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"AN OVERVIEW OF ANTIFUNGALS' AGENT: CLASSIFICATION, MECHANISM OF ACION AND USES"

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ABSTRACT

Malaria is a potentially fatal parasitic illness caused by Plasmodium spp., transmitted by infected female Anopheles mosquitoes. Antimalarial medications are used to treat acute infections, chemoprophylaxis in targeted populations, eradicate latent hepatic parasites and limit transmission. Key classifications include quinolines, artemisinins, antifolates, hydroxynaphthoquinones and antimicrobials. These work by disrupting haem detoxification, causing reactive intermediate damage, inhibiting mitochondrial electron transport, interfering with folate metabolism and disrupting protein synthesis in the apicoplast. A variety of factors influence treatment options including parasite species, severity of illness, local resistance and patient specific factors. Combining antimalarials (ACT) is central to treatment of uncomplicated P falciparum. Severe malaria needs urgent parenteral treatment, usually with artesunate. Primaquine or tafenoquine can be used in suitable patients to prevent relapse. This review provides an overview of key antimalarials including their classifications, mechanisms, uses, side effects, resistance and new areas of research.

KEYWORDS: Antimalarial agents, Malaria, Plasmodium spp., Artemisinin, Chloroquine, Primaquine, Mechanism of Action, Drug Resistance, ACT.

1. INTRODUCTION

Malaria is caused by Plasmodium parasites. The most common species that infect humans include P falciparum, P vivax, P malariae, P ovale and P knowlesi. P falciparum is associated with severe illness. P vivax and P ovale have a latent stage in the liver causing relapse [1,2].

Once inside the liver the sporozoites reproduce causing merozoites to be released. These cause symptoms such as fever, chills and anaemia due to repeated cycles within the erythrocytes.

Severe malaria can lead to cerebral dysfunction, respiratory distress, metabolic issues and renal damage. Timely diagnosis and treatment are vital.

Antimalarial treatments have advanced from quinine and old quinolines to Artemisinin based treatment. There is a risk of resistance so treatment should be tailored to the species, severity, local resistance, pregnancy, age, comorbidities and co-medications [1,3].

2. SIMPLIFIED PLASMODIUM LIFE CYCLE

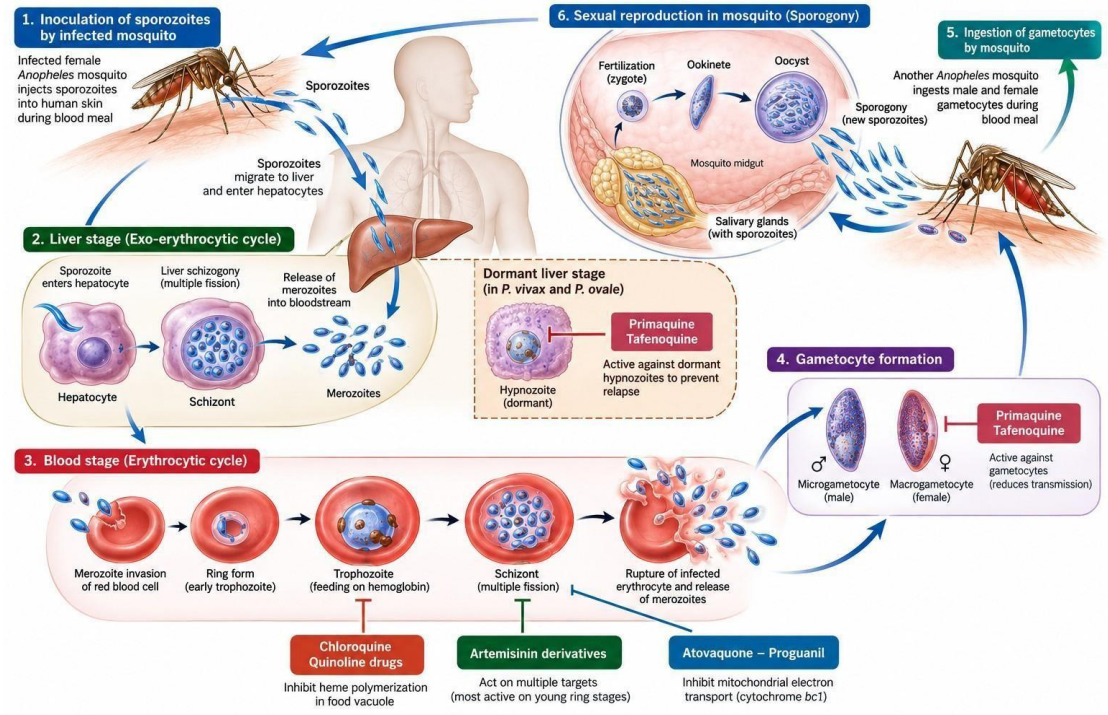
Vector Liver Stage Blood Stage Symptoms

Transmission

Sporozoites enter Reproduction Invasion of RBC Fever & chills

Gametocytes

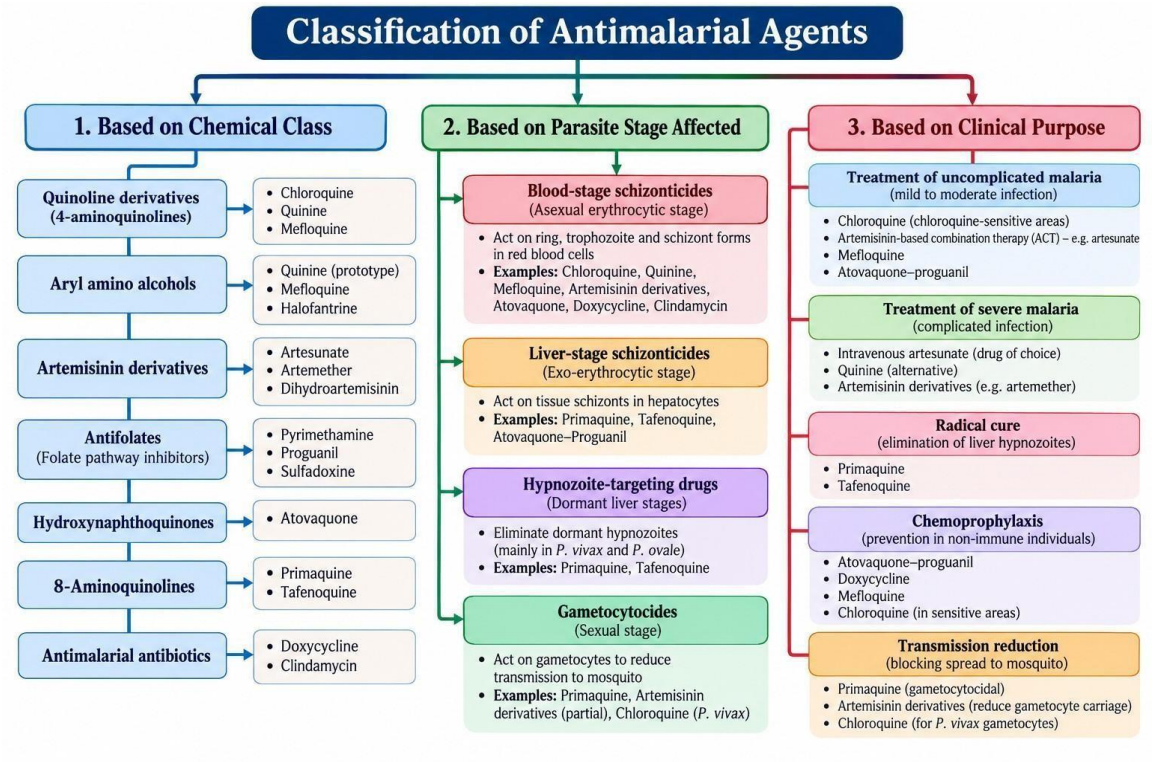
Simplified parasite life cycle



This explains why there are various treatments available. Blood stage treatments treat acute infection, whilst primaquine or tafenoquine can be used in suitable patients to treat the latent liver stage of P vivax or P ovale [1,3].

ANTIMALARIAL AGENTS: CLASSIFICATION, MECHANISM OF ACTION AND USES

3. CLASSIFICATIONS



There are many ways to categorise antimalarial agents. This can depend on the chemical make up, molecular target, use in practice and the stage of the parasite they act on. This can overlap:

Quinolines – chloroquine, amodiaquine, quinine, mefloquine, lumefantrine, primaquine, tafenoquine.

Artemisinins – artesunate, artemether, dihydroartemisinin.

Antifolates – pyrimethamine, proguanil, sulfadoxine/pyrimethamine.

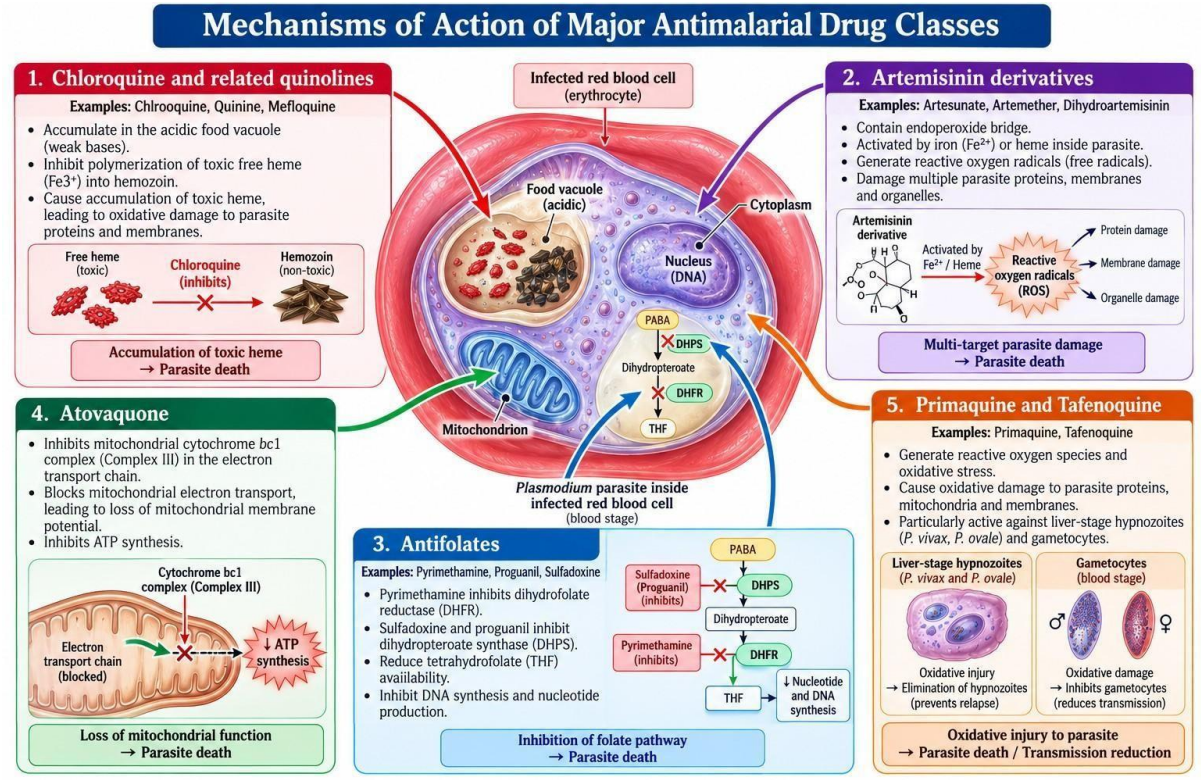
Hydroxynaphthoquinone – atovaquone (usually combined with proguanil).

Antimicrobials – doxycycline, tetracycline, clindamycin.

Combination therapy – artemether/lumefantrine, artesunate/amodiaquine, dihydroartemisinin/ piperaquine, atovaquone/proguanil.

4. MECHANISMS

Antimalarial drugs target key processes required for the parasite to survive. Below is a diagram showing key mechanisms of action and examples of drugs involved.



Target in parasite Drug

Effect

Key process

Disrupts/Damage Impairs growth

Haem detoxification, reactive damage, electron transport, folate, apicoplast. Different classes of drugs target different processes within the parasite.

4.1 Haem Detoxification – Chloroquine and quinine disrupt the processing of haem in sensitive parasites during the blood stage [4,5].

4.2 Artemisinin Damage – Artesunate, artemether, dihydroartemisinin have the endoperoxide bridge. Once activated reactive intermediates occur causing damage to various points in the parasite. Rapid reduction in parasite load means these are often combined with longer acting drugs [3,5].

4.3 Electron Transport – Atovaquone inhibits the cytochrome bc1 complex in the parasite to disrupt mitochondrial function [4].

4.4 Folate Metabolism – Pyrimethamine inhibit DHFR, sulfadoxine inhibits DHPS and proguanil (metabolised to cycloguanil) inhibits DHFR. This causes disruption in folate nucleotide synthesis [4,5].

4.5 Apicoplast – Doxycycline, tetracycline and clindamycin disrupt protein synthesis within the parasite and essential functions in the apicoplast. Due to the delayed onset these are often used in selective combinations or as prophylaxis [4].

5. KEY CLASSES AND USES

5.1 4-Aminoquinolines – Chloroquine and amodiaquine accumulate in the digestive vacuole causing disruption of haem detoxification. Chloroquine is only useful if there is resistance to the drug. Amodiaquine is used in combination with artesunate in recommended scenarios. Side effects can include itching and gastrointestinal symptoms. Prolonged exposure to chloroquine can lead to retinal toxicity.

5.2 8-Aminoquinolines – Primaquine and tafenoquine act on the latent liver stage of the parasite. They help prevent relapse in P vivax and P ovale. G6PD should be assessed as there can be haemolysis in deficiency. Pregnancy and other patient factors affect suitability [1,3].

5.3 Artemisinins – Artesunate, artemether and dihydroartemisinin. ACT is central to treatment of uncomplicated P falciparum. Parenteral artesunate is the recommended first line treatment for severe malaria. Oral treatment should be given with a full ACT once tolerated [1,3].

ANTIMALARIAL AGENTS: CLASSIFICATION, MECHANISM OF ACTION AND USES

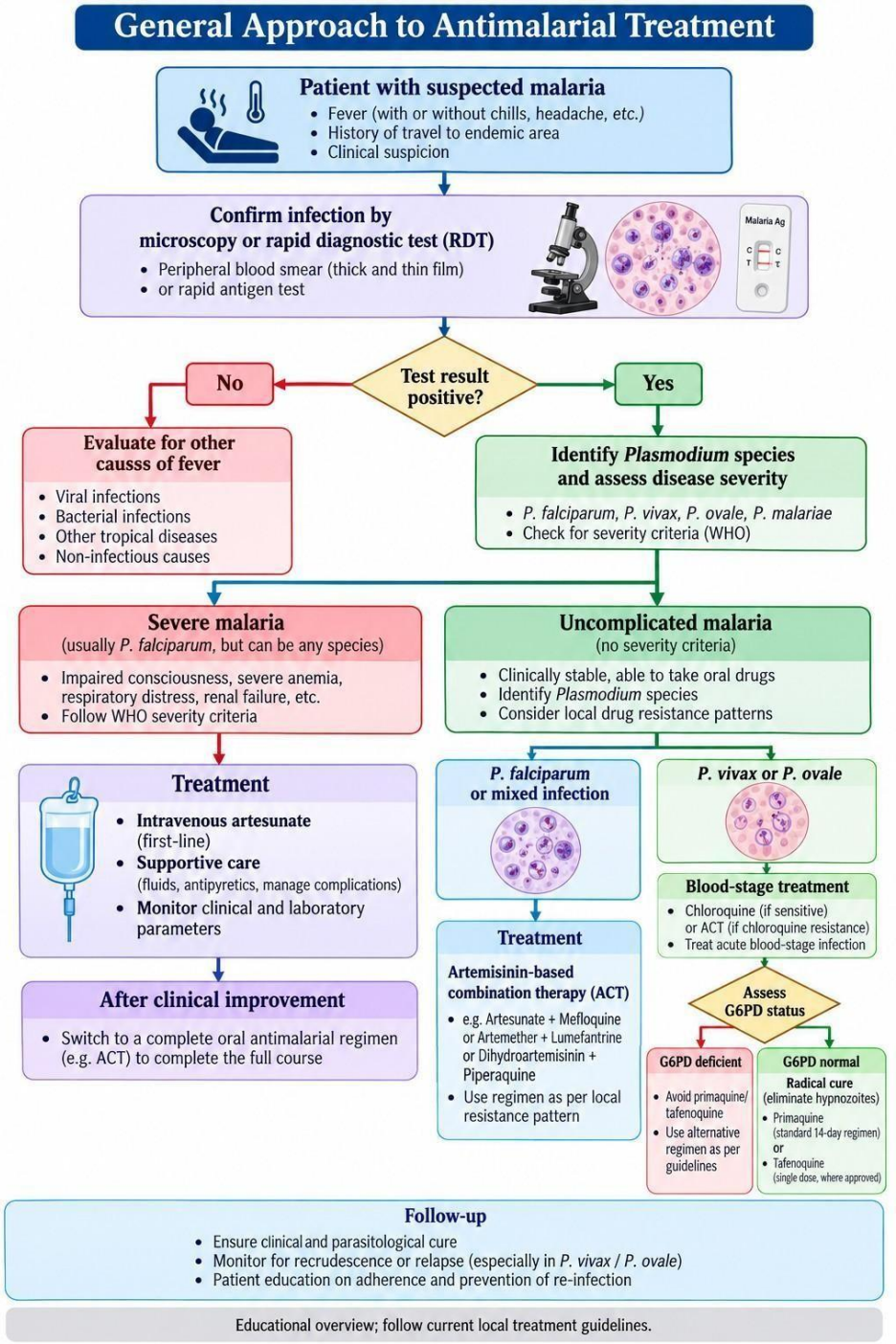
5.4 Quinoline Methanols – Quinine, mefloquine, lumefantrine, piperaquine. Act on the blood stage. Quinine can cause cinchonism and hypoglycaemia. Mefloquine can cause neuropsychiatrical effects. Used as part of combination therapy.

5.5 Antifolates – Pyrimethamine, proguanil and sulfadoxine/pyrimethamine. Disrupt folate metabolism. Sulfadoxine/pyrimethamine is used in selected preventative programmes depending on guidelines and resistance. Resistance and hypersensitivity are key limitations.

5.6 Atovaquone – Inhibits electron transport in mitochondria. Used in combination with proguanil in suitable populations. Consider gastrointestinal effects, contraindications and risk of resistance.

5.7 Antimicrobials – Doxycycline, tetracycline and clindamycin. Have antimalarial effects by affecting the apicoplast. Used in selective combinations or prophylaxis. Restrictions apply to certain ages, pregnancy and depending on clinical scenario.

6. CLINICAL MANAGEMENT PATHWAY



The diagram below shows a simplified example of how treatment may be managed. This is for educational purposes only and should not replace clinical assessment and national guidelines.

Uncomplicated Recommended ACT Malaria confirmed Assess severity

Monitor response

Test and identify species Uncomplicated / severe Full treatment / monitoring Severe malaria

Urgent IV/IM artesunate

This is a simplified example.

7. DRUG RESISTANCE

Resistance occurs when heritable changes in the parasite reduce susceptibility. This can cause delayed clearance, recrudescence and treatment failure. Chloroquine resistance occurs due to changes in drug transport and build up. DHFR and DHPS can have mutations reducing susceptibility to antifolates. Partial resistance to artemisinins has been seen in relevant P falciparum populations due to mutations in kelch13. Resistance to partner drugs can also cause issues with the effectiveness of ACT [5,6].

Exposure Selection Spread

Treatment pressure

Less susceptible parasites Resistance markers

Monitoring & ACT guidelines

Resistance can be influenced by parasite genetics, drug use and local transmission.

Resistance can vary depending on location and time. Accurate diagnosis, using recommended combination therapy, completing treatment and monitoring therapeutic efficacy will help ensure treatment is effective.

ANTIMALARIAL AGENTS: CLASSIFICATION, MECHANISM OF ACTION AND USES

8. SIDE EFFECTS AND PRECAUTIONS

Drug/Class Key Precautions

Chloroquine Itching, gastrointestinal effects. Retinal toxicity with prolonged exposure.

Primaquine/Tafenoquine Risk of haemolysis with G6PD deficiency. Assess suitability. Quinine Cinchonism, hypoglycaemia and cardiac effects in susceptible patients.

Mefloquine Neuropsychiatric effects. Specific contraindications.

Sulphadoxine/pyrimethamine Hypersensitivity. Can cause severe reactions. Atovaquone/proguanil Gastrointestinal effects. Consider contraindications and interactions. Doxycycline Photosensitivity and gastrointestinal irritation. Population specific restrictions.

Table 1: This table highlights some key side effects and precautions. This is not an exhaustive list.

When choosing a drug consider pregnancy, age, renal and liver function, G6PD status, cardiac risk, co-medications and local treatment guidelines. Individual treatment decisions should be made by qualified clinicians.

9. CHALLENGES AND NEW DEVELOPMENTS

Key challenges include drug resistance, species specific biology, toxicity, delayed diagnosis, lack of access to effective drugs and the need for new classes of drugs. New targets, long acting drugs, better

combinations, paediatric formulations and molecular monitoring are being researched. Promising compounds are still being investigated to ensure they have appropriate pharmacokinetics, toxicity and are effective in practice [4-6].

10. CONCLUSION

Antimalarial agents are important in the treatment and prevention of malaria. Effectiveness depends on the molecular target, stage of parasite, species and local resistance. ACT is central in the treatment of uncomplicated P falciparum. Urgent parenteral treatment is required for severe malaria. Primaquine or tafenoquine can be used in suitable patients to prevent relapse. Monitoring resistance, safe prescribing practices, accurate diagnosis and developing new drugs are important priorities.

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