MALARIA & TRAVEL MEDICINE

435 medicine teamwork

[Important | Notes | Extra | Editing file]

lecture objectives:

- Epidemiology and etiology of malaria.
- Clinical presentation.
- Risks to travelers.
- Malaria and pregnancy.
- Diagnostic work up.
- Treatment and prophylaxis.

Done By: Fahad AlAbdullatif - Malak Alshareef - Rana Albarrak

Edited by: Rahaf Binabbad

Revised By: Luluh Alzeghayer

References: Slides - Kumar - Step up

Malaria

Malaria is a protozoal infection caused by a few plasmodium species that spread by mosquito, once it enters the bloodstream it infects and destroys mainly **liver cells** and **RBCs** causes a variety of symptoms.

Epidemiology:

- Endemic disease.
- Usually does not occur at altitudes above 1500 m).
- World wide ease of travel.
- Most important parasitic disease of humans.
- Transmitted in over 100 countries.
- Affecting more than 3 billion people world wide.
- Causing 1-2 billion deaths per year.
- Prevalent in Tropical Climates, Parts of Africa and Middle East. cannot live in very cold areas
- **Transmitted Via female Mosquito Bite**.

Etiology:

4 Plasmodia (species)**:**

- **Plasmodium Falciparum.** The most serious & dangerous one & the dominant sp. in KSA
- Plasmodium Vivax.
- Plasmodium Ovale.
- Plasmodium Malariae.

Pathogenesis:

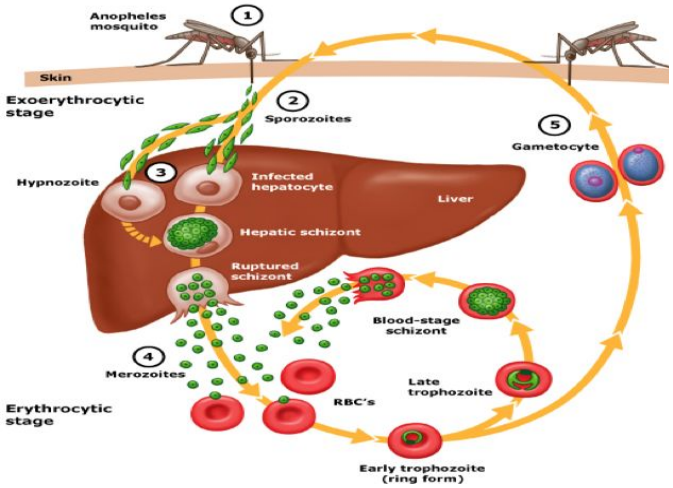
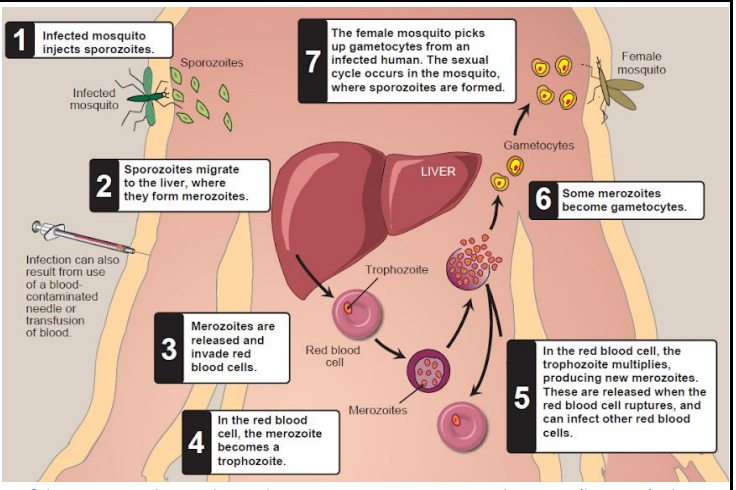
- RBCs invasion:
  1. Plasmodium Falciparum > Invades RBC of **All** Ages.
  2. Plasmodium Vivax > Invades Only **young** RBC's.
  3. Plasmodium Ovale > Invades **Young** RBC's.
  4. Plasmodium Malariae > Invades **Old** RBC's.
- **Microvascular pathology: secondary Ischemia & Adherence of Non-deformable parasitized RBC to endothelium.** مهم جدًا والسبب خلف مضاعفات الملاريا.
  - normal RBCs can be squeezed through small vessels whereas RBCs that are filled with parasites become rigid & cannot be squeezed → causing occlusion of vessels & ischemia.
- Renal failure: hemolysis, Ischemia secondary to microvascular pathology.
- Deep Coma: hypoglycemia, microvascular adherent parasitized RBC.
- Pulmonary edema: secondary to capillary leak Syndrome (without congestive cardiac failure) As deformed infected RBCs congest and block pulmonary vasculature (Microvascular pathology) → leading to capillary leak → Pulmonary Edema
- Immune-Complex Nephrotic Syndrome: secondary to **P. Malariae**
- Splenomegaly: typically resolves 6-12 months after treatment with anti-malarial meds.
- Splenic Rupture: late splenic rupture with trauma 1-3 months after initial infection. associated with **P. Vivax.**

Incubation Period and Life Cycle

- Sporozoites reach the liver within 1-2 hours following female Anopheles mosquito bite.
- Pt. asymptomatic for 12-35 days until RBCs stage of parasite life cycle.

Life cycle of malaria:

1. Infected female Anopheles mosquito feeding on human → giving him **Sporozoites (infective stage)**
2. In the bloodstream **Sporozoites** go to the LIVER --> living inside hepatocytes
3. Mature into **Schizonts** → bursting into tons of **Merozoites**
4. Back to the bloodstream → infecting healthy RBCs **(Ring -> Trophozoites -> schizonts ->** bursting into many **merozoites)** → massive RBCs destruction
5. Another female Anopheles mosquito bites infected human → picking plasmodium **Gametocytes**
6. Inside the mosquito the **Gametocytes** mature into sporozoites & so on..

P. Vivax & P. Ovale life cycle	P. falciparum and P. malariae life cycle
	
P.Vivax & P. Ovale can develop what's called HYPNOZOITES which can **stay dormant (sleeping)** in the liver & result in **reinfection** up to years after the parasites have been cleared from blood!!	P. falciparum and P. malariae have NO persistent exoerythrocytic (hepatic) phase. (i.e. no hypnozoites)

Clinical features:

Major clinical Features:

- Recurring Fever(Cardinal feature)
- Chills. (Assoc. with RBC lysis – mature schizonts)

Malaria Paroxysm (attack):

Three successive stages:

Rigors, Headache associated with pale **COLD** skin (1-2 Hr) يقعد ساعة ساعتين يرجف من البرد	→	Delirium, Tachypnoea, **HOT** Skin(Several hours)	→	Fever (Marked **SWEATING** and fatigue) (last 2-4 hours)

▶ **Notes Regarding Malaria Paroxysm:**

- **Paroxysms** (malaria attacks) **associated with synchrony** تتزامن مع **of merozoite release.**
- Between paroxysms temperature is normal and patient feels well (IMP)
- Classically the attacks:
  - occur every two days with (P. vivax, and P. ovale) "tertian parasites"
  - and every 3 days with (P.malariae) "quartan parasite"
  - whereas (P.falciparum) show IRREGULAR attacks ,or hectic (continuous fever) (especially In non-immune)

▶ **General Notes about the clinical features:**

- Early clinical features are non-specific begins as flu-like symptoms (headache - fatigue - vomiting) malaria should be suspected in anyone returning from endemic areas & complaining from these symptoms!
- Clinical features vary with: Geography, Epidemiology, Age and High risk group (Children, Pregnant women, pts who had splenectomy, Non-immune travelers to malarious areas),patients who are at high risk may go through complications and death.

Diagnosis:

- Detailed targeted history including travel History and clinical examination together with High Index of Suspicion (HIS)
- 🔑 **Blood film** (via microscopy, remains the gold standards)
- **Serology**: not useful in managing acutely ill patient. Not for diagnosis. For screening of donor blood.
- **DNA probe(PCR)**: similar thick film sensitivity,largely a research tool ,so it's not routinely done
- Infection with more than one parasite spp: 5-7%.

Blood film: simple & cost effective

- Usually done by **Giemsa** or wright's stain.
    - Correct identification of malarial Species is essential for treatment because of **P.Falciparum resistance to Chloroquine & other Drugs.**
    - On Giemsa stain: Cytoplasm: light blue, nucleus: dark blue

➔ In **P. Falciparum**:

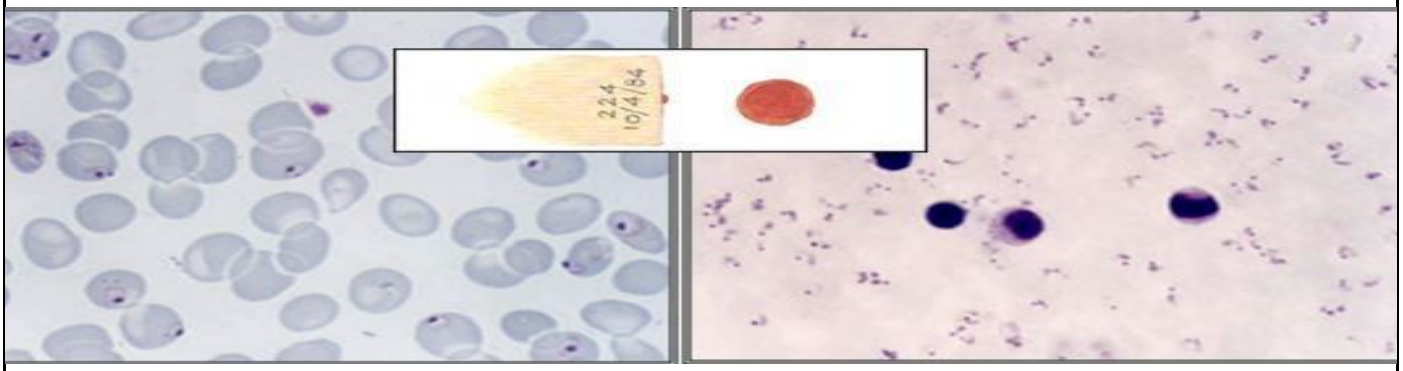
1. **Only ring stage asexual parasite and gametocytes** seen in peripheral Blood. (ring stage is earlier than gametocytes)
2. While RBC with **Trophozoites or Schizonts** stage: sequestered in peripheral, Microvasculature, and **NOT** circulating peripheral blood.

➔ **All asexual erythrocytic stages of P. Vivax, Ovale & malariae circulate in peripheral blood, thus seen on Blood Smear.** **p. vivax, p. ovale & p. malariae → all stages can be seen on blood film. p. falciparum → only Ring stage & maybe gametocytes.**

- Acutely ill Patient : Differential Diagnosis is P. Falciparum Or P. Vivax Because:
  1. P. Ovale & P. Vivax present as acute infection but clinically and morphologically are the same.
  2. P. malariae: present as a chronic Infection not acute.

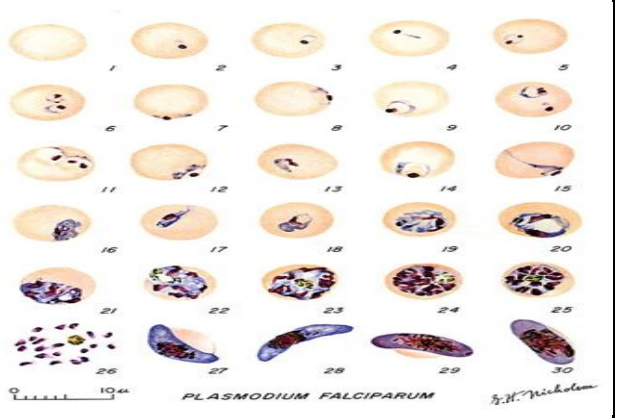
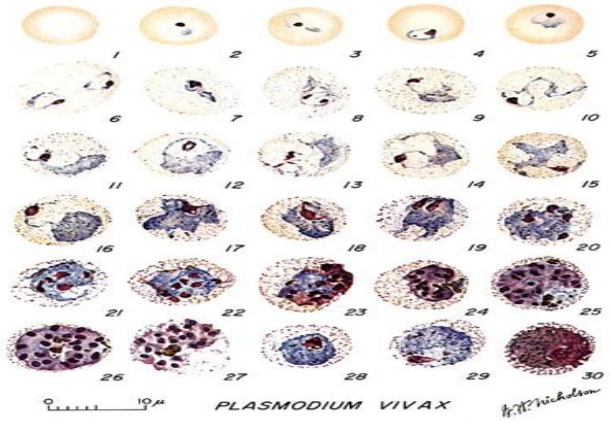
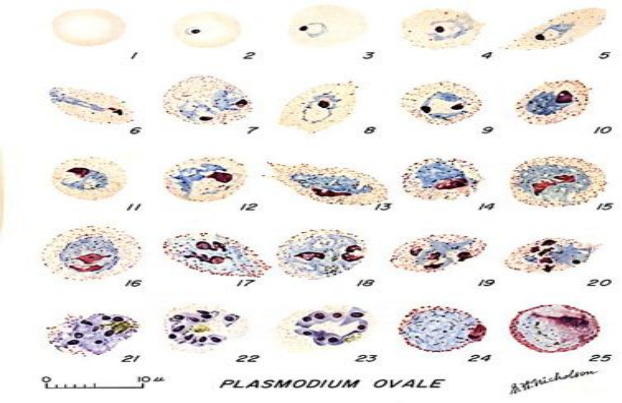
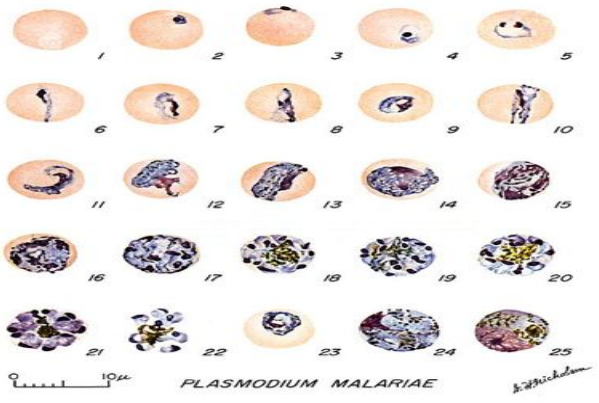
Ideally, the thick smears are used to detect the presence of parasites (esp. when low parasitaemia) while the thin smears are used for species-level identification & quantification.

Thin blood film (essential for confirming diagnosis)	Thick blood film
• **RBC morphology preserved.** • in P. Vivax; infected RBC → RBC enlargement with parasite maturation. • Schuffner's dots (Eosinophilic dots in RBC cytoplasm. Seen only in p.ovale & p.vivax). • May see Maurer's clots in RBC cytoplasm. (seen in p. falciparum)	• **RBC lysed.** • You may examine 10X. Blood more than in thin film. • More diagnostic in lower degree of parasitemias.



Left: thin blood smear. Right: thick blood smear.

for further reading:

Organism	Blood Stage Parasites	Thin Blood Smears
1- Plasmodium falciparum:	1: Normal red cell 2-18: Trophozoites (2-10: ring-stage trophozoites) 19-26: Schizonts (26 is a ruptured schizont) 27-28: Mature macrogametocytes (female) 29-30: Mature microgametocytes (male)	
2- Plasmodium vivax:	1: Normal red cell. 2-6: Young trophozoites (ring stage parasites). 7-18: Trophozoites. 19-27: Schizonts. 28-29: Macrogametocytes (female). 30: Microgametocyte (male).	
3- Plasmodium ovale:	1: Normal red cell. 2-5: Young trophozoites. 6-15: Trophozoites. 16-23: Schizonts. 24: Macrogametocytes (female). 25: Microgametocyte (male).	
4- Plasmodium malariae	1: Normal red cell. 2-5: Young trophozoites (rings). 6-13: Trophozoites. 14-22: Schizonts. 23: Developing gametocyte. 24: Macrogametocyte (female). 25: Microgametocyte (male).	

Differential Diagnosis of Malaria in Acutely ill Patients Based on Peripheral blood Smear:

	P. Falciparum	P. Vivax/P. Ovale
Multiple Infected RBC	common	rare
Mature (Trophozoite and schizont) parasites	absent*	common
RBC enlargement with later parasite stages	absent	common**

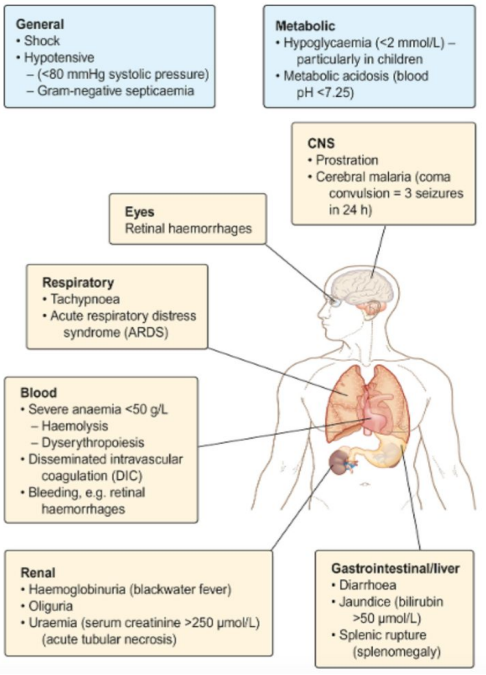
- *Mature (trophozoites & schizont) stage P. falciparum. Typically sequestered (hided) in the peripheral microvasculature.
- **RBC enlargement in P. vivax typically occurs with later stage parasites that do not circulate in P. falciparum infection.

Complications:

▸ **Notes:**

✓ Major clinical features of malaria are those of the complications. (The clinical features of Malaria are basically its complications).The major clinical feature of malaria is complications!!!!once the complications has occured يفترض كل واحد يعرف ان التشخيص ملاريا

✓ Majority of complications (apart from anemia) are associated with P. Falciparum. (> 10 parasites /mcl)



Anemia related complications:

- Anemia presents in most severe infections and **parallels** parasitaemia, and it's **due to:**
  - Hemolysis of infected RBCs
  - Delayed reticulocyte release from bone marrow
  - Immune-mediated hemolysis of non-infected RBCs

- In non-immune patients (Primary infections):
  - Black water fever (Haemoglobinuria) uncommon and usually presents with severe disease.
  - Exaggerated haemolytic response to quinine[1]-sensitized RBCs

- Jaundice: Mild unconjugated jaundice is common, and **parallels hemolysis**. Hepatocellular dysfunction may contribute to jaundice. The more hemolysis → the more jaundice

- Tissue hypoxia: Hypoxia results from anemia + altered microcirculation (Maturation of erythrocyte schizonts in P. falciparum takes place in tissue capillaries and venules).

- P. falciparum parasitized RBC sequestered in microcirculation, because of:
  - Altered deformability of parasitized RBC
  - Adhesion involving parasite-derived proteins within RBC and glycoproteins on vascular endothelium.

[1] Quinine is a medication used to treat malaria and babesiosis.

Other complications:

Early complications	
Cerebral Malaria -RBC changes → occlusion of cerebral microcirculation -Manifested by confusion, coma & convulsions.	- Most severe common complication. high mortality rate. **What are the risk factors for poor prognosis in cerebral malaria?** • Increased creatinine • Increased bilirubin • Increased lactates **Factors that DO NOT modify outcome in cerebral malaria:** • Depth of coma • Temperature • Vomiting • Seizures • Parasite load • Anemia • HIV infection (HIV infection also did not affect clinical or biological presentation of cerebral malaria)
Renal Failure Hemolysis > Hg deposition in renal tubules > tubular necrosis	- Most severe common complication - ATN (acute tubular necrosis) - Dehydration - Hypotension - Hyperviscosity
Pulmonary Edema	- Pulmonary capillary dysfunction → capillary leak - Manifested by SOB - ARDS – may complicate acute phase of severe malaise. Fluid overload may contribute. This is none cardiac edema, the heart is normal.
Hypoglycemia Very imp. can cause death even after appropriate treatment.	Why they have hypoglycemia? - Glucose consumption لأن البارا سايتس تتغذى على سكريات أجسامنا - Lactic acidosis. Liver unable to start gluconeogenesis - Quinine/quinidine stimulate insulin secretion. It's more of a side effect rather than a complication The brain doesn't tolerate hypoglycemia at all, that's why we should be very careful and prevent that.
Bleeding	- Thrombocytopenia Immune-complex attacks platelets leading to Thrombocytopenia, and sometimes they present with **Conjunctival Bleeding**. - Consumption coagulopathy
Other	- Shock: Endotoxemia - Diarrhea - Hyponatremia (? SIADH)

Late complications
- Tropical splenomegaly in P. Falciparum endemic areas. → caused by repeated attacks - Nephrotic Syndrome with P. malariae. Caused by Immune-complex attacking the kidney - Burkitt's lymphoma (Plasmodium falciparum - EBV)

Malaria and Hemoglobinopathies:

➔ **Heterozygous sickle cell trait:** children are less likely to contract P. falciparum. كريات الدم عندهم معطوبة، فما تجذب البارا سايتس

➔ **Hemoglobin S-C disease**: No such protection, rather mortality is higher than normal!

➔ **Thalassemics**: partially protected (? Fetal Hb).

➔ **G-6-phosphatase RBCs**: less prone to P. falciparum. P. falciparum has influenced human evolution, with the appearance of protective mutations such as sickle cell, thalassaemia, G6PD deficiency and HLA-B53.

Malaria and Pregnancy: If you get a pregnant lady with malaria you SHOULD admit her, until she becomes stable

- ➔ Mortality
- ➔ Anemia, hypoglycemia, pulmonary edema: common
- ➔ Abortion
- ➔ Stillbirth
- ➔ Premature delivery high infant mortality
- ➔ Low birth weight
- ➔ Placental insufficiency
- ➔ High parasitaemia? placenta is a favorable site for P. falciparum.

Congenital Malaria:

- Transplacental infection:

Infection During Pregnancy→ Placental Malaria (accumulation of parasites within the placenta) → Low Birth weight (because The parasite interferes with transmission of vital substances through the fetal placenta) → Increased Infant Mortality

- ➔ Can be all 4 species
- ➔ Commonly *P.v.* and *P.f.* in endemic areas
- ➔ *P.m.* infections in nonendemic areas due to long persistence of species

- Neonate can be diagnosed with parasitemia within 7 days of birth or longer if no other risk factors for malaria (mosquito exposure, blood transfusion)
- Fever, irritability, feeding problems, anemia, hepatosplenomegaly, and jaundice
- Be mindful of this problem even if mother has not been in malarious area for years before delivery

Treatment:

Principles of treatment:

Treatment should be guided by three main factors (CDC):

1) The infecting *Plasmodium* species
2) The clinical status of the patient
3) The drug susceptibility of the infecting parasites as determined by the geographic area where the infection was acquired and the previous use of antimalarial medicines

Resistance patterns: Just for your knowledge

Chloroquine-resistant P. falciparum	*Chloroquine-sensitive P falciparum*
Eastern Hemisphere: All of sub-Saharan Africa, Saudi Arabia, Yemen, Iran, Pakistan, Afghanistan, China, Nepal, and all of Southeast Asia **Western Hemisphere:** Panama, Haiti, Brazil, Peru, Bolivia, Colombia, Venezuela, Ecuador, French Guiana, Guyana, and Suriname	**Eastern Hemisphere:** Turkey, Iraq, Syria, Georgia, Azerbaijan, Tajikistan, Turkmenistan, and Kyrgyzstan **Western Hemisphere:** Argentina, Paraguay, Mexico, Guatemala, Costa Rica, Honduras, Nicaragua, El Salvador, and Dominican Republic
Mefloquine-resistant P falciparum	***Chloroquine-resistant P vivax***
Southeast Asia: Regions of Vietnam, Laos, Thailand, Burma, and Cambodia	Papua New Guinea and Indonesia

Treatment: If you have to treat before knowing the infected agent, treat as p.falciparum.

Note that:
-Nearly all p. Falciparum today is resistant to **Chloroquine**!!! (except few areas of Central America & Middle East)
-**Primaquine** should be given if Plasmodium vivax or Plasmodium ovale is likely.

Uncomplicated P. Falciparum infection:	**One of the following:** ➔ Artemether-Lumefantrine ➔ Atovaquone-proguanil ➔ Quinine ➔ Mefloquine
Uncomplicated P. Malariae, P. Knowlesi, or chloroquine-sensitive P. Falciparum infection:	➔ Chloroquine phosphate or ➔ Hydroxychloroquine
Uncomplicated P vivax or P ovale infection, expected to be chloroquine-susceptible:	➔ Chloroquine phosphate or ➔ Hydroxychloroquine
Uncomplicated P vivax infection, expected to be chloroquine-resistant:	**One of the following:** ➔ Quinine ➔ Atovaquone-proguanil ➔ Mefloquine ➔ Amodiaquine

Complicated Malaria: You don't have to worry about the doses

1. Quinidine gluconate 10 mg/kg loading dose over 1-2h, then 1.2 mg/kg/h for at least 24h
2. Once parasitemia is < 1% and patient can take oral medication, switch to quinine 650 mg PO TID to complete 3-d course (7-d course if malaria was acquired in southern Asia)
3. In addition, give doxycycline 100 mg IV or PO BID for 7d.
4. For **pregnant** women, instead of doxycycline, give clindamycin 20 mg base/kg/day PO divided TID for 7d

Chemoprophylaxis:

مهم جدًا عند زيارة أحد الـ**endemic regions** - يؤخذ قبل السفر بأسبوعين و يستمر أربع أسابيع بعد الرجوع.

One of the following:

- ➔ Atovaquone-proguanil
- ➔ Chloroquine phosphate
- ➔ Doxycycline
- ➔ Mefloquine
- ➔ Primaquine. Contraindicated in **pregnancy**, **children** and patients with **G6PD deficiency** due to the risk of red blood cell breakdown

Area visited	Prophylactic regimen	Alternative
No chloroquine resistance	Chloroquine 300 mg weekly	Proguanil 200 mg daily
Limited chloroquine resistance	Chloroquine 300 mg weekly	Doxycycline 100 mg daily
	plus	*or*
	Proguanil 200 mg daily	Malarone 1 tablet daily
		or
		Mefloquine 250 mg weekly
Significant chloroquine resistance	Mefloquine 250 mg weekly	Doxycycline 100 mg daily
		or
		Malarone 1 tablet daily

Other Measures in Treating Severe Malaria	
Antibodies against TNF-a	Steroids
- They reduce fever - They have no effect on mortality & morbidity, Why? Effects of other cytokines as IL – 1, TNF- b on pathogenesis of complicated severe malaria	- Harmful, by controlled trials - Dexamethasone longer duration of coma + worse outcomes than patient receiving quinine alone (NEWJ 1982, Warrel et al)
Reducing mosquito-human contact	Malaria vaccine

Additional Supportive Measures:

- Blood Tx / Exchange Tx
- Hypoglycemia treatment and prophylaxis especially in pregnant women.
- Avoidance of IVF overload
- Dialysis
- Heparin for consumption coagulation
- Pregnant woman should receive prophylaxis
- Non-immune travelers

FUTURE PERSPECTIVE:

Success to control or eradicate malaria faced by obstacles:

- Increasing drug resistance in P. falciparum and appearing (R) in P. vivax
- Basis of protection against infection and disease not understood.
- Biologic basis of vector capacity responsible for mosquito-borne malaria transmission is unknown.
- Increasing anopheline mosquito resistance to insecticide.

MCQs

1) A 27-year-old woman, who has recently returned from holiday in Africa, presents to accident and emergency with a 7-day history of fevers, sweats, headache, malaise and lethargy.On examination, her temperature is 39°C. Cardiorespiratory and gastrointestinal examinations are unremarkable. What is the most likely differential diagnosis?

A. Malaria
B. Tuberculosis
C. Influenza
D. Typhoid
E. Dengue fever

2) A 45-year-old man presents to accident and emergency, having returned from a holiday to India a week ago. He has subsequently been unwell with nausea and reduced appetite. Over the past 2 days he has become jaundiced. He mentions that his two brothers with whom he went on holiday have also become jaundiced in the last 2 days. On examination, he is apyrexial and there is a palpable liver edge. Liver function tests reveal a raised ALT, AST and bilirubin. All other blood tests are normal. What is the most likely diagnosis?

A. Hepatitis A
B. Hepatitis B
C. Hepatitis C
D. Gilbert's syndrome
E. Malaria

3) A 24-year-old man presents to accident and emergency with fevers, lethargy, myalgia and a cough. He has also developed an itchy rash on his feet. He returned home from a charity trip to Malawi last month and is worried he might have malaria. On examination, a papular rash is noted around his feet and there is a palpable liver edge. Initial blood tests show a raised white cell count with an eosinophilia. What is the most likely diagnosis?

A. Leishmaniasis
B. Schistosomiasis
C. African trypanosomiasis
D. Malaria
E. Influenza

4)A 30-year-old man presents to accident and emergency with a 5-day history of fevers, sweats and lethargy. On further questioning, he mentions that he has just returned from a 6 week trip to Tanzania. On examination his temperature is 40°C. What is the most likely diagnosis?

A. Influenza
B. Malaria
C. Typhoid
D. Infectious mononucleosis
E. Cholera

Answer key:

1 (A) | 2 (A) | 3 (B) | 4 (B) |