Farmaci Antimalarici

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Malaria

Malaria is caused by a parasite called *Plasmodium*, which is transmitted via the bites of *infected* mosquitoes. In the human body, the parasites multiply in the liver, and then *infect* red blood cells.

Symptoms of malaria include fever, headache, and vomiting, and usually appear between 10 and 15 days after the mosquito bite. If not treated, malaria can quickly become life-threatening by disrupting the blood supply to vital organs. In many parts of the world, the parasites have *developed resistance* to a number of malaria medicines.

Key interventions to control malaria include: prompt and effective treatment with artemisinin-based combination therapies; use of insecticidal nets by people at risk; and indoor residual spraying with insecticide to control the vector mosquitoes.

More about malaria

**Highlight**

*From malaria control to malaria elimination*

A manual for elimination scenario planning

**General information**

*World Malaria Day 2014*

*World Health Day 2014: Protect yourself from vector-borne diseases*

*Fact sheet on malaria*

*Q&As on artemisinin resistance*

**Technical information**

*Diagnosis*

*Treatment*

*Vector control*

*Vaccines: malaria*
Trends in reported malaria incidence, 2000–2012

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
http://www.who.int/gho/malaria/en/

Cases

207 million
estimated cases in 2012
(range: 135-287 million)

Deaths

627 000
estimated deaths in 2012
(range: 473 000-789 000)

Elimination

20 of the 97
countries with ongoing malaria transmission are classified by WHO as being in either malaria pre-elimination or elimination phase
Protozoan Infections

PROTOZOA ARE TYPICAL PARASITES THAT OCCUPY HOST CELLS, MULTIPLY IN THEM, AND THEN DESTROY THEM

The most widespread protozoan infections caused by pathogenic protozoa are:

- MALARIA
- LEISHMANIASIS
- TRYPANOSOMA
- AMEBIASIS
- GIARDIA
- TOXOPLASMOSIS
- TRICHOMONA

Malaria: red blood cells with Plasmodium
Trypanosoma Protozoa in blood
Toxoplasma parasites
Protozoan Infections

All types of protozoa are single-cell organisms that:
• can adapt to various conditions
• are much more versatile than bacteria
• have a fairly complex life cycle

MANY FORMS

These forms require **different approaches** when treating patients that have protozoan infections
Protozoan Infections

PREVENTION STRATEGIES:

Restrict the spread of the disease
Improve sanitary/hygienic conditions

Vaccination campaign
Chemotherapeutic approach

Many strategies
Protozoan Infections: MALARIA

Malaria is the most widely spread of all the diseases caused by protozoa. The causative agents of malaria are plasmodia (Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae and Plasmodium ovale). Malaria is spread by mosquitoes, in particular by the bite of (female) Anopheles mosquito.

*Anopheles mosquito:* the **vector** of MALARIA

The life **cycle** of MALARIA parasites
Protozoan Infections: MALARIA

The life cycle of MALARIA parasites

ANOPHELES MOSQUITO

Zygote

Gametes

Sexual cycle

Gametocytes

Sporozoites

Tissue schizonts

Tissue Schizonticides

Schizonticides

BLOOD

Merozoites

Trophozoites

Asexual cycle

Malaria

HUMAN

LIVER
Protozoan Infections: MALARIA

Malaria is spread by mosquitoes, in particular by the bite of (female) Anopheles mosquito

Malarial plasmodia have two developmental cycles:
- asexual cycle, which takes in the body of an infected person (schizogony);
- sexual cycle, which takes place in the body of the mosquito (sporogony).

When a person is bit by a mosquito, sporocytes that were formed in the blood of the mosquito (from male and female hematocytes) enter the body. These enter liver cells, where they form primary tissue schizonts, which grow, divide, and transform into merozoites. Merozoites then enter the blood of the person and diffuse into erythrocytes, where they develop further. After maturing in erythrocytes, schizonts again divide and transform into merozoites. These merozoites are periodically released from the occupied erythrocyte cells and attack a new group of erythrocytes, starting the process over. This process lasts for 3–4 days. The moment when erythrocytes are destroyed and the merozoites enter the blood is expressed by an onset of malarial fever, which is referred to as the perierythrocytic form of malaria.

The life cycle of MALARIA parasites
Protozoan Infections: MALARIA

Malaria is spread by mosquitoes, in particular by the bite of (female) *Anopheles mosquito*

However, upon being infected by the plasmodia *P. vivax, P. malariae* and *P. ovale*, another pathway of development is possible, which is called the exoerythrocytic form of malaria. This is when parasites in the merozoite stage of development remain in or enter the liver cells again. This restarts the erythrocytic cycle of development of plasmodia and the onset of relapse. In tropical malaria, the paraerythrocytic forms are not present.

The life cycle of MALARIA parasites
Protozoan Infections: MALARIA

Malaria is spread by mosquitoes, in particular by the bite of (female) Anopheles mosquito

The life cycle of MALARIA parasites

<table>
<thead>
<tr>
<th>Species</th>
<th>Type of Tertian</th>
<th>Erythrocytic Cycle (h)</th>
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<tbody>
<tr>
<td>P. vivax</td>
<td>Benign tertian</td>
<td>48</td>
</tr>
<tr>
<td>P. malariae</td>
<td>Benign quartan</td>
<td>72</td>
</tr>
<tr>
<td>P. ovale</td>
<td>Benign tertian</td>
<td>48</td>
</tr>
<tr>
<td>P. falciparum</td>
<td>Malignant tertian</td>
<td>48</td>
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</tbody>
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Protozoan Infections: MALARIA

Malaria is spread by mosquitoes, in particular by the bite of (female) *Anopheles mosquito*

Severe events from malaria (*P. Falciparum*):
- Cerebral malaria / Coma
- Hypoglycemia
- Lactic acidosis
- Non-cardiogenic pulmonary edema
- Renal impairment
- Hematologic abnormalities
- Liver dysfunction

The life cycle of MALARIA parasites
Protozoan Infections: MALARIA

- Chemotherapeutic drugs:

  Antimalarial drugs to prevent or treat malaria:

  mefloquine, primaquine, chloroquine, pyrimethamine, amodiaquin, quinine, chloroguanide.

  **Chemotherapy of malaria consists of affecting various stages of the life cycle of the parasite.**

  Antimalarial drugs are subdivided into three corresponding groups:
  1. those that have an effect on erythrocyte stage of the life cycle → **Tissue Schizonticides**
  2. those that destroy exoerythrocytic (or hepatic stage) → **Schizonticides**
  3. those that affect both stages simultaneously

  Quinine → the oldest drug used against malaria.
Protozoan Infections: MALARIA

• Chemotherapeutic drugs:

Currently, aminoquinolines such as chloroquine and its analog (primarily for affecting the parasite during the erythrocyte stage), and primaquine (for affecting the parasite during the exoerythrocyte stage) are used to treat malaria.

Recently, mefloquine, and a natural compound quinghaosu (artemisin), as well as various antibiotics (i.e. Azithromicyn and Doxycycline) in combination with antimalarial drugs have begun to be used.

In treating resistant forms of malaria, tetracyclines are also used in combination with pyrimethamine, sulfonamides, sulfones, and dapsone.
First Anti-malarial drug

Cinchona Tree

- Stereogenic center
- R=H: Cinchonine, Cinchonidine
  - R=OCH3: Quinine, Quinidine

Antiarrhythmic agent
First Anti-malarial drug

Cinchona Tree

\[ R=OCH_3 \quad \text{Quinine} \]
\[ R=H \quad \text{Cinchonidine} \]
First Anti-malarial drug

Cinchona Tree

R=OCH₃ Quinidine
R=H Cinchonine
Protozoan Infections: MALARIA

Drugs effective against the erythrocyte stage of plasmodia infection

4-methanolquinolines

This group includes mefloquine, as well as cinchona alkaloids that are made from the bark of the cinchona tree, of which only quinine is still used for treating malaria.
Protozoan Infections: MALARIA

Drugs effective against the erythrocyte stage of plasmodia infection

4-Aminoquinolines

Chloroquine, amodiaquin, and hydroxychloroquine are synthetic compounds. Most important structural characteristic: the type of substituent at C7 and C4 of the quinoline ring.

- An amine substituent is necessary at C4 of the quinoline ring, which can vary while retaining antimalarial activity of the compound.
- The necessary conditions for expression of antimalarial activity is the presence of a chlorine atom at C7 of the quinoline ring. The prototype of this group of compounds is chloroquine.
Protozoan Infections: MALARIA

Drugs effective against the erythrocyte stage of plasmodia infection

**CHLOROQUINE**

7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline

Chloroquine is the drug of choice for preventing and treating acute forms of malaria caused by *P. vivax*, *P. malariae*, *P. ovale*, as well as sensitive forms of *P. falciparum*.

The mechanism of its action is not completely clear, although there are several hypotheses explaining its antimalarial activity:

Chloroquine and its analogs **inhibit synthesis of nucleic acids of the parasite by affecting the matrix function of DNA**. This happens by preliminary binding of the drug through hydrogen bonds with the purine fragments, and subsequent introduction of the chloroquine molecule between the orderly arranged base pairs into the spirals of the DNA of the parasite. Thus **chloroquine prevents transcription and translation**, which significantly limits the synthesis of DNA and RNA in the parasite. The **selective toxicity** of chloroquine in particular with respect to malarial plasmodia is also attributed to the **ability of the parasitized red blood cells to concentrate the drug in amounts approximately 25 times greater than in normal erythrocytes**.

There is also a different hypothesis. Chloroquine has a high affinity for tissues of the parasite and is concentrated in its cytoplasm. As a weak base, **it increases the pH of the intracellular lysosome and endosome**. A more acidic medium in these organelles is needed for the parasite to affect mammalian cells.
Protozoan Infections: MALARIA

Drugs effective against the erythrocyte stage of plasmodia infection

As a result, chloroquine inhibits growth and development of parasites. The main quality of chloroquine that exceeds all other antimalarial drug is its effect on erythrocytic schizonts (hematoschizotropic action).

However, chloroquine also possesses amebicidal action.

It has also been observed to have immunodepressive properties.

It is used for all types of malaria, for chemotherapy, as well as for non-gastric amebiasis, and amebic abscesses of the liver.

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Protozoan Infections: MALARIA

Drugs effective against the erythrocyte stage of plasmodia infection

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Protozoan Infections: MALARIA

Drugs effective against the exoerythrocyte stage of plasmodia infection

8-Aminoquinolines

Moving the side chain from the fourth position of the quinoline ring to the eighth position completely changes the compound’s spectrum of activity.

Primaquine

Unlike the 4-substituted aminoquinolines, primaquine has practically no effect on erythrocyte forms of the malaria parasite. Its activity is limited to tissue forms of the parasite in mammals and in the mosquitoes themselves.

This makes primaquine an especially valuable drug, allowing radical recovery and simultaneous prevention, which is usually not achieved by using erythrocyte drugs.

The place of action of primaquine is the mitochondria of the malarial parasite. It seems likely that primaquine interferes in the process of electron transfer, causing damage to mitochondrial enzymatic systems. This is expressed in the swelling and vacuolization of the parasite’s mitochondria. Host mitochondria are not affected.
Protozoan Infections: MALARIA

Drugs effective against the exoerythrocyte stage of plasmodia infection

8-Aminoquinolines

Primaquine is the most effective and most toxic drug from the whole series of known 8-aminoquinolines. It is generally used for treating exoerythrocyte forms of malaria caused by *P. vivax* and *P. ovale*. It also acts on the sexual forms of the plasmodia, which die in the human body upon using this drug. Primaquine is used for treating and preventing late relapses of 3- and 4-day malaria as well as tropic malaria.
Protozoan Infections: MALARIA

Drugs effective against the erythrocyte stage of plasmodia infection

**PRIMAQUINE**

8-[(4-amino-1-methylbutyryl)amino]-6-methoxyquinoline

![Chemical structures and reactions]
Protozoan Infections: MALARIA

Drugs effective against the erythrocyte stage of plasmodia infection

PRIMAQUINE

8-[(4-amino-1-methylbutyryl)amino]-6-methoxyquinoline

PRIMAQUINE
Protozoan Infections: MALARIA

Drugs effective against hepatic and erythrocyte forms of plasmodia infection

Biguanides and diaminopyrimidines turned out to be active compounds against both exoerythrocyte and erythrocyte forms of plasmodia. The structural similarity of these drugs with the pteridine fragment of folic acid undoubtedly determines their affinity with binding regions of dihydrofolate reductase. All of these compounds are inhibitors of dihydrofolate reductase in bacteria, plasmodia, and humans. Fortunately, they have a significantly high affinity for bacterial and protozoan dihydrofolate reductases.

Chloroguanidine was introduced into medical practice as an antimalarial drug as a result of work on a large series of guanidine derivatives. It is presumed that this compound transforms into an active dihydrotriazine compound in the body.

A while later, pyrimethamine was suggested as a result of intensive research of antimetabolites of folic acid. Trimethoprim is the result of later research. Pyrimethamine, for example, inhibits parasite dihydrofolate reductase at levels several hundred times lower than required to inhibit dihydrofolate reductase in humans. This is the basis of their selective toxicity. The selective toxicity can be increased upon supplying additional folic acid to the host organism, which the parasite cannot use. In fact, diaminopyrimidines (trimethoprim, pyrimethamine) were initially suggested as medicinal and preventative drugs against malarial infections. It was shown that all powerful inhibitors of dihydrofolate reductase can remove the malarial parasite with relatively minor consequences in the host. Biguanides and diaminopyrimidines can be used individually for prevention; however, the maximal effect is achieved when used in combination with sulfonamides. It has been shown that a few sulfones and sulfonamides may be of interest as drugs for treating malaria. Experimental research uncovered the pronounced synergism between sulfonamides and chloroguanide and pyrimethamine.
Protozoan Infections: MALARIA
Drugs effective against hepatic and erythrocyte forms of plasmodia infection

CHLORGUANIDE (Proguanil)
$N^1$-(4-chlorophenyl)-$N^5$-isopropylbiguanide

Chloroguanide is active with respect to exoerythrocyte and erythrocyte forms of plasmodia. It is most beneficial for suppressive therapy. It is used for preventing malaria, and it should be started 2 weeks before entering a malarial zone and should be taken for 8 weeks. To treat and prevent chloroquine resistance of malarial forms caused by $P. falciparum$ Mefloquine has been used.
Protozoan Infections: MALARIA

Drugs effective against hepatic and erythrocyte forms of plasmodia infection

**CHLORGUANIDE (PROGUANIL)**

\[ N^1-(4-\text{chlorophenyl})-N^5-\text{isopropylbiguanide} \]

**CHLORGUANIDE**

(Proguanil)

**CYCLOGUANIL**

pro-drug
Protozoan Infections: MALARIA
Drugs effective against hepatic and erythrocyte forms of plasmodia infection

![Pyrimethamine molecule]

**PYRIMETHAMINE**
2,4-diamino-5-\((4'\text{-chlorophenyl})\)-6-ethylpyrimidine

This powerful **inhibitor of dihydrofolate reductase** is used for preventing and treating malaria caused by plasmodia *P. vivax*, *P. malariae*, *P. ovale*, including *P. falciparum*. **Pyrimethamine, an antagonist of folic acid, exhibits antimicrobial action against causative agents of malaria and simultaneously possesses sporontocide action.**

It is also effective with respect to the causative agent of toxoplasmosis. It is used for preventing malaria and treating toxoplasmosis.

It can only be used for preventative measures; however, because resistance develops quickly and because of the fact that the maximal effect is achieved by using it in combination with sulfadoxine, a combined drug which is prescribed under the name fansidar, which contains a pyrimethamine–sulfadoxine ratio of 1:20. A combination of pyrimethamine, sulfonamide, and quinine is the drug of choice for acute attacks of malaria and its chloroquine-resistant forms. **Pyrimethamine in combination with sulfadiazine or trisulfapyrimidinide is the drug of choice for toxoplasmosis.**
Protozoan Infections: MALARIA
Drugs effective against hepatic and erythrocyte forms of plasmodia infection

PYRIMETHAMINE
2,4-diamino-5-(4'-chlorophenyl)-6-ethylpyrimididine
Protozoan Infections: MALARIA

Drugs effective against the erythrocyte stage of plasmodia infection

R = =O: Artemisinine
R = OCH₃: b-Artemether
R = OCH₂CH₃: b-Arteether
R = OCOCH₂CH₂COONa: a-Sodium Artesunate

- Sesquiterpene lactone
- Peroxide bridge

- The molecular targets of both artemisinin in Plasmodia and tumor cells are still under debate. In both cases there is strong evidence to suggest that the primary activator is an iron source, be it in the form of Fe²⁺, heme or both.
Protozoan Infections: MALARIA
ANTIMALARIAL DRUGS: PRINCIPAL SIDE-EFFECTS

Quinine:
• Cinconism (nausea, vomiting, tinnitus)
• Hemolytic anemia.

Chloroquine:
• Corneal Opacity

Primaquine:
• Hemolysis in patients with G6PD deficiency

Chlorguanide
• Nausea and diarrhoea