Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

Malaria & Travel Medicine

Objectives :

1. Know the Epidemiology & Etiology.
2. Know the Clinical presentation.
3. Know the Risk to travelers.
4. Know the Malaria and pregnancy.
5. Know the Diagnostic Workup.
6. Know the Treatment & prophylaxis.

Done by :

Team leader: Salem Al-Ammari

Team members: - Abdulaziz Alabdulkareem . -Abdullah alsergani

-Fahad Alhussaen. -Aseel Badukhon

Revised by :

Yazeed Al-Dossare

Resources :

Doctors slides
436 team work
Doctor note : Dr. Awadh Alanazi

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.

- In 2017, an estimated 219 million cases of malaria occurred worldwide, compared with 239 million cases in 2010 and 217 million cases in 2016.
- Most malaria cases in 2017 were in the WHO African Region (200 million or 92%), followed by the WHO
- South-East Asia Region with 5% of the cases and the WHO Eastern Mediterranean Region with 2%.
- Fifteen countries in sub-Saharan Africa and India carried almost 80% of the global malaria burden.
- Five countries accounted for nearly half of all malaria cases worldwide: Nigeria (25%), Democratic Republic of the Congo (11%), Mozambique (5%), India (4%) and Uganda (4%).
- The 10 highest burden countries in Africa reported increases in cases of malaria in 2017 compared with 2016. Of these, Nigeria, Madagascar and the Democratic Republic of the Congo had the highest estimated increases, all greater than half a million cases. In contrast, India reported 3 million fewer cases in the same period, a 24% decrease compared with 2016.
- The incidence rate of malaria declined globally between 2010 and 2017, from 72 to 59 cases per 1000 population at risk. Although this represents an 18% reduction over the period, the number of cases per 1000 population at risk has stood at 59 for the past 3 years.

Epidemiology

(Grey text here is included in the lecture but you're not expected to memorize it)

Plasmodium Falciparum

is the most prevalent malaria parasite in the WHO African Region, accounting for 99.7% of estimated malaria cases in 2017, as well as in the WHO regions of South-East Asia (62.8%), the Eastern Mediterranean (69%) and the Western Pacific (71.9%).

Plasmodium Vivax

P. vivax is the predominant parasite in the WHO Region of the Americas, representing 74.1% of malaria cases.

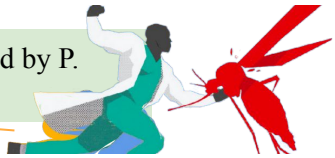
- In 2017, there were an estimated 435,000 deaths from malaria globally, compared with 451,000 estimated deaths in 2016, and 607,000 in 2010.
- Children aged under 5 years are the most vulnerable group affected by malaria. In 2017, they accounted for 61% (266,000) of all malaria deaths worldwide.
- Endemic 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.
- Transmitted Via female Mosquito Bite.
- The mosquito require moderate temperature, it can't live in extreme hot or cold weather. Can't live in Riyadh, Al Baha, and Khamis Mushait.
- People living in endemic malaria areas have an some kind of immunity against malaria but its not permanent .

Etiology

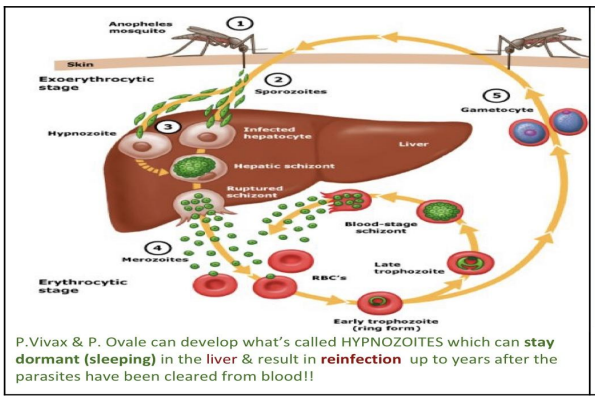
Malaria is caused by the Plasmodium parasite. The parasite can be spread to humans through the bites of infected mosquitoes (Female Anopheles mosquitoes). There are many different types of plasmodium parasite, but only 5 types cause malaria in humans:

Plasmodium Falciparum	Plasmodium vivax	Plasmodium ovale	Plasmodium malariae	Plasmodium knowlesi
Mainly found in Africa, it's the **most common** type of malaria parasite and is responsible for most malaria deaths worldwide.	Mainly found in Asia and South America, this parasite causes milder symptoms than Plasmodium falciparum, but it can stay in the liver for up to 3 years, which can result in relapses.	Fairly uncommon and usually found in West Africa, it can remain in your liver for several years without producing symptoms. P. Vivax and P. Ovale look the same under the microscope and their way in causing the disease.	This is quite rare and usually only found in Africa. Usually does not cause a serious disease.	This is very rare and found in parts of southeast Asia.

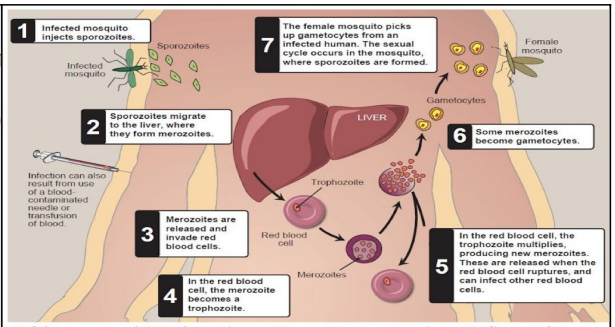
Any patient suspected to have Malaria, we assume and treat him as if its caused by P. Falciparum. Because it's the worst and most serious type.



Incubation period and 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. (no hypnozoites)

- 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 → injects Sporozoites (infective stage) 2. In the bloodstream Sporozoites go to the LIVER & live inside hepatocytes (hypnozoite)/ Or infect the liver cell and kills it.
3. Mature into Schizonts → bursting into tons of Merozoites
4. Back to the bloodstream → infects healthy RBCs go 2 ways, 1.(Ring -> Trophozoites -> RBC schizonts -> bursting into many merozoites) → massive RBCs destruction. 2.(Ring -> Gametocytes)
5. Another female Anopheles mosquito bites infected human → picking plasmodium Gametocytes
6. Inside the mosquito the Gametocytes mature into sporozoites & so on..

Pathogenesis

RBCs invasion

1- Plasmodium Falciparum: invades RBC at all ages.
2- P.Malariae: only old RBC.
3-P. ovale and P. vivax: invade young RBC's.

Microvascular pathology

Secondary Ischemia Adherence of Non-deformable parasitized RBC to endothelium.
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.
In P. F, infected RBC adhere to vascular endothelium in post-capillary venules in brain, kidney, liver, and lungs causing vessel congestion which results in organ damage

Renal failure

Hemolysis, Ischemia secondary microvascular pathology.

Deep coma

Hypoglycemia, microvascular adherent parasitized RBC.

Pulmonary edema

Secondary to capillary leak Syndrome (without congestive cardiac failure).

Immune-Complex Nephrotic syndrome

Secondary to P. Malariae, this is only in chronic cases.

Clinical Features

Clinical features vary with: Geography, Epidemiology, and Age. High risk population includes:

Children	Pregnant women	Non-immune travelers to malaria endemic areas

Major clinical Features:

- Recurring Fever, depends on the type of parasite.
- Chills. (Associated with RBC lysis – mature schizonts).

Clinical Features

Severe infection	Chronic infection
Severe P. Falciparum infection: (> 10 parasite/ mcl). Acute complications: - Renal failure - Coma secondary to hypoglycemia, TNF, or microvascular pathology - Pulmonary Edema -Thrombocytopenia -G. Enteritis – especially diarrhea.	***Chronic*** P. Falciparum infection: P. Falciparum is usually acute but can be chronic when the mature parasite stays in the spleen causing splenomegaly. - Splenomegaly typically resolves after treatment with anti-malarial medications (6-12 months). - P. Malariae associated Immune complex nephrotic syndrome. - P. Vivax – late splenic rupture with trauma 1-3 mon. after initial infection.

Malaria Paroxysm (attack):

3 successive stages:

Rigors, Headache associated with pale **COLD** skin (1-2 Hr) not specific

Delirium, Tachypnoea, **HOT** Skin Fever (Several hours) Due to the vasoconstriction

Fever (**SWEATING** and fatigue) patient usually goes to sleep in this stage

Notes Regarding Malaria Paroxysm:

-Paroxysms associated with synchrony of merozoite release.
- Between paroxysms temperature is normal and patient feels well and Asymptomatic.
- Falciparum may not exhibit classic paroxysms. (continuous fever)
- Classically the attacks (Periodicity):
  - occur every 48 hours with (P. vivax, and P. ovale) “tertian parasites”
  - and every 72 hours with (P.malariae) “quartan parasite”
  - whereas (P.falciparum) show IRREGULAR attacks ,or hectic (especially In non-immune)

Diagnosis

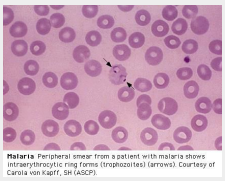
Detailed targeted history including travel history and clinical examination together with High Index of Suspicion (HIS).

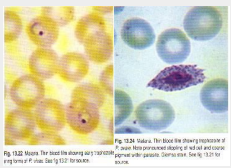
1 Blood film

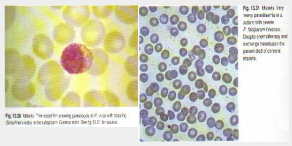
- Giemsa stain or wright's stain.
- Correct identification of malarial Species is essential for treatment because of P. Falciparum is resistant to Chloroquine & others.
- On Giemsa stain – Cytoplasm: light blue, nucleus: dark blue
- In P.F
  - 1- only ring stage a sexual parasite and gametocytes seen in periph. Blood.
  - 2- While RBC with Trophozoites or Schizonts stage – sequestered in peripheral, Microvasculature, and NOT circulating P-blood.
- All asexual erythrocytic stages of P. Vivax, Ovale & malariae circulate in peripheral blood, thus seen on Blood Smear.

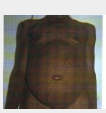
Acutely ill patients

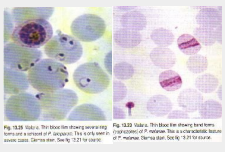
- DDX: P.F. vs P. Vivax, because
- (a) P. Ovale – Vivax – clinical, morphological
- (b) P. malariae - ch. Infection



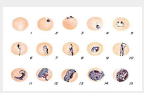








1: Normal red cell.
2-5: Young trophozoites (rings).
6-13: Trophozoites. 14-22: Schizonts.
23: Developing gametocyte 24: Macrogametocyte (female).
25: Microgametocyte (male).



2 Serology

not useful in managing acutely ill patient.

3 DNA probe (PCR)

similar thick film sensitivity. Infection with more than one parasite spp: 5-7%.

Diagnosis

Differential diagnosis of malaria in acutely ill patients based on peripheral blood smear:

Findings	P. FALCIPARUM	P. VIVAD & P. OVALE
Multiple infected RBCs	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 in the peripheral microvasculature.

RBC enlargement in P. vivax typically occurs with later stage parasites that do not circulate in P. falciparum infection.

Malaria complications

- Major clinical features of malaria are those of the complications.
- Majority of complications (apart from anemia) associated are with P. Falciparum

Anemia

Anemia presents in most severe infections and parallels parasitemia and it is due to:

1. Hemolysis of infected RBC.
2. Delayed retics. release from BM.
3. Immune – mediated hemolysis of non-infected RBC.

In non immune patients (primary infection):

1-Black water fever (hemoglobinuria)

2-Exaggerated hemolytic response to quinine – sensitized RBC.

Jaundice

-Mild unconjugated jaundice common, and parallels hemolysis.

-Hepatocellular dysfunction may contribute to jaundice.

Tissue Hypoxia

-Hypoxia results from altered microcirculation + anemia.

-Maturation of erythrocyte schizonts in P. falciparum takes place in tissue capillaries and venules.

Parasitized RBCs

P. falciparum parasitized RBC sequestered in micro circulation because:

1-Altered deformability of parasitized RBC.

2-Adhesion involving parasite – derived proteins within RBC and glycoproteins on vascular endothelium.

Malaria complications

Other complications

Cerebral malaria
-Most severe common complication.
-Factors do not modify the outcome include: Depth of coma, temperature, vomiting, seizures, parasites load, anemia, HIV infection did not affect clinical or biological presentation of cerebral malaria and appears not to affect outcome.

Renal Failure
Most severe common complication;
-ATN
-Dehydration.
-Hypotension.
-Hyperviscosity

Pulmonary edema
ARDS – may complicate acute phase of severe malaise. Fluid overload may contribute

Hypoglycemia:
-Glucose consumption.
-Lactic acidosis.
-Quinine/quinidine --- increase insulin secretion

Bleeding:
-Thrombocytopenia.
-Consumption coagulopathy.

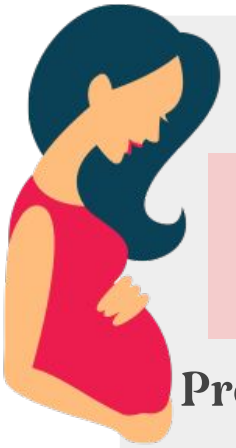
Shock: endotoxemia

Diarrhea

Hyponatremia: SIADH

Late complications

- Tropical splenomegaly in P. Falciparum endemic areas.
- N. syndrome with P. malariae.
- Burkitt's lymphoma (PF - EBV)



Pregnancy & Malaria

Malaria during pregnancy leads to:

Mortality. Abortion. Stillbirth.

Anemia, hypoglycemia, pulmonary edema: > common.

Premature delivery high infant mortality.

Low birth weight Placental insufficiency.

High parasitemia ? placenta favorable site for P. falciparum.

Congenital malaria:

-Transplacental infection:
➔ 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.

- If treatment must be initiated before the species is known treat as P.falciparum.
- P. falciparum should be presumed to be chloroquine resistant, except in a few areas of Central America and the Middle East.
-Primaquine should be given if Plasmodium vivax or Plasmodium ovale is likely.

Treatment of complicated malaria

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 (7d course if malaria was acquired in southern Asia) to prevent the relapse. In addition, give doxycycline 100 mg IV or PO BID for 7d.

3. For pregnant women, instead of doxycycline, give clindamycin 20 mg base/kg/day PO divided TID for 7d.

Treatment of uncomplicated malaria

1-P. Falciparum infection:
Artemether-Lumefantrine AKA, Artesunate Atovaquone-proguanil , Quinine, if Artemether is not available, Quinine can be used but it causes cardiotoxicity and insulin secretion. Mefloquine

2-Uncomplicated P. Malariae,P. Knowlesi, P vivax or P. ovale infection.
chloroquine-sensitive P. Falciparum infection:
Chloroquine phosphate, Hydroxychloroquine

3-Uncomplicated P vivax infection, expected to be chloroquine resistant:
Quinine, Atovaquone-proguanil , Mefloquine, Amodiaquine

Uncomplicated (meaning creatinine,bilirubin and lactate levels are normal > no end organ damage)

Resistance patterns

1-Chloroquine-resistant 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
2-Mefloquine-resistant P falciparum
Southeast Asia: Regions of Vietnam, Laos, Thailand, Burma, and Cambodia
3-Chloroquine-sensitive P falciparum
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
4-Chloroquine-resistant P vivax:
Papua New Guinea and Indonesia

Treatment

Chemoprophylaxis

One of the following:

- Atovaquone-proguanil
- Chloroquine phosphate
- Doxycycline
- Mefloquine, safe for pregnant women.
- Primaquine , usually a 6 week course. 4 weeks before traveling, continue there and 1 week after.

Other measures to treat severe malaria

1-Antibodies against TNF-a
-They reduce fever
-They have no effect on mortality & morbidity, Why? Because of the effects of other cytokines as IL – 1, TNF- b on pathogenesis of complicated severe malaria.

2-Reducing mosquito-human contact

3-Steroids Never use steroids in malaria patient
- Harmful, by controlled trials.
- Dexamethasone > longer duration of coma + worse outcomes than patient receiving quinine alone.

4-Malaria vaccine (No vaccines for malaria)

Additional supportive measures

- Blood Tx / Exchange Tx in children
- Hypoglycemia treatment and prophylaxis especially in pregnant women.
- Avoidance of IVF overload.
- Dialysis, In cases of ATN caused by malaria.
- Heparin for consumption coagulation and DIC caused by malaria.
- Pregnant woman & Non-immune traveler should receive prophylaxis.

Future Perspective:

Success to control or eradicate malaria faced by obstacles:
- Increasing drug resistance in P. falciparum and appearing resistance 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.

Just go through them:

World Health Organization

وزارة الصحة
Ministry of Health

Kingdom of Saudi Arabia
Ministry of Health
Public Health Agency
Infectious Diseases Control General Directorate
Malaria Department

The national policy of malaria case management in The Kingdom of Saudi Arabia

1. Treatment of simple uncomplicated falciparum malaria:

1.1 First-line Treatment: ***Artesunate (AS) + Sulfadoxine – Pyrimethamine* (SP)**

Age in years	Weigh in Kgs	Day 1		Day 2	Day 3
		SP (500 S+25 P mg tab)	AS (50mg tab)	AS (50mg tab)	AS (50mg tab)
5 - 11 Months	5 - 10 Kgs	½	½	½	½
1 - 6 years	11 - 24 Kgs	1	1	1	1
7 - 13 years	25 - 50 Kgs	2	2	2	2
> 13 years	> 50 Kgs	3	4	4	4

❖ A single dose of primaquine (0.25 mg base/kg bw, maximum dose 15 mg) should be added on the first day of treatment to ACT for uncomplicated falciparum malaria as a gametocytocidal medicine.

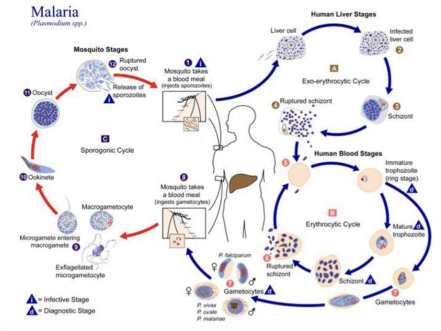
1.2 Second-line Treatment: ***Artemether* 20mg + *Lumefantrine* 120mg**

Age in years	Weigh in Kgs	Day1		Day2		Day3	
		AM	PM	AM	PM	AM	PM
< 5		Not recommended					
<3 years	5 - 14	1	1	1	1	1	1
3 - 8 years	15 - 24	2	2	2	2	2	2
9 - 14 years	25 -34	3	3	3	3	3	3
>14 years	> 34	4	4	4	4	4	4

❖ A single dose of primaquine (0.25 mg base/kg bw, maximum dose 15 mg) should be added on the first day of treatment to ACT for uncomplicated falciparum malaria as a gametocytocidal medicine.

2. Treatment of malaria caused by P. vivax, or P. ovale and malariae:

Chloroquine 25mg base / kg divided over three (3) days, *(Chloroquine 4 tablets day 1, 4 tablets day 2, 2 tablets day 3)* combined with *Primaquine* 0.25 mg / kg bw taken daily with food for 14 days *for vivax and ovale* , *(Primaquine 15 mg tabs daily for 14 days for adult)*



3.Treatment of severe malaria:

Treatment		Day 1		Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
		Time 0	12 hrs						
First option	*Artesunate* I.V / I.M	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg	2.4mg/kg
Second option	*Artemether* I.M	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg	1.6mg/kg
Third option	*Quinine* I.V	20mg/kg in 5% Glucose(loading dose)		After 8hrs of loading dose start the maintenance dose as, 10mg/kg /8 hourly till the patient can take by mouth then shift to the oral.					

4. Treatment of malaria in pregnancy: **N.B.** Malaria in pregnancy should be considered severe and treated in hospital

Pregnancy in weeks	Uncomplicated malaria	Severe malaria
0-12 (1st trimester)	*Quinine + Clindamycine*	*Quinine + Clindamycine*
13- delivery (2nd &3rd trimester)	* First option: (AS + SP) * Second option: *Quinine + Clindamycine*	*Artesunate* Or *Quinine + Clindamycine*
Puerperium	AS + SP	*Artesunate* Or *Quinine + Clindamycine*

For any queries; *Please call:* *0112917743 or 0114738275*

Summary

Malaria paroxysm:

1. Rigors, Headache associated with pale COLD skin (1-2 Hr)
2. Delirium, Tachypnoea, HOT Skin (Several hours)
3. Fever (Marked SWEATING and fatigue)

Diagnosis:

1. detailed history “travailing” & physical examination
2. Blood film (Giemsa stain or wright’s stain)
3. Serology
4. DNA probe(PCR): similar thick film sensitivity.

Treatment:

Uncomplicated P.F, One of the following:
➔ Artemether-Lumefantrine
➔ Quinine
Complicated:
➔Quinidine gluconate
Until parasitemia is < 1%
➔switch to quinine + doxycycline “prevent relapse”
For pregnant women, instead of doxycycline, give clindamycin

Prophylaxis:

Primaquine, Mefloquine “pregnancy”.

Complications:

-Hypoglycemia
-Hemoglobinuria
-Splenomegaly
-Thrombocytopenia
-Cerebral malaria
-Anemia

Poor prognosis risk factor in cerebral malaria:
1.Increased Creatinine.
2.Increased Bilirubin.
3.Increased Lactate.

Questions

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 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

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 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

Answer key: 1 (A) | 2 (B) | 3 (B) | 4 (A) |