocytosis

- Thrombocytosis

Because Sulphonamides can precipitate at neutral pH and produce crystals, urinary tract obstruction can result and subsequent haematuria (blood in urine) & urinary tract infection

Prevention of Side Effects

- ① Giving the most soluble Sulphonamides
- ② It is also advisable to alkalinize urine, so, this can be achieved by the administration of bicarbonate such as Sodium Bicarbonate.

## ANTI-FUNGAL AGENTS

Human-human fungal infection has increased dramatically in incident and severely in recent times.

Fungal infections can be systemic e.g. duodenal candidiasis, vaginal candidiasis, etc. They can also be topical or fungal; such as Eczema, dermatophytosis, Miosis, Tinea

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Griseofulvin  $\Rightarrow$  Griseofulvin of Grisevin is a very insoluble fungistatic drugs derived or isolated from species of penicillium by Oxford & co-workers in 1949

### Anti-Fungal Activity

It is very effective against Vaikus Dermatophytes especially Tinea (ringworm) of the toe-nails and fingers. It is also effective against Micro-Sporum Epidermophyton and Tryptophyton.

## MECHANISM OF ACTION

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The mechanism of action at the cellular level is unclear but it is deposited in newly forming skin when it binds to keratin protecting the skin from new infections. Because the action is to protect the new skin structures from infections, Griseofulvin must be administered for 2 - 6 weeks for skin by hair infection to allow the replacement of the infected keratin.

Nail infections require therapy for months to allow regrowth of the protected nail. It is given orally. Absorption is variable because of its solubility. However, the absorption would be enhanced by fatty meals whereas barbiturates decreases absorption. It is excreted mostly as metabolites.

**ANSWER EMMANUEL**

### SIDE EFFECT

The common side effect associated with Griseofulvin include:-

- ① Nausea
- ② Photosensitivity
- ③ Vomiting
- ④ Rash
- ⑤ Porphyria
- ⑥ Hepatitis

## POLYENE ANTIFUNGAL AGENTS

### AMPHOTERICIN - B

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Although these are amphotericin A and B fungicidal antibiotics produced by streptomycetes woodleyi, amphotericin A is not in clinical use. Amphotericin B was isolated by Gold and co-workers in 1956.

Amphotericin-B is an amphoteric polyene macrolide (Many atoms) Polyene - many double bonds it is nearly insoluble in water, and therefore prepared as colidal suspension of amphotericin B and sodium deoxycholate for intravenous injection.

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#### ANTI-FUNGAL ACTIVITY

It is a systemic anti-fungal agent which is effective against candida species, cryptococcus neoformans, histoplasma, capsidatum, aspergillus and other systemic fungal infections.

## Mechanism of Action

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Amphotericin-B is selective in its fungicidal effect because it exploits the difference in lipid composition of fungal and mammalian cell membrane. It is its antifungal activity is dependent on its binding to a steroid moiety, cholesterol present in the membrane of sensitive fungal. This interaction results in the formation of pores (channels) giving rise to increased permeability in the membrane and thus allowing leakage of a variety of small molecules that are inside the cell.

Other mechanism of action includes :-

Oxidative damage to the fungal cell and has capability to enhance cell mediated immunity of the host.

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## PHARMACOKINETICS OF AMPHOTERICIN-B

Amphotericin-B is negatively absorbed from the GIT after oral administration and after intramuscular administration, thus it must be given intravenous administration for it to be effective. In the plasma, it is about 90% bound to protein.

and it penetrates poorly into body fluids and tissues.

## RESISTANCE

Resistance has been reported in some patients and the mutants of such enzymes has been seen to contain decreased concentration of ergosterol in their cell membrane. Others have been found to ~~not~~ contain increased concentration of precursors of ergosterol but with ~~lower~~ lower affinity to the drugs.

## ANTIMICROBIAL AGENTS

### SIDE-EFFECT

Amphotericin - B is a very toxic drug and thus given as prescribed by a doctor.

Side effects include

- ① Fever
- ② Vomiting
- ③ Anorexia
- ④ Nausea
- ⑤ Hypotension
- ⑥ Hypocalcemia
- ⑦ Nephrotoxicity and ototoxicity

## NYSTATIN

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It is one of the polyene antifungal antibiotics. It was discovered in New York States laboratory and named accordingly.

It is a tetracyclic macrolyde antibiotics produced by Streptomyces rosei. It has similar structure as amphotericin-B and Share similar mechanism of action, but more toxic and it's not used for parenteral administration. It is not absorbed to a significant degree from the skin, and remains mucous membrane, GIT or Vagina. It is useful against candidiasis. Oral use is often limited by the unpleasant taste. It is supplied in preparations intended for cutaneous, vaginal or oral administration and thus, available in form of cream, tablet, suspension and ointment.

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### Miscellaneous Antifungal agents

- ① Benzoic acid and Salicylic acid in the ratio of 2:1 to form the popular whitefield's ointment. The preparation combines the fungistatic action of the benzoic acid and the keratolytic action of Salicylic acid.

## PHARMACOLOGY (Continued)

### Miscellaneous Antifungal agents

It is used mainly in the treatment of tinea pedis, (tinea of the leg), also in the treatment of tinea capitis.

#### SIDE-EFFECTS

The common side effects include:-

- ① Mild Irritation

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#### DRUG NAME ERTHROMYCIN

- ② Propionic and Caprylic acid  
These are promoted in the treatment of ~~psoriasis~~ Dematositosis ~~but~~ but has low efficacy

#### Assignment

- Compare and contrast between Aminosulfonylides and tetracycline based on  
① Structure  
② Mechanism of action  
③ Side effects

## ANTI-MALARIALS

11, 2019 April, 2023

Human Malaria is caused by plasmodium species.  
This include:

- (i) Plasmodium falciparum
- (ii) Plasmodium vivax
- (iii) Plasmodium Malaria
- (iv) Plasmodium Ovale

Although all may cause significant illness but plasmodium falciparum is responsible for nearly all serious complications associated with Malaria infection and tests.

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### AIMS OF MALARIAL THERAPY

- (1) Causal prophylaxis: This is aimed at preventing infection after a mosquito bite (the infected ones). To achieve this, an adequate concentration of the drug must be in circulation to exert a lethal effect on the parasite during their Pre-Erythrocytic stages. Because man is a main reservoir of the infection, causal prophylaxis also prevent further infections of the parasite to another mosquito. To achieve causal prophylaxis, the drugs used are:-

## Chloroquine and Proguanil

(2) Suppressive Treatment: This is aimed at inhibiting the Erythrocytic stage of the developing parasite so that the infected person is free of clinical manifestation.

The drug for treatment includes

- Pyrimethamine

- Proguanil (Mefloquine)

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3) The Clinical Cure: This is aimed at preventing the acute attack of the parasite by eliminating Erythrocytic Schizogony of the parasite and manner, terminate the clinical attack.

Such agents are called "Schizonticide". Examples include:-

- Chloroquine
- Mefloquine

(4) Radical Cure: This is to completely eliminate the established infection in the body. This is done, not only by eradicating the erythrocytic stage but also the exo-erythrocytic

Stage, and this is done on people living in malaria region. Example of drugs used includes:-

- Primaquine

(5) Suppressive Cure : This is complete elimination of malaria parasite from the body by continual suppressive treatment. Example of drugs used includes :-  
- Rimeethamine, which is continued for about 10 weeks after leaving the malaria region.

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(6) Gameto Cidal ~~—etherapy~~: This is ~~for~~ ~~malaria~~ ~~the~~ ~~asexual~~ form of malaria parasite in human blood and thereby eliminating the reservoir on which the mosquito infections are developed. To achieve this, prompt and adequate treatment must be given... find out ~~eg~~ of Drugs used for Gametocidal T & White They are: Chloroquine

### Anti-Malaria Drugs

① 4 - Aminoquinolines: Its derivatives are;

- \* Choroquines

- oxy choroquine

- Hydroxy - Choroquine

- Amodiaquine

CHLOROQUINE  $\Rightarrow$  It is effective against the asexual

erythrocytic stage of the parasite. It also kills the

gamete cytic of *P. vivax*. It has no significant effect

on the exo-erythrocytic stage of plasmodium even in

high doses. It is therefore recommended for prophylaxis.

If controls parasitemia and other clinical symptoms

are abolished within 24 hours. It is a suppressive agent

for *P. vivax*. Chloroquine is well tolerated by many

patients and easy to administer. It is deposited in

large quantities in tissues. It is highly bound to

tissues and hence a loading dose is administered.

Chloroquine is slowly excreted from the body. The

excretion could be increased by acidification of the

urine. It undergoes metabolic degradation in the body

into desethyl chloroquine. Its mechanism of action is

not certain but is believed that it inhibits some

enzymes and also interacts with the DNA of the

parasites. ANYAMELE EMMANUEL

#### SIDE EFFECTS OF CHLOROQUINE

- Gastro - Intestinal tract (GIT) upset

- Itching (Pruritis)

- Cardiovascular problems: especially when given in large doses.

- Headache

- Visual Problems

- It may decolorize nail beds mucous membrane

### Cautions

- It should not be given in neurological disorders and GIT problems.

- It should also not be given in blood disorders.

### AMODIAQUINE $\Rightarrow$ It is used for over-malaria

attack but not used extensively as chloroquine.

It is more active than chloroquine in-vitro and also

more active when in-vivo than chloroquine against

Certain strengths (species) of *P. falciparum* and in

patients with insensitivity to chloroquine.

### ② 8 - Aminoquinolines

- Primaquine  $\Rightarrow$  It is effective against primary

exoerythrocytic stage of *P. vivax* & *P. falciparum*

With more active against *P. falciparum*. It also

exerts marked gametocidal effect against all forms

of plasmodia especially those of *P. falciparum*.

It is a drug of choice against plasmodia because it destroys the tissue forms of plasmodia.

It is well and readily absorbed from the GIT.

It is also rapidly metabolized in the body with very little amount excreted unchanged. Its mechanism of action is not well known but believed to bind the DNA just like chloroquine.

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#### SIDE EFFECTS

- GIT upset; which will be in form of abdominal cramp
- Mild anaemia, could be seen resulting from haemolysis of the blood.
- Leucocytosis (increase in WBC)
- Haemoglobinuria

### ③ Diamino Pyrimidine; Example is:

- Pyrimethamine
- Trimethoprim

These group of drugs are used for suppressive prophylaxis (treatment). They are all anti-metabolites, for e.g. Pyrimethamine interferes with the

Synthesis of folic-acid which is necessary for the

Synthesis of Purine & Pyrimetham Pyrimidine.

- Pyrimethamine is well absorbed following oral administration but is slowly excreted from the body. It is also excreted in the milk of nursing mothers.

### SIDE EFFECTS

It has no side effect when given in normal doses, but large doses result in ~~inflammation~~ ~~inflammation~~ ~~inflammation~~

- Convulsion
- Megaloblastic anaemia
- Bone-Marrow Depression and collapse

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(④) The Sulphonamides & Sulphones, Tetracycline

- Tetracycline has shown marked activity against tissue set schizonts of chloroquine resistant *P. falciparum*. Treatment takes a long time and could cause anti-bacterial resistance.