MALARIA

MALARIA IS A PROTOZOAN DISEASE TRANSMITTED BY THE *ANOPHELES MOSQUITO*

IT IS ENDEMIC IN TROPICS AND SUBTROPICS → OUTSIDE OF AUSTRALIA, MEDITERRANEAN REGIONS AND THE USA

FIVE SPECIES → PLASMODIUM VIVAX, MALARIAE, OVALE, FALCIPARUM AND KNOWLESI (NEWEST ORGANISM)

500 MILLION DEVELOP MALARIA ANNUALLY WITH >1 MILLION DEATHS

MOSQUITO VECTOR IS BECOMING LESS SUSCEPTIBLE TO INSECTICIDES AND FALCIPARUM IS BECOMINE MORE RESISTANT TO ANTIMALARIAL MEDICATIONS

MORTALITY RATE OF SEVERE MALARIA IS ANYWHERE FROM 10% TO AS HIGH AS 50% IF UNTREATED

THE DIAGNOSIS OF MALARIA MUST BE CONSIDERED IN ANY PERSON RETURNING FROM THE TROPICS WITH AN UNEXPLAINED FEBRILE ILLNESS

EPIDEMIOLOGY:

- Certain species may predominate in a geographical location
  - P vivax most common in Indian subcontinent and central America
  - P falciparum most prevalent in Africa, Haiti and New Guinea
    - Chloroquine resistance among falciparum malaria continues to spread → use of pyrimethamine, quinine, mefloquine and doxycycline as well as artemesins required

Table 153-1 Geographic Distribution of Malaria, Including Resistant Strains

Geographic Region	Areas with Malaria	Countries with Chloroquine-Resistant *Plasmodium falciparum*
Central America	All countries	None
Caribbean	Dominican Republic and Haiti	None
South America		
Temperate	Argentina	None
Tropical	All countries	All countries except Paraguay
East Asia	China	China
Eastern South Asia	All countries except Brunei and Singapore	All infected areas
Middle South Asia	All countries	All countries
Western South Asia and Middle East	Iraq, Oman, Saudi Arabia, Syria, Turkey, and United Arab Emirates	All countries except Syria and Turkey
Northern Africa	All countries except Tunisia	None
Sub-Saharan Africa	All countries except Reunion and Seychelles	Widespread
Southern Africa	All countries except Lesotho and Saint Helena	Widespread
Oceania	Limited to Papua New Guinea, Solomon Islands, and Vanuatu (small foci elsewhere)	Widespread

PATHOPHYSIOLOGY:

- The organism is transmitted primarily by the bite of AN INFECTED FEMALE ANOPHELES MOSQUITO → sporozoites injected into bloodstream → liver, hepatic parenchymal cells invaded → thousands of MEROZOITES cause cell rupture → invade erythrocytes
    - In vivax and ovale infections, a portion of cells become dormant for up to months
- Eventually the erythrocytes LYSES and new merozoites are released to invade uninfected red cells → occurs at 2-3 day intervals and produces the classic periodicity of symptoms
    - The recurring febrile paroxysm of malaria corresponds to haemolysis of infected erythrocytes and release of antigenic products with activation of macrophages → haemolysis can be high with P falciparum infection because parasitaemia can be overwhelming and erythrocytes of all ages are susceptible
- Parasitized erythrocytes lose their flexibility and obstruct the microcirculation → TISSUE ANOXIA of lungs, kidneys, brain and other vital organs
    - Non-cardiac pulmonary oedema, renal failure and cerebral malaria may result

INCUBATION PERIOD:

- Ranges from 8 days to several weeks or more
- Incomplete suppression of disease bby partially active chemoprophylaxis and incomplete immunity can prolong incubation by months to even years
- For those with Falciparum → 80% cases manifest within one month, but only in 36% cases of vivax

CLINICAL FEATURES:

- PERIODIC FEVERS IS HALLMARK → prodrome of malaise, myalgia, headache and low-grade fevers often with chills
- In some → headache, chest pain, cough, abdominal pain, arthralgias or diarrhoea may be prominent → early manifestations easily confused with viral syndrome
- Illness usually progresses to high-grade fevers, orthostatic dizziness and extreme weakness → fever abates and patient develop diaphoresis → these paroxysm will eventually become regular
    - CLASSIC PAROXYSMS OFTEN LACKING IN MALARIA DUE TO FALCIPARUM OR IN PERSONS WHO RECEIVED SOME FORM OF CHEMOPROPHYLAXIS
- Most patients appear acutely ill with high fevers, tachycardia, tachypnoea → splenomegaly and abdominal tenderness are common in advanced disease
- Fever, malaria parasitaemia and coma/altered mental state are signs of cerebral malaria

COMPLICATIONS OF MALARIA INFECTION:

- CAN OCCUR RAPIDLY IN UNTREATED INFECTION → especially with falciparum

- ANY SPECIES OF PLASMODIUM CAN RESULT IN:
    - Haemolysis
    - Splenic enlargement and even rupture
- Immune-mediated glomerulonephritis is also common but tends to occur with P. malariae
- With ability to cause high parasitaemia levels and sequestration with capillary sludging → falciparum can be fatal
- Cerebral malaria is characterised by coma, delirium and seizures → mortality over 20% → LP indicated to exclude bacterial meningitis or encephalitis
    - CSF is usually normal in cerebral malaria, except for a slightly elevated opening pressure and protein concentrations → perhaps mild pleocytosis
- Other acute life-threatening complications associated with falciparum malaria:
    - Noncardiogenic APO (similar to ARDS)
    - Renal failure (ATN)
    - Severe metabolic anomalies → lactic acidosis and profound hypoglycaemia
    - ANY TARGET ORGAN IS SUSCEPTIBLE TO AFFECTS OF SEVERE TISSUE HYPOXIA due to cytoadherence of parasitised erythrocyte
- The very young, the elderly and pregnant women are at greatest risk for complications of falciparum

DIAGNOSIS:

- Diagnosis rests on high index of suspicion and a well-prepared thick blood smear → result is recorded as the number of parasites seen per high power field
    - Outside of falciparum malaria, the other malarias usually cause much lower parasitaemias, hence a long and careful search for parasites is mandated
- Parasitaemia fluctuates over time → hence in highly suspicious cases, failure to detect parasites is NOT AN INDICATION TO WITHOLD THERAPY
    - First smear is positive in >90% cases → but if negative obtain repeat smears at least twice daily for 2-3 days to exclude it
    - Repeat smears also indicated to assess response to treatment
- Lab findings:
    - Normocytic, normochromic anaemia with findings suggestive of haemolysis (leukopenia, thrombocytopaenia, ↑ESR, ↑LDH with mild anomalies of liver and renal function

TREATMENT:

- Treatment based on severity of the illness, the agent and whether the patient may be infected with chloroquine resistant organisms
- COMBINATION THERAPY IS STANDARD
- Initial resuscitation may require oxygen for hypoxia, intubation for severe respiratory distress or septic shock
    - IV fluids for insensible losses or vomiting
    - IV glucose for hypoglycaemia

- DO NOT DELAY TREATEMTN WHILE AWAITING LABORATORY CONFIRMATION
- SEE BELOW FOR THERAPEUTIC GUIDELINES FOR TREATMENT

Uncomplicated *Plasmodium falciparum* malaria

Artemether+lumefantrine is the drug of first choice for the treatment of uncomplicated *Plasmodium falciparum* malaria. Initial treatment in hospital is recommended. Use:

1 **artemether+lumefantrine tablets 20+120 mg**
adult and child more than 34 kg: 4 tablets (child 5 to 14 kg: 1 tablet; 15 to 24 kg: 2 tablets; 25 to 34 kg: 3 tablets) orally with fatty food or full-fat milk, at 0, 8, 24, 36, 48 and 60 hours, making a total adult dose of 24 tablets in 6 doses

OR

2 **atovaquone+proguanil tablets 250+100 mg (adult formulation)**
adult and child more than 40 kg: 4 tablets (child 11 to 20 kg: 1 tablet; 21 to 30 kg: 2 tablets; 31 to 40 kg: 3 tablets) orally with fatty food or full-fat milk, daily for 3 days

OR THE COMBINATION OF

3 **quinine sulfate 600 mg (adult less than 50 kg: 450 mg) (child: 10 mg/kg up to 600 mg) orally, 8-hourly for 7 days [Note 1]**

PLUS EITHER

doxycycline 100 mg (child more than 8 years: 2.5 mg/kg up to 100 mg) orally, 12-hourly for 7 days, which need not commence on day 1

OR (for pregnant females or children)

clindamycin 300 mg (child: 5 mg/kg up to 300 mg) orally, 8-hourly for 7 days.

⚠ **Atovaquone+proguanil should not be used for treatment of malaria in patients who took these drugs as prophylaxis.**

NOTE CLINDAMICIN CAN BE USED AS AN ALTERNATIVE TO DOXYCYCLINE

Severe malaria

Urgent treatment of severe malaria is essential if the patient has any of the following:

- any degree of altered consciousness, jaundice, oliguria, severe anaemia or hypoglycaemia
- a parasite count above 100 000/mm^3 (greater than 2% of red blood cells parasitised)
- the patient is vomiting or clinically acidotic.

Chloroquine-resistant *Plasmodium falciparum* must be assumed to be the infective agent. Once mandatory IV therapy has been started, seek expert advice. A large multicentre randomised controlled trial has shown mortality in severe *P. falciparum* malaria is lower when IV artesunate [Note 2] is used rather than IV quinine [Note 3]. Artesunate should be used in preference to IV quinine only if it is immediately available. Use:

1 **artesunate (adult and child) 2.4 mg/kg IV, on admission and repeat at 12 hours and 24 hours, then once daily until oral therapy is possible. When patient is able to tolerate oral therapy, give a full course (6 doses) of artemether+lumefantrine, as for uncomplicated *Plasmodium falciparum* malaria**

OR (if parenteral artesunate is not immediately available)

2 **quinine dihydrochloride IV, as outlined below.**

NOTE ABOVE THAT IV ARTESUNATE IS PREFERRED AS IT WAS SHOWN TO DECREASE MORTALITY COMPARED TO IV QUININE

ALSO → ASSUME CHLOROQUINE RESISTANCE IN SEVERE CASES (ALTERED CONSCIOUSNESS, JAUNDICE, SEVERE ANAEMIA, HYPOGLYCAEMIA, PARASITE COUNT >100,000, VOMITING OR ACIDOTIC)

If quinine is used, an initial loading dose should be given unless the patient has received 3 or more doses of quinine or quinidine in the previous 48 hours, or mefloquine prophylaxis in the previous 24 hours, or a mefloquine treatment dose within the previous 3 days. Frequent measurements of blood pressure and blood glucose are required as quinine stimulates insulin secretion and can cause hypoglycaemia. Cardiac monitoring is advised if there is pre-existing heart disease.

For loading dose, use:

1 **quinine dihydrochloride (adult and child) 20 mg/kg IV over 4 hours**

OR

2 **quinine dihydrochloride (adult and child) 7 mg/kg IV over 30 minutes, followed immediately by 10 mg/kg IV over 4 hours.**

For maintenance dose, use:

quinine dihydrochloride (adult and child) 10 mg/kg IV over 4 hours, 8-hourly, commencing 4 hours after loading regimen is completed and continuing until the patient is able to begin oral treatment (see below).

If IV quinine is required for longer than 48 hours, seek expert advice as a dose adjustment may be necessary especially in patients with renal impairment (see Table 2.31).

When the patient has clinically improved, oral treatment can be commenced. Give a full course (6 doses) of artemether+lumefantrine, as for uncomplicated *Plasmodium falciparum* malaria. If artemether+lumefantrine is not available, use oral quinine combined with doxycycline or clindamycin, as for uncomplicated *Plasmodium falciparum* malaria, to complete a total of 7 days of treatment with quinine.

Other forms of malaria

For *Plasmodium vivax* acquired **outside** Indonesia, Timor-Leste or Pacific Island Nations (including Papua New Guinea, Solomon Islands and Vanuatu), and for *Plasmodium malariae* and *Plasmodium ovale*, use:

chloroquine 620 mg base (= 4 tablets of chloroquine phosphate 250 mg) (child: 10 mg base/kg up to 620 mg base) orally, initially, then 310 mg base (= 2 tablets) (child: 5 mg base/kg up to 310 mg base) 6 hours later and on days 2 and 3, making a total adult dose of 10 tablets [Note 4].

For *Plasmodium vivax* acquired **in** Indonesia, Timor-Leste or Pacific Island Nations (including Papua New Guinea, Solomon Islands and Vanuatu), and for less severe *Plasmodium knowlesi* [Note 5], use:

1 **artemether+lumefantrine, as for uncomplicated *Plasmodium falciparum* malaria**

OR

2 **mefloquine 750 mg (child: 15 mg/kg up to 750 mg) orally, initially, then 500 mg (child: 10 mg/kg up to 500 mg) 6 to 8 hours later.**

⚠ **Mefloquine should not be used for treatment of malaria in patients who took this as prophylaxis.**

For severe *P. knowlesi* malaria, treat as for severe malaria.

If the patient is unable to tolerate oral therapy, which is best taken with food, treat as for severe malaria and seek expert advice.

To eliminate liver forms of all *P. vivax* infections, irrespective of where acquired, **add**:

primaquine 30 mg (child: 0.5 mg/kg up to 30 mg) orally, daily with food, or if nausea occurs 15 mg (child: 0.25 mg/kg up to 15 mg) orally, 12-hourly with food. Treat for a minimum of 14 days or, in adults more than 70 kg, until a total cumulative dose of 6 mg/kg is reached [Note 6].

To eliminate liver forms of *P. ovale* infections, **add**:

primaquine 15 mg (child: 0.25 mg/kg up to 15 mg) orally, daily with food for 14 days.

If the patient relapses after the primaquine treatment, seek expert advice.

Exclude glucose-6-phosphate dehydrogenase (G6PD) deficiency before using primaquine, as severe haemolysis may occur in these patients. If the patient is G6PD deficient, seek expert advice.

NOTE ABOVE THAT FOR SEVERE PLASMODIUM KNOWLESI INFECTION, TREAT AS FOR SEVERE MALARIA (SEE ABOVE)

ATOVAQUONE-PROGUANIL (MALARONE) IS HIGHLY EFFECTIVE, WITH CURE RATES OF 90% → DO NOT USE AS TREATMENT IF THIS HAS BEEN USED AS CHEMOPROPHYLAXIS

SIX DOSES OF ARTEMETHER/LUMEFANTRINE (COARTEM) OVER THREE DAYS HAS CURE RATES OF >95%

MEFLOQUINE IS GENERALLY EFFECTIVE AGAINST CHLOROQUINE-RESISTANT FALCIPARUM MALARIA

CHLOROQUINE IS THE DRUG OF CHOICE FOR TREATMENT OF INFECTION DUE TO P VIVAX, OVALE AND MALARIAE → parasite loads should decrease significantly in first 24-48 hours

TREATMENT COMPLICATIONS:

- Commonly encountered adverse effects summarised below:

Table 153-7 Adverse Effects, Precautions, and Contraindications of Antimalarial Drugs

Drug	Minor Toxicity	Major Toxicity	Precautions/Contraindications
Chloroquine	Nausea/vomiting, diarrhea, pruritus, postural hypotension, rash, fever, headache, dizziness	Rare; hypotension and shock after parenteral therapy	Avoid in patients with severe psoriasis and some types of porphyria, caution with decreased liver function.
		Retinopathy after prolonged use	
Quinine or quinidine	Cinchonism (nausea and vomiting, headache, tinnitus, dizziness, visual disturbance)	Hypotension, cardiac dysrhythmias, hypoglycemia, Coombs-positive hemolysis, abortions, neuromuscular paralysis (myasthenia)	Contraindicated in cardiac disease.
			Caution in pregnancy, myasthenia gravis.
Mefloquine	Nausea/vomiting, cramps, diarrhea, anorexia, dizziness, headaches, nightmares, and bradycardia	Rare unless underlying heart disease with bradycardia or the patient is on selected cardiotoxic medications (dysrhythmias, arrest); acute toxic confusional states may occur, as can seizures	Precaution during pregnancy and in children weighing <10 kg.
			Avoid if the patient is receiving quinidine.
			Avoid if the patient has heart conduction disturbance or if underlying seizure or major neuropsychiatric disorders.
Doxycycline	GI disturbances, phototoxicity, vaginal candidiasis	Rare; esophageal ulcerations if not taken with fluids	Contraindicated during pregnancy, in children <8 y of age.
			May depress prothrombin time in patients receiving anticoagulants.
Artemether-lumefantrine (Coartem®)	Headache, dizziness, anorexia, and asthenia	Rare; severe skin rash, QT prolongation	Avoidance with other drugs that may prolong QT interval.
			Drug interactions with CYP 3A4 and CYP 2D6.
Atovaquone-proguanil (Malarone®)	Nausea, vomiting, cramps, oral ulcers, headaches, dizziness	Rare serious allergic reactions and alopecia reported.	Contraindicated in pregnancy and in children <5 kg (no safety data) and in patients with creatinine clearance <30.
Primaquine*	Nausea, vomiting, diarrhea, cramps, methemoglobulinemia	Massive hemolysis in patients with G6PD deficiency	Contraindicated in G6PD deficiency, pregnancy.
		Exacerbation of systemic lupus erythematosus or rheumatoid arthritis	

- Supportive care is critical for patients with complications and includes close haemodynamic monitoring, fluid replacement, correction of metabolic abnormalities and additional support as needed → dialysis, mechanical ventilation
- EXCHANGE TRANSFUSION has been life-saving in some patients with parasitaemia in excess of 10%
- GLUCOCORTICOIDS ARE OF **NO BENEFIT IN CEREBRAL MALARIA** → and should not be used
- Quinine and quinidine are potent inducers of insulin release and may cause severe hypoglycaemia