Malaria: the clinical basics

Cristin Weekley, BA, & D. Scott Smith, MD
Stanford University
February 2013

Prepared as part of an education project of the Global Health Education Consortium and collaborating partners
Learning Overview (Clinical)

1. What is malaria?
2. Malaria Parasites
3. Life Cycle
4. Transmission
5. Who is at Risk?
6. Symptoms
7. Diagnosis
8. Treatment

**IMPORTANT NOTE:** This module provides information about diagnosis and treatment that is current as of January 2013. However, treatments can vary widely depending on predominant vectors, drug resistance levels, patient conditions, drug availability, local practice norms, and of course, the advent of new treatments. You should always consult current treatment protocols and local authorities before providing treatment and not regard this module as a definitive treatment guide.
What is malaria?

• A disease caused by parasites transmitted to humans from infected female *Anopheles* mosquitoes

• The protozoan parasites of the genus *Plasmodium* infect the red blood cells (RBCs)

• Symptoms include fever, chills, and flu-like illness

• If left untreated, the development of severe complications can cause death

• Malaria is preventable and curable

Merozoites breaking out of RBCs.

Image source: http://www.biology.ccsu.edu/doan/ProjectHope/Malaria%20red.jpg
Malaria Parasite Species

• Parasites are inoculated into a human host
• By feeding female anopheline mosquitoes
• The species that infect humans worldwide:
  – *Plasmodium falciparum* (15%)
  – *Plasmodium vivax* (80%)
  – *Plasmodium ovale*
  – *Plasmodium malariae*
  – *Plasmodium knowlesi* (<1%)

Malaria Parasites Species

*Plasmodium falciparum*

- Almost entirely confined to tropics and subtropics
- Accounts for 15% of malaria infection
- Clinically and morphologically different from other malarias
  - Gametocytes are elongate/sausage-shaped
  - Schizogony usually does not take place in peripheral blood of falciparum malaria
  - *P. falciparum* attacks all stages of red blood cells

Image source: http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1000048
Malaria Parasites Species
*Plasmodium falciparum*

Source: http://www.map.ox.ac.uk/browse-resources/transmission-limits/Pf_limits/world/
Malaria Parasites Species

*Plasmodium vivax*

- ‘Vivax’ = vigorous (Latin)
- Accounts for 80% of malaria infection
- Predominant malaria parasite in the world
  - Only malarial parasite whose range extends into temperate regions
  - Seldom causes severe disease

Malaria Parasites Species
Distinguishing Characteristics

**P. falciparum**
- Cytoadherence
- Cerebral & placental pathology
- Infects RBCs of all ages
- Gametocytes develop late
- Anemia can be severe
- Deadliest form

**P. Vivax**
- No cytoadherence
- Infects reticulocytes (young RBCs)
- Gametocytes develop early
- Milder symptoms
- Most prevalent form
Malaria Parasites Species

*Plasmodium ovale*

- Only been known since 1922
- Widely distributed in tropical Africa, especially West African coast
- Main distinctive morphologic feature is **ovoid shape** of many of infected RBCs
- Other features:
  - Parasite not as ameboid as *P. vivax*
  - Nuclei in all stages are larger

Malaria Parasites Species

*Plasmodium malariae*

- Is rarer than *P. vivax* or *P. falciparum*
- Occurs primarily in subtropical and temperate areas where other malaria spp. are found
- Distinguishing characteristics:
  - Asexual cycle lasts 24 hours longer than other spp.
  - Infected cell is not enlarged

Malaria Parasites Species

*Plasmodium knowlesi*

- Primarily a primate malaria of Southeast Asia
- Current overall incidence of infection in humans is low, but is consistently misdiagnosed, which can be fatal
- Transmitted by *Anopheles leucosphyrus* mosquitoes


Distribution and prevalence of *knowlesi* malaria in Malaysia
Life Cycle Vocabulary

- **Trophozoite**: the feeding stage of a protozoan parasite (intracellular)

- **Schizogony**: the process of asexual reproduction in which the nucleus undergoes multiple divisions prior to cell division
Life Cycle Vocabulary

• **Merozoite**: a product of schizogony which can infect new host cells, where it can undergo another round of schizogony or become a gametocyte

• **Gametocyte**: A cell, derived from a merozoite, that can undergo development to a gamete
Life Cycle in Humans

Source: http://dpd.cdc.gov/dpdx/HTML/Malaria.htm
Notes on the Life Cycle in Humans

The malaria parasite life cycle involves two hosts. During a blood meal, a malaria-infected female Anopheles mosquito inoculates sporozoites into the human host (1). Sporozoites infect liver cells (2) and mature into schizonts (3), which rupture and release merozoites (4). (Of note, in *P. vivax* and *P. ovale* a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks, or even years later.) After this initial replication in the liver (exo-erythrocytic schizogony (A)), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony (B)). Merozoites infect red blood cells (5). The ring stage trophozoites mature into schizonts, which rupture releasing merozoites (6). Some parasites differentiate into sexual erythrocytic stages (gametocytes) (7). Blood stage parasites are responsible for the clinical manifestations of the disease.

The gametocytes, male (microgametocytes) and female (macrogametocytes), are ingested by an Anopheles mosquito during a blood meal (8). The parasites’ multiplication in the mosquito is known as the sporogonic cycle (C). While in the mosquito's stomach, the microgametes penetrate the macrogametes generating zygotes (9). The zygotes in turn become motile and elongated (ookinetes) (10) which invade the midgut wall of the mosquito where they develop into oocysts (11). The oocysts grow, rupture, and release sporozoites (12), which make their way to the mosquito's salivary glands. Inoculation of the sporozoites into a new human host perpetuates the malaria life cycle (1).

Source: http://dpd.cdc.gov/dpdx/HTML/Malaria.htm
Life Cycle – Asexual in Humans

1. Mosquito injects sporozoites (during blood meal)
2. Sporozoites invade liver cells specifically
3. Schizogony in the liver (6-15 days)
4-5. Merozoites from liver invade RBCs
6. Erythrocytic schizogony produces 4-36 merozoites that invade new RBCs
   (B. Repeat erythrocytic cycle)
7. Some merozoites differentiate into gametocytes and are ingested by mosquito…
8. Mosquito ingests gametocyte from human
9. Gametocytes mature to male and female gametes
10. Fertilization in 24 hours → motile ookinete
11. Burrows through midgut to encyst in the basal lamina as oocysts
12. Sporozoites emerge, migrate to the salivary glands
1. Sporozoites injected into host during blood meal → liver (30 min)
Each sporozoite that invades a liver cell produces 30,000-40,000 merozoites in 6 days.
Notes on the figure: Life Cycle of *Plasmodium falciparum*

Elements that are important for the pathogenesis of severe malaria are shown. Erythrocytes containing *P. falciparum* in mature intraerythrocytic stages (trophozoites and schizonts) adhere to vascular endothelium, thereby avoiding clearance by the spleen. High numbers of circulating parasites and elaboration of host and parasite factors in the vasculature of various organs lead to the manifestations of severe malaria.

Transmission – Within Humans

• After they are released into the blood, each merozoite invades a red blood cell, where it produces 8-24 daughter cells in 48 hours

• Daughter cells released into the blood and are ingested by a feeding mosquito

Source: http://www.cdc.gov/malaria/facts.htm
Image source: www.jhsph.edu/bin/n/v/22malaria.jpg

Male gametocyte of Plasmodium falciparum (yellow) surrounded by RBCs

After a single sporozoite (the parasite form inoculated by the female mosquito) of *P. falciparum* invades a liver cell, the parasite grows in 6 days and produces 30,000-40,000 daughter cells (merozoites) which are released into the blood when the liver cell ruptures. In the blood, after a single merozoite invades a red blood cell, the parasite grows in 48 hours and produces 8-24 daughter cells, which are released into the blood when the red blood cell ruptures.
Transmission

- Common means of transmission:
  - Bite of *Anopheles* mosquito
- Very unusual means of transmission:
  - Congenital malaria (from mother to infant)
  - Blood transfusion
  - Sharing intravenous needles
  - In non-endemic areas, can be transmitted by mosquitoes infected after biting infected immigrants/travelers

Transmission

- Even in tropical and subtropical areas, transmission will NOT occur:
  - At high altitudes (>2500m)
  - During cooler seasons in some areas
  - In deserts (excluding the oases)
  - In some islands in the Pacific Ocean, which have no local *Anopheles* species capable of transmitting malaria
  - In some countries where transmission has been interrupted through successful control
Who is at risk?

• Approx. half of world population at risk for malaria in 2012
• 104 countries and territories endemic for malaria in 2012
• Estimated 219 million cases annually
• 660,000 deaths from malaria each year

• 80% of malaria deaths occur in just 14 countries and 80% of cases occur in 17 countries

World Malaria Report 2012

- This Report is an excellent source of information and is frequently cited in this module
- In last 5 years: impressive increase in international funding for malaria prevention, control, and elimination
- Rapid expansion in distribution of life-saving commodities in sub-Saharan Africa
- Last decade: estimated 1.1 million malaria deaths averted
- Strategy: T-3: test, treat, track

Changes in malaria incidence and mortality

Approximately half of countries with ongoing malaria transmission are on track to meet the World Health Assembly (WHA) and RBM target: to achieve a 75% reduction in malaria cases by 2015, compared to levels in 2000. While 50 countries are on track to reach the target, progress in more than a third of countries cannot be assessed due to limitations in their reported data. Further progress towards international malaria targets depends on achieving substantial gains in the highest burden countries (36). Of 99 countries with ongoing malaria transmission, 58 submitted sufficiently complete and consistent data on malaria cases between 2000 and 2011 to enable an assessment of trends to be made. Based on these reported data, 50 countries, including 9 countries in the African Region, are on track to meet the WHA and RBM target to reduce malaria case incidence by 75% by 2015. A further 4 countries are projected to achieve reductions of between 50% and 75%. Malaria case incidence increased in 3 countries of the Region of the Americas (37). Of the 104 endemic countries in 2012, 79 countries are classified as being in the malaria control phase, 10 are in the pre-elimination phase, 10 are in elimination phase. Another 5 countries without ongoing transmission are classified in the prevention of re-introduction phase (38). There were an estimated 219 million cases of malaria (range 154–289 million) and 660,000 deaths (range 610,000–971,000) in 2010. The estimates for 2010 have been updated since they were first published in the World Malaria Report 2011 after a process of country consultation. Country level malaria estimates available for 2010 show that 80% of estimated malaria deaths occur in just 14 countries and approximately 80% of estimated cases occur in 17 countries. Together, the Democratic Republic of the Congo and Nigeria account for over 40% of the estimated total of malaria deaths globally. The Democratic Republic of the Congo, India and Nigeria account for 40% of estimated malaria cases (39). Malaria is strongly associated with poverty. Estimated malaria mortality rates are highest in countries with a lower GNI per capita. Countries with higher proportions of their population living in poverty (less than US$ 1.25 per person per day) have higher mortality rates from malaria. Within countries, parasite prevalence rates in children are highest among poorer populations and in rural areas (40). Progress in reducing malaria case incidence and mortality rates has been faster in countries with lower numbers of cases and deaths. Nonetheless, greater numbers of cases and deaths are estimated to have been averted between 2001 and 2010 in countries which had the highest malaria burdens in 2000. If the malaria incidence and mortality rates estimated for 2000 had remained unchanged over the decade, 274 million more cases and 1.1 million more deaths would have occurred between 2001 and 2010. The majority of cases averted (52%) and lives saved (58%) are in the 10 countries which had the highest estimated malaria burdens in 2000. Such estimations indicate that malaria programmes are having their greatest impact where the burden is highest (41). There are many inherent uncertainties in any approach to producing estimates of malaria case incidence and mortality, and in analyses based on these estimates. The global malaria community needs to increase its efforts to support malaria endemic countries in improving diagnostic testing, surveillance, vital registration, and routine health information systems, so that accurate information on malaria morbidity and mortality can be obtained.

Who is at risk?

A map of the estimated incidence of malaria per 1000 population in 2007

Who is at risk?

- Children under 5 years and non-breastfeeding infants
- Pregnant women
  - 3-fold increase in severe disease and mortality
  - Increased risk of miscarriage, stillbirth
  - May have markedly reduced parasitemia (placental sequestration)
- Malnourished
- HIV-infected individuals

Image source: http://www.who.int/malaria/pregnantwomenandinfants.html
Who is at risk?

• Level of prior exposure to malaria predicts severity of disease
  • In areas of low to medium transmission
    – All ages have risk
  • In areas of high transmission
    – Children have highest risk (<5 y/o)
    – Persons from low transmission areas at risk

Image source: http://www.cdc.gov/Features/WorldMalariaDay/
Who is at risk?

• During times of population movement (i.e., refugees or internally displaced persons (IDPs))
  – Those from low endemicity areas
    • No pre-existing immunity and more severe disease at all ages

IDP orphans from Banda Aceh, Indonesia

Image Source: IDP orphans from Banda Aceh, Indonesia, February 2005 (D. Scott Smith).
Who is at risk? 
Protective Factors

- Biological characteristics and behavior traits can influence risk of developing malaria
- Newborns are protected by maternal antibodies
  - Antibodies decrease with time, explaining the vulnerability in children who have stopped breastfeeding

Source: http://www.cdc.gov/malaria/distribution_epi/human_epidemiology.htm
Who is at risk?
Protective Factors

• Two protective genetic traits: sickle cell trait and absence of Duffy blood group
  – Both common in Sub-Saharan Africa

Distribution of Malaria

Distribution of Sickle Cell Gene

Notes: Two genetic traits present from birth have shown to be protective against malaria: the sickle cell trait (heterozygote for the abnormal hemoglobin gene HbS), and the absence of the Duffy blood group (negative persons have RBCs that are resistant to infection by *P. vivax*). Both traits are frequently found in Africa.
Signs and Symptoms

Central
- Headache

Systemic
- Fever

Muscular
- Fatigue
- Pain

Back
- Pain

Skin
- Chills
- Sweating

Respiratory
- Dry cough

Spleen
- Enlargement

Stomach
- Nausea
- Vomiting

Symptoms

- 7 to 30 days after an infective bite, symptoms appear.
- The blood stage parasites are what cause the symptoms of malaria.
- Infected patients are categorized as having either:
  - Uncomplicated malaria
  - Severe malaria

Symptoms
Uncomplicated Malaria

- Initial symptoms non-specific
  - Headache
  - Muscle aches
  - Nausea, vomiting
- Then malarial paroxysms begin
  - Shaking chill (10-15 min)
  - High fever (typically 10 h; up to 36 h)
  - Cycle repeats every 36-72 hours (species specific)
- Primary attack lasts 2-24 weeks (spp. specific)

Signs
Uncomplicated Malaria

- Fever
- Splenomegaly
- Hepatomegaly
- Anemia

Splenomegaly in a patient with malaria in Papua New Guinea

Image source: Courtesy of Dr. Robert Siegel, MD, PhD
Symptoms
Severe Malaria

• Clinical Manifestation:
  • Prostration
  • Impaired consciousness
  • Respiratory distress
  • Multiple convulsions
  • Abnormal bleeding
  • Jaundice
  • Pulmonary edema
  • Circulatory collapse

A young child with cerebral malaria, convulsing while in a coma

Image source: http://www.fic.nih.gov/about/images/2001statement_fig2.jpg
Symptoms Severe Malaria

• Is nearly always due to *P. falciparum* infection
• Complications can include:
  – Cerebral malaria (neurologic abnormalities), severe anemia due to hemolysis, pulmonary edema/acute respiratory distress syndrome, abnormalities in blood coagulation and thrombocytopenia, cardiovascular collapse, shock
• Most often occurs in persons with absent or decreased malaria immunity

Source: http://www.cdc.gov/malaria/disease.htm
Symptoms

• Infected individuals can also be asymptomatic
• Anti-malarial drugs taken for prophylaxis can delay the onset of symptoms by weeks or months
• In *P. vivax* and *P. ovale* infections, patients having recovered from the first illness may suffer additional, “relapse” attacks, after months or years without symptoms
• This is due to the reactivation of their dormant liver stage (hypnozoites)

Diagnosis

• There are two ways to diagnose malaria in humans:
  – *Clinical diagnosis* – based on clinical criteria (signs and symptoms)
    – Very low specificity; unreliable; inaccurate
  – *Parasitological diagnosis* – based on detection of parasites in the blood
    – Requires skill; time-consuming; laborious

Image source: Courtesy of Dr. Robert Siegel, MD, PhD (above, demonstrating splenomegaly); Courtesy of MENTOR-Initiative
Clinical Diagnosis

- Since signs and symptoms of malaria are nonspecific, it’s clinically diagnosed mostly on the basis of fever or history of fever

- Where malaria risk is low:
  - Diagnosis based on exposure to malaria and history of fever in previous 3 days

- Where malaria risk is high:
  - Diagnosis based on history of fever in previous 24h and/or presence of anemia

Conjunctival pallor in patient with severe anemia

Parasitological Diagnosis

• Two methods of parasitological diagnosis:
  – Light microscopy (blood smears)
  – Rapid diagnostic tests

Image Source: MENTOR-Initiative (light microscopy is used to diagnose malaria).
Malaria *Plasmodium falciparum* Rapid Diagnostic Test by Orchid; Photo for MENTOR-Initiative by D. Scott Smith
Parasitological Diagnosis
Light Microscopy

• Giemsa-stained blood smears
  – Thick: best used as screening procedure
    – Count 200 White Blood Cells (WBCs)
      – Parasitaemia = no. of parasites*8000/no. of WBCs
  – Thin: best for specific diagnosis
    – Infected RBCs/100 RBCs

Image source: WHO files, demonstrating a thin smear for malaria diagnosis.
Parasitological Diagnosis
Light Microscopy

• Blood smears allow identification of the infecting species
  – Important because treatment varies depending on *Plasmodium* species

Parasitological Diagnosis
Light Microscopy

- **P. falciparum**
  - Trophozoites (ring form) in a thin blood smear

- **P. Vivax**
  - Trophozoites in a thin blood smear

- **P. malariae**
  - Trophozoites (ring form) in a thin blood smear

- **P. ovale**
  - Trophozoites (ring form/developing) in a thin blood smear

Image Source: http://dpd.cdc.gov/dpdx/HTML/ImageLibrary/Malaria_il.htm
Parasitological Diagnosis
Rapid Diagnostic Tests

- Developed as a way to quickly identify malaria in the field
- Simpler to perform than microscopic methods
- However, RDTs show positive results up to 14 days after effective treatment of malaria because remnants of the parasite remain
  - Thus, do not use RDTs for follow-up of suspected treatment failures

Parasitological Diagnosis
Rapid Diagnostic Tests

• Offer sensitivity/specificity close to or above that of high-quality blood smear analysis in the hands of expert microscopists

• At parasite densities above 100 parasites/microliter of blood, RDTs can detect *P. falciparum* with a sensitivity of >90%

• This is generally higher than the sensitivity normally achieved with skilled microscopy
ParaCheck Pf

Malaria Plasmodium falciparum Rapid Diagnostic Test by Orchid; Photo for MENTOR-Initiative by D. Scott Smith
Demonstrates components of cassette for doing test. From Shoklo Malaria Research Unit
EXAMPLES of rapid Malaria diagnostics: Binax NOW, made in Scarborough, Maine and FDA approved in June 2007 (detects all 4 species). Visitect Malaria Pf (detects only *Plasmodium falciparum*)
Treatment

- Should commence as soon as possible
- The treatment depends on:
  - species of infecting parasite
  - area where the infection was acquired and its drug-resistance status
  - clinical status of the patient
  - any accompanying illness or condition, pregnancy, and drug allergies
Treatment

• Treatment should be based on laboratory-confirmed diagnosis where possible

• Different kinds of treatment:
  – Suppressive therapy (chemoprophylaxis)
  – Clinical cure
  – Radical cure

Notes:
• Suppressive therapy: attempts to destroy parasites as they enter bloodstream with small doses of drugs effective against erythrocytic stages
• Clinical cure: larger doses of drugs to eliminate large numbers of erythrocytic parasites present in a clinical attack
• Radical cure: implies elimination of not only bloodstream infection but also the tissues stages in liver as well; patient may still be infectious after this because of gametocytes remaining in circulation blood or hypnozoites in liver that aren’t killed by drugs

Treatment

• Determination of infecting species important because:
  – *P. falciparum* can cause rapidly progressive severe illness or death while other species rarely cause severe illness
  – *P. vivax* and *P. ovale* require treatment for hypnozoite forms that remain dormant in liver
  – *P. falciparum* and *P. vivax* have different drug resistance patterns in different regions
Treatment

• Most drugs used in treatment are active in the blood stage:
  – Chloroquine, sulfadoxine-pyrimethamine (Fansidar), mefloquine (Lariam), atovaquone-proguanil (Malarone), quinine, doxycycline, artemesin derivatives
  – Primaquine is active against the dormant liver stages

• WHO recommends artemesin-based combination therapy (ACT)

Treatment Notes

ACTs are recommended as the first-line treatment for malaria caused by *P. falciparum*, the most dangerous of the *Plasmodium* parasites that infect humans. By 2011, 79 countries and territories had adopted ACTs as first-line treatment for *P. falciparum* malaria. *P. vivax* malaria should be treated with chloroquine where it is effective, or an appropriate ACT in areas where *P. vivax* is resistant to chloroquine. Treatment of *P. vivax* should be combined with a 14-day course of primaquine to prevent relapse (27). From reports of manufacturers and the Affordable Medicines Facility-malaria (AMFm) initiative, the number of ACT treatment courses delivered to the public and private sectors globally increased from 11 million in 2005 to 76 million in 2006, and reached 278 million in 2011. The increases in ACT procurement in 2011 occurred in large part as a result of the AMFm initiative, managed by the Global Fund. Although the AMFm accounted for a substantial portion of public sector sales, the total amount of ACTs procured for the public sector showed a year-on-year decrease between 2010 and 2011 (28). It has been difficult to track the extent to which patients with confirmed malaria received antimalarial medicines because information linking diagnostic testing and treatment has been limited in both household surveys and routine health information systems. An estimate of the proportion of patients in the public sector potentially treated with ACTs (and not a less effective antimalarial) can be made by comparing the number of ACT treatments distributed by national programmes with the number of presumed (treated without testing) and confirmed (by microscopy or RDT) *P. falciparum* malaria cases reported (or estimated cases if reported data are lacking). This proportion varies by WHO Region, reaching 52% in the African Region in 2011 (29). In 12 countries in the African Region with household surveys during 2010–2011, the proportion of febrile children given antimalarial treatment who received ACTs was greater among children treated in the public sector and in the formal private sector than in the informal private sector or in the community. In some countries the proportion of all febrile children given antimalarials who receive ACTs remains low, which implies that a proportion of patients with malaria do not receive appropriate treatment (30). In the African Region in 2011, the total number of tests (both microscopy and RDTs) was less than half the number of ACTs distributed by national malaria control programmes, indicating that ACTs are given to many patients without confirmatory diagnostic testing.

Treatment – Drug Classifications

• **Blood Schizonticides**
  - may be used for suppression or treatment of an acute attack of malaria
  - Most have no effect on either the pre-(exo)erythrocytic stages of the parasites or gametocytes
  - Quinine (Quinidine)
  - Chloroquine (Aralen, Nivaquine)
  - Hydroxychloroquine (Plaquenil)
  - Amodiaquine (Camoquin)
  - Pyrimethamine (Daraprim)
  - Mefloquine (Lariam)
  - Tetracycline
  - Doxycycline
  - Halofantrine
  - Proguanil (Paludrine)
  - Artemisinine (Qinghaosu)

Treatment – Drug Classifications

- Tissue Schizonticides
  - Act as *causal prophylactics* by destroying developmental stages of parasite in the liver
  - Only *primaquine* is effective against tissue stages

Image Source: http://dpd.cdc.gov/dpdx/HTML/Malaria.htm
Treatment – Drug Classifications

- **Gametocyticides**
  - Chloroquine and amodiaquine are effective against gametocytes of *P. vivax*, *P. ovale*, and *P. malariae* but not mature gametocytes of *P. falciparum*
  - Primaquine works against all four spp.

- **Chloroquine**
- **Amodiaquine**
- **Primaquine**

Image Source: http://dpd.cdc.gov/dpdx/HTML/Malaria.htm
Notes:
Graphic title: “Transmission of Plasmodium falciparum and the effects of antimalarials.”

* indicates that parasites are sensitive to the drug unless otherwise stated. Positive and negative arrows indicate the effect of the drug, enhancement (+) and suppression (-), respectively, on the parasite stage or its development.
Schizonts are multinucleated stages of parasites that undergo mitotic division within host cells. Hepatic-stage schizonticides such as atovaquone-proguanil and primaquine kill malaria parasites during the brief period of initial active development within hepatocytes in the liver, and they act on the liver schizonts of all four species of organisms that cause human malaria. Only primaquine is able to kill quiescent hypnozoites (Plasmodium vivax and P. ovale only), thus preventing secondary attacks (relapses) of clinical malaria. As compared with other drugs, atovaquone-proguanil and primaquine each act at two separate points in the life cycle. Atovaquone-proguanil acts on hepatic schizonts during initial infection but does not act on hypnozoites, so it does not prevent late-onset relapses of P. vivax and P. ovale. Blood-stage schizonticides such as atovaquone-proguanil, doxycycline, mefloquine, and chloroquine interrupt schizogony within red cells, preventing clinical manifestations of malaria infection. Not all parasite life-cycle stages are shown in this figure.
Life Cycle of *Plasmodium falciparum*
Notes on Figure of the Life Cycle of Plasmodium falciparum

Elements that are important for the pathogenesis of severe malaria are shown. Erythrocytes containing P. falciparum in mature intraerythrocytic stages (trophozoites and schizonts) adhere to vascular endothelium, thereby avoiding clearance by the spleen. High numbers of circulating parasites and elaboration of host and parasite factors in the vasculature of various organs lead to the manifestations of severe malaria.

Drug Resistance

• Drug resistance has been confirmed in *P. falciparum* and *P. vivax*
• *P. falciparum* is usually completely resistant to chloroquine
• Resistance in *P. falciparum* has been documented with nearly all other drugs, though this is less widespread
• *P. vivax* resistant to chloroquine in SE Asia, India, and S. America

Source: http://www.cdc.gov/malaria/drug_resistance.htm
Summary (1)

• Malaria is a protozoan parasite with 5 species that affect humans
• Malaria transmission involves a mosquito vector of the *Anopheles* species
• Children under 5 years old and pregnant women are most at risk for malaria
• Sub-saharan Africa is the most affected region in the world, accounting for 90% of deaths from falciparum malaria.
Summary (2)

- Symptoms of malaria include fever, but later, coma and prostration are seen in severe malaria.
- Diagnosis is made by microscopy looking at blood smears, but also with Rapid Diagnostic Tests (RDTs).
- Treatment is critical in terms of timing, kind of drug and administration with respect to the specifics of the patient and the local resistance patterns.
- Understanding the biology and lifecycle of malaria lends insight into strategy for diagnosis, treatment and prevention (see previous module).
Liver stage: 6 – 14 days
Blood stage: 48 – 72 hrs
Incubation period: 21 days
Credits

• Cristin Weekley, BA Stanford University; MPH student at UC Berkeley School of Public Health

• D. Scott Smith, MD, MSc, DTM&H
  Chief of Infectious Disease & Geographic Medicine, Kaiser Permanente, Redwood City, California
  Adjunct Assistant Clinical Professor
  Dept. of Human Biology and
  Dept. of Medical Microbiology & Immunology
  Stanford University Medical School
  ssmith@stanford.edu
The Global Health Education Consortium and the Consortium of Universities for Global Health gratefully acknowledge the support provided for developing teaching modules from the:

*Margaret Kendrick Blodgett Foundation*
*The Josiah Macy, Jr. Foundation*
*Arnold P. Gold Foundation*

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 3.0 United States License.