The Deadly Vampire

CCM Interhopsital Grandround

September 2015

Intensive Care Unit

Tseung Kwan O Hospital

Our patient

- F/44, NKDA, good past health
- Fever since 9/8/2015
- Vomiting and diarrhoea of watery stool for 4-5 times daily since 11/8
- No skin rash, joint pain or swelling
- No URTI symptoms, cough, sputum
- No urinary symptoms
- Persistent fever, increased confusion and hyperpigmentation of urine
- Admitted to hospital on 14/8

Our patient

- High fever of 39 degree
- BP 108/64 P 122 sinus tachycardia SpO_2 98% RA
- Heart sound dual without murmur, clear chest
- Abdomen soft and non-tender
- No skin rash, eschar or joint swelling
- WBC **13.3** Hb 12.1 plt **32** neutrophil 10 lymphocyte 1.7
- Atypical lymphocyes and myelocytes
- RFT 128/4.7/11.5/74 LFT **77/210/123** INR 1.2
- CT brain: no abnormality detected

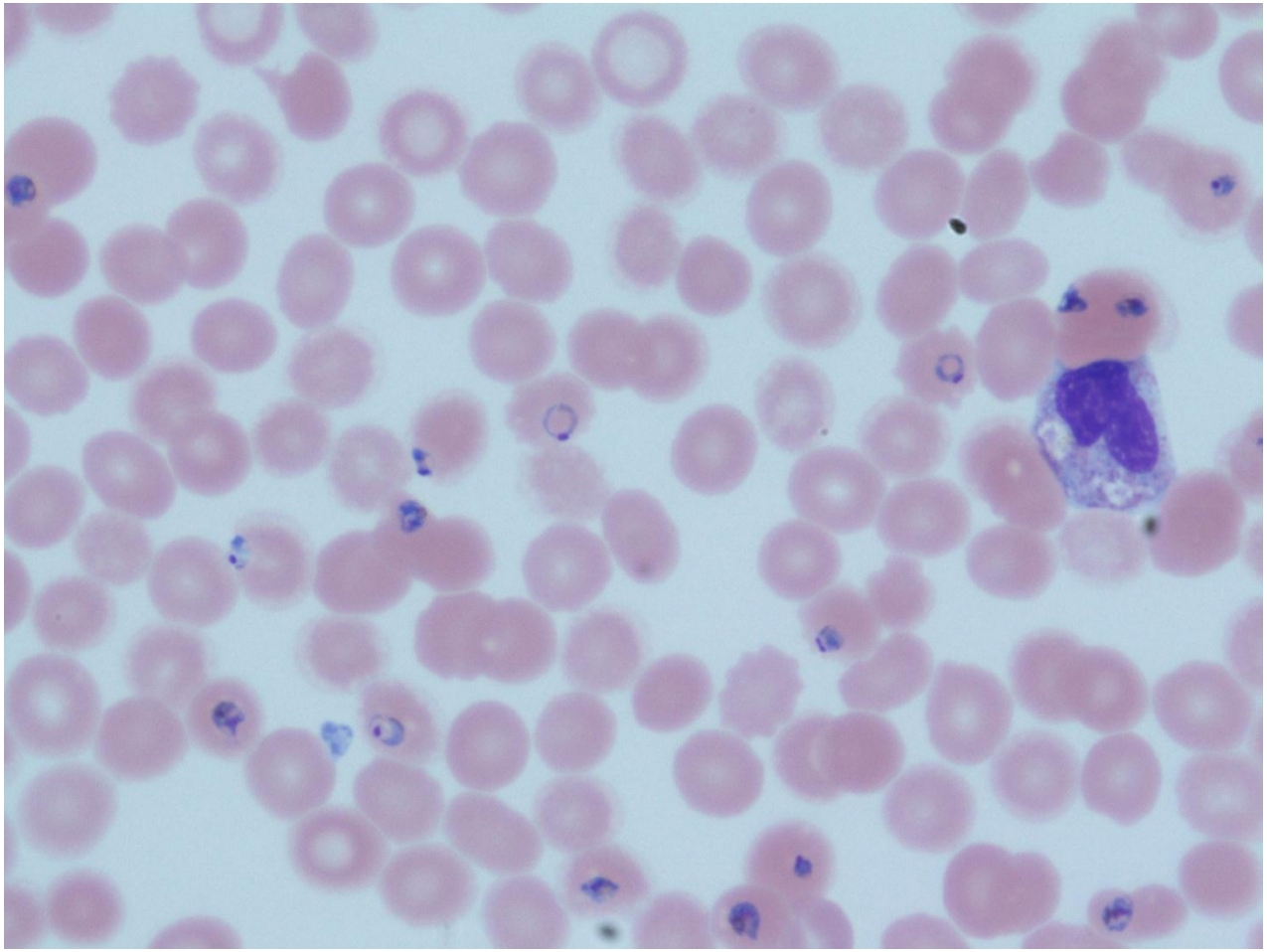
Our patient

- Decreased consciousness with GCS 11/15
- Transferred to intensive care unit the next day
- GCS deteriorated to 7/15 and intubated
- Shock requiring nor-adrenaline infusion
- Oilgouric
- WBC 13.3 Hb 10.7 plt **38**
- RFT 137/3.6/**19.1/212** LFT **61/192/110** INR **1.6**
- ABG pH 7.40 pCO_2 2.9 pO_2 18.8 HCO_3 **13.4**

Our patient

- Patient travelled to Republic of Mauritius and Madagascar from 21/7 to 3/8
- Close contact with local exotic monkeys
- Mosquito bite

What is the diagnosis?



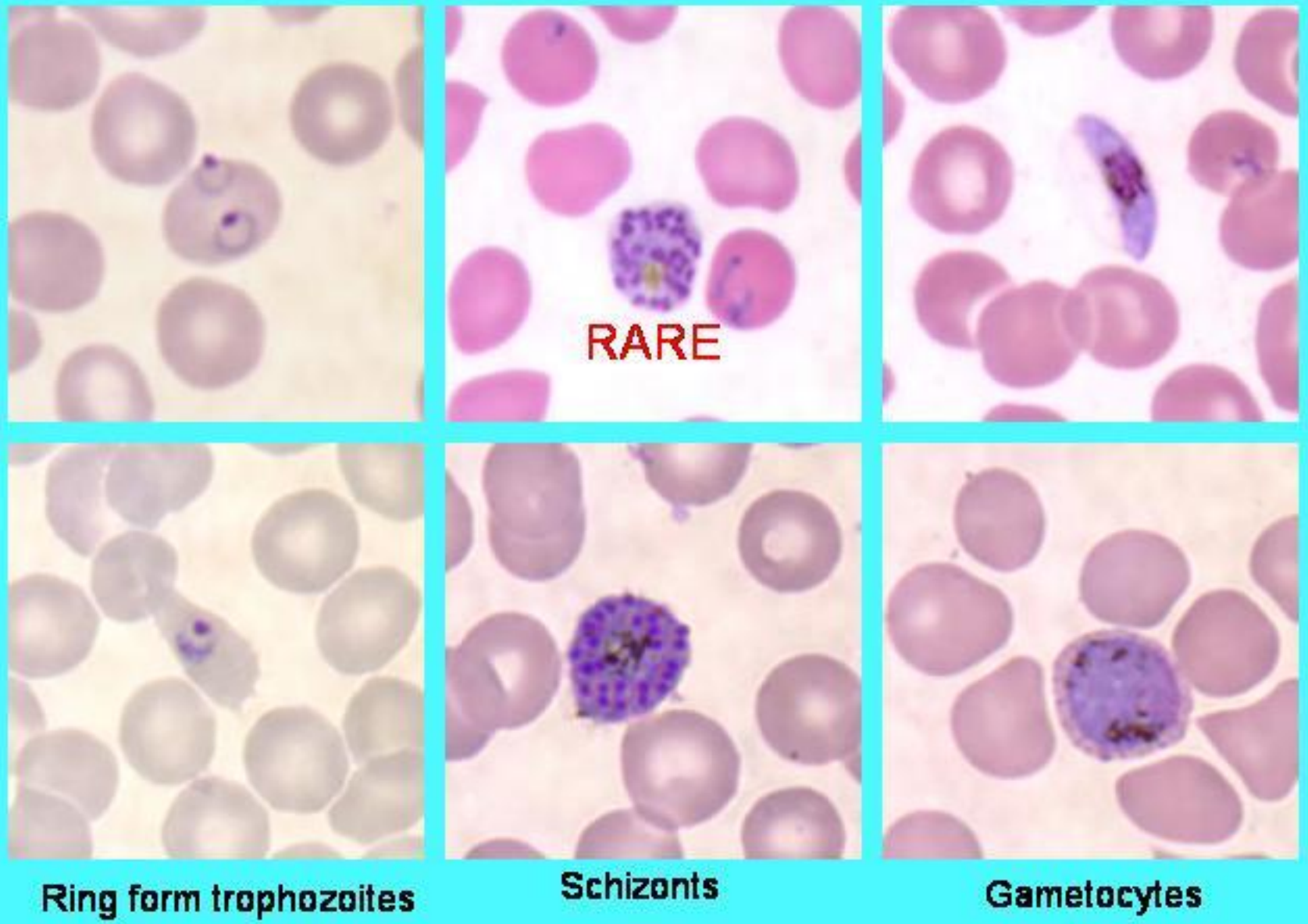
Patient’s blood film on admission

Diagnosis

- Presence of plasmodium falciparum trophozoites (ring form) in many of red blood cells – estimated parasitaemia 11.3% of RBC
- Diagnosis is **falciparum malaria with multi-organ failure**

- Our patient did not receive any malaria chemoprophylaxis before the trip
- She had been to Eastern Africa 2 years ago and received malaria chemoprophylaxis at that time
- This time she thought the chance of mosquito bite was low as it was winter at the place she went

P. falciparum vs. *P. vivax*



Differential diagnosis – fever in returning travellers

- Typhoid fever
- Dengue fever
- Leptospirosis
- Viral haemorrhage fever – Ebola
- Meningitis
- Pneumonia
- Other source of sepsis with multi-organ failure

Our patient

- Diagnosis was made on the day of admission
- Given IV artesunate 240mg daily and IV doxycycline 100mg BD
- Empirical IV rocephin 1 gram every 12 hours after blood culture
- Daily blood smear to monitor the density of malaria parasite

Our patient

- ? Nystagmus, no seizure documented clinically
- Start IV dilantin 100mg q8h
- EEG on 17/8 : moderate to severe diffuse cerebral dysfunction, no epileptiform discharge
- IV dilantin subsequently stopped
- Lumbar puncture: clear CSF, WBC 2 RBC nil, gram stain: nil WBC, no organism seen, fungal smear negative, no growth obtained form culture, protein **0.68** (0.1 – 0.44) glucose 3.2 (2.2-3.9)
- GCS remained **E2VTM1**
- Fundoscopy: a few blot haemorrhage, no papilloedema

Our patient

- Refractory hypotension requiring escalation of inotropes
- On dopamine, adrenaline, nor-adrenaline and vasopressin infusion
- Bedside echo: LVEF 50%, no RWMA, no significant valvular lesion, no pericardial effusion, IVC diameter 1.1cm with respiratory variation
- Auric, worsening renal function with hyperkalaemia and metabolic acidosis
- Continuous veno-venous haemodiafiltration (CVVHDF) was delivered
- Ventilatory support and oxygenation remained low

Our patient

- Progressive drop in Hb down to **6.6**
- No clinical evidence of active bleeding
- Both direct and indirect bilirubin were elevated
- Lowest platelet count **34**
- LFT further deranged
- INR **1.8** LDH **891**
- Supportive blood product transfusion given
- Repeated episodes of **hypoglycaemia** corrected with dextrose

Falciparum malaria

- Epidemiology
- Diagnosis
- Pathogenesis
- Clinical features
- Management
- Prognosis
- Chemoprophylaxis

Epidemiology

- About 207 million cases globally up to 2012 resulting in about 627,000 deaths
- 90% of deaths occur in Africa, 77% being children < 5 years
- 6749 cases of imported malaria reported within European Union in 2010
- France, UK, Germany and Italy account for 80% of all cases
- 1688 cases reported in the USA
- Most cases of falciparum malaria are acquired in Sub-Saharan Africa

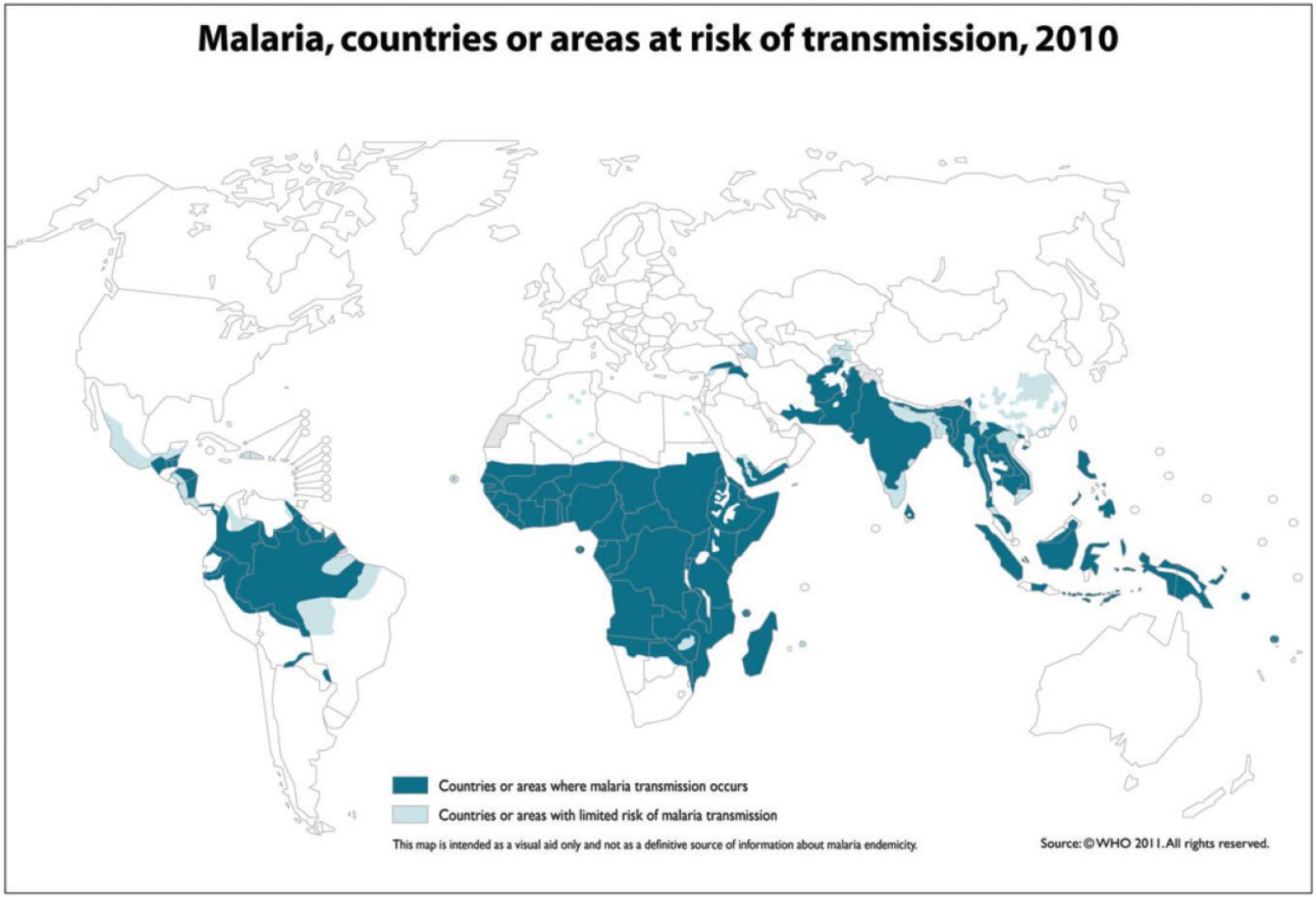


Fig 1 Countries and areas with risk of malaria transmission. Map from WHO International Travel and Health Programme, http://www.who.int/ith/en/. Reproduced with permission of the World Health Organisation.

Local situation

- More than 2000 cases in 1946 with shift of epidemiology to imported cases since the 1970's
- Upsurge in 1989 related to Vietnamese migrants

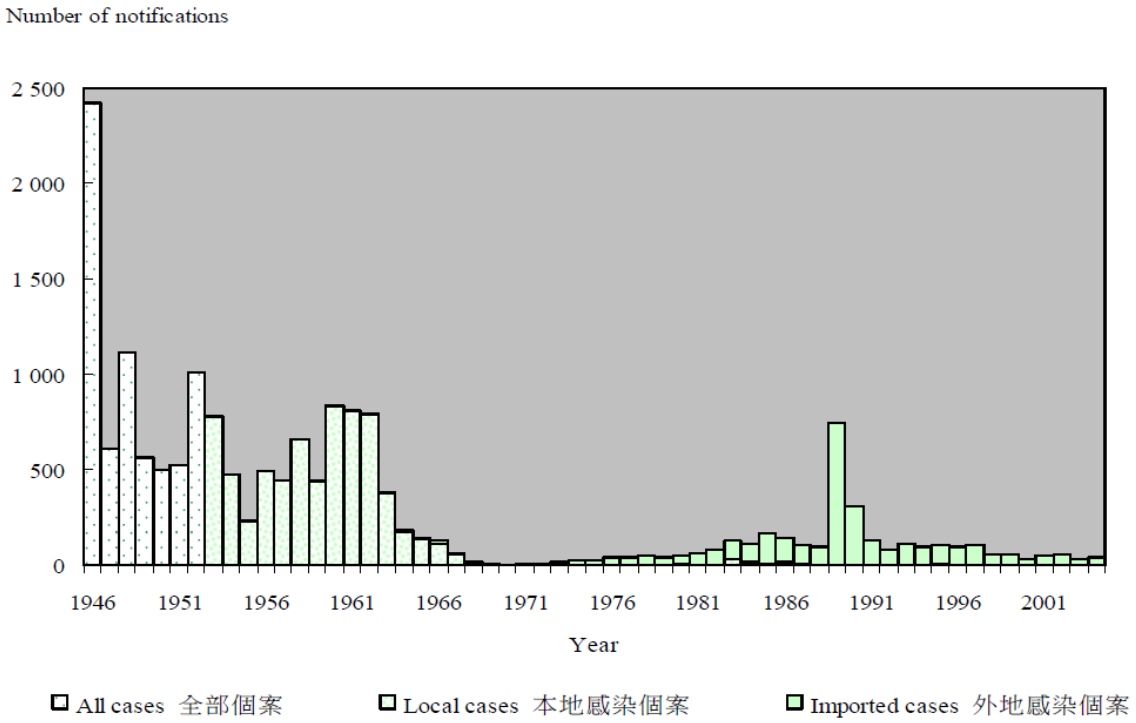


Figure 1 Malaria in Hong Kong (1946-2004)

Local situation

- 521 cases reported from 1996 to 2005
- 514 (98.7%) were imported cases
- Median age 31 years
- 65.2% HK residents 26.9% tourists
- 48.2% were imported from India, Pakistan and Nepal
- 63% P. vivax, 28.4% P. falciparum, 4.2% P. malariae and 0.8% P. ovale
- 2.7% had mixed infection of two or more parasites

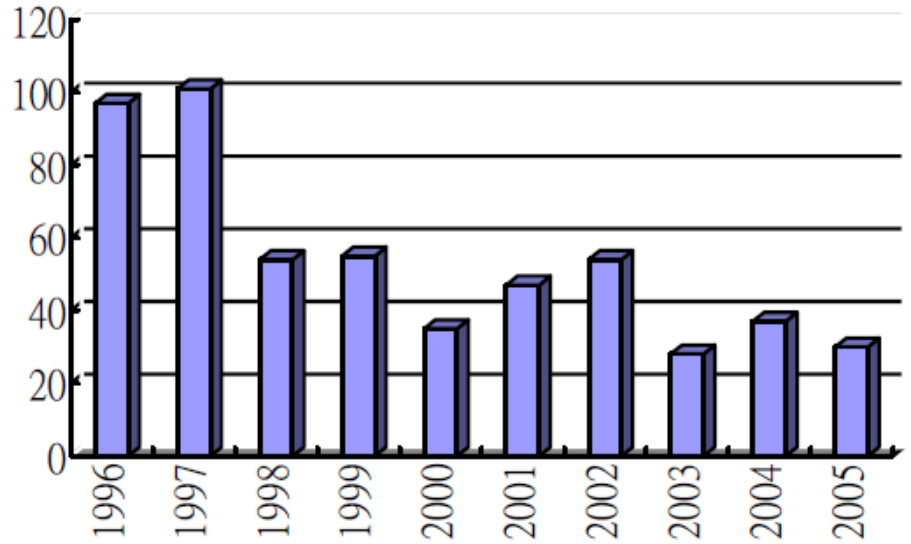


Figure 2 Number of malaria cases notified (1996-2005 June)

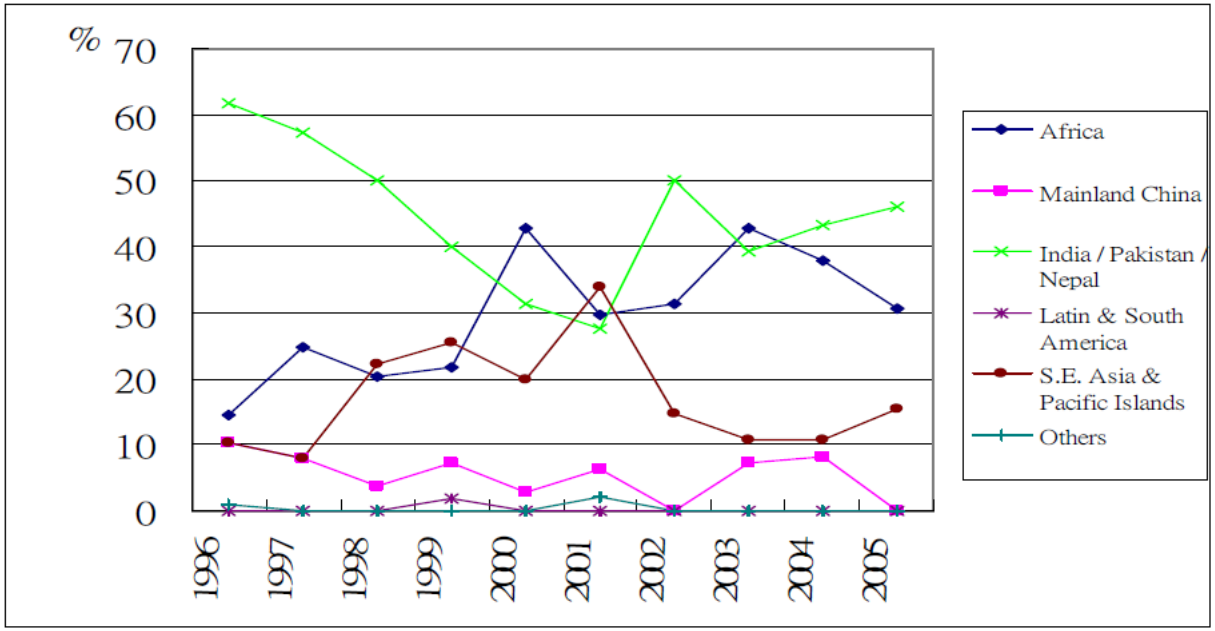


Figure 3 Imported cases by country of import (1996-2005 June)

Local situation

- 7 fatal cases from 1996-2005
- P. falciparum is the infective agent in 6 of them
- 4 were imported from Africa
- Of the 340 infected HK residents since 1996, 281 (84.1%) did not receive any chemoprophylaxis
- Two principal local malaria vectors – Anopheles minimus and Anopheles jeyporiensis
- Latest species collection in Luk Keng in 2002

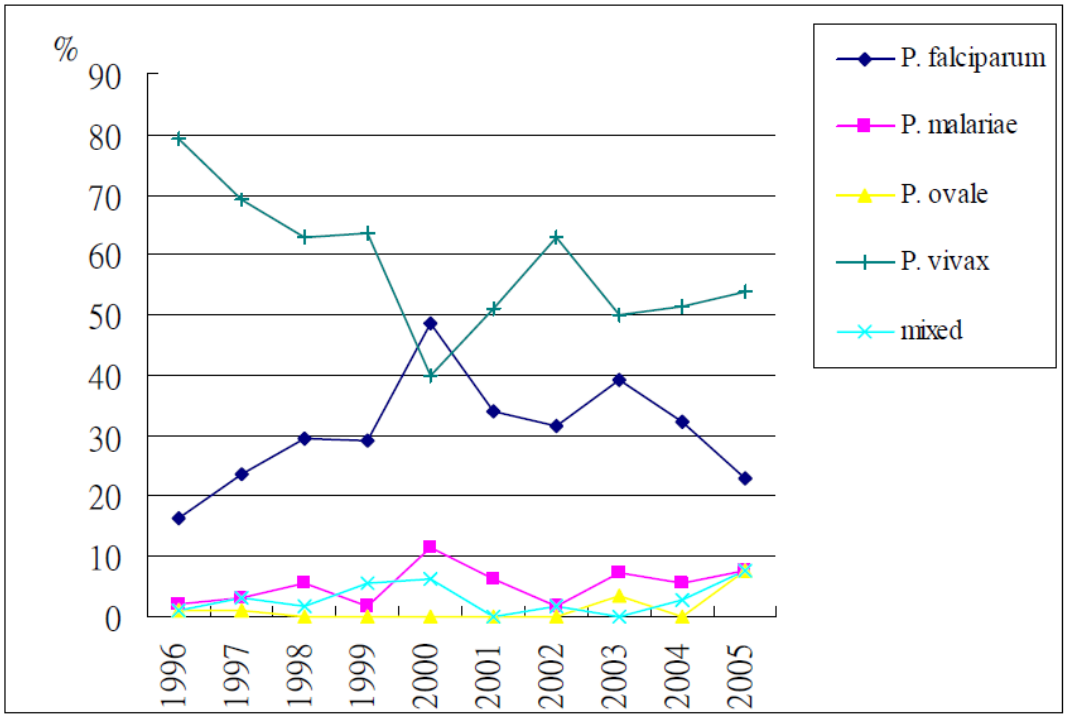


Figure 4 Type of parasites identified (1996-2005 June)

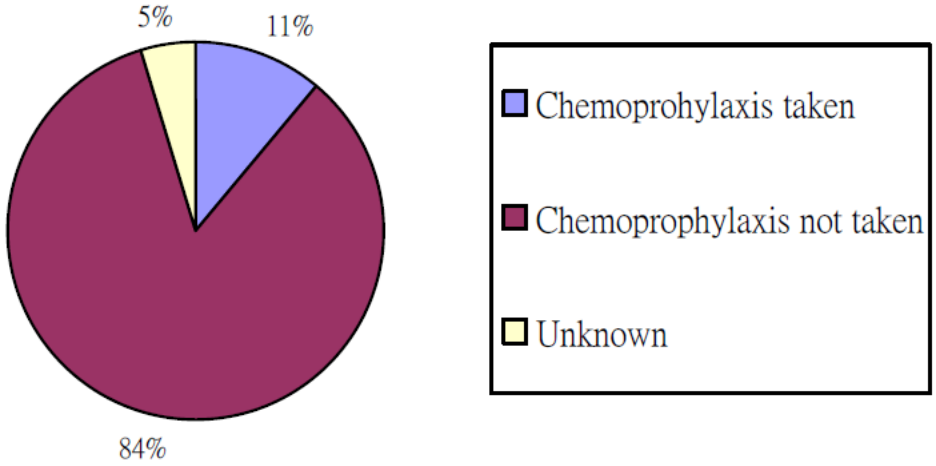


Figure 5. History of taking chemoprophylaxis among imported cases affecting local residents

Diagnosis

- Rapid diagnostic test to detect antigens
- Light microscopy of blood smear
- Molecular test

Light microscopy

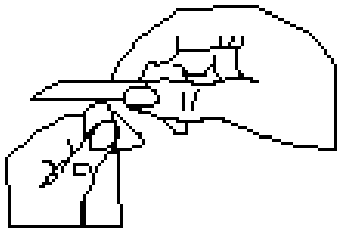
- Labor intensive and require substantial training and expertise
- Smear should be prepared soon after blood collection to avoid alteration in parasite morphology and staining properties
- Seen under 1000x magnification for at least 200 to 500 fields and for 20 to 30 minutes
- Counting asexual parasite and white blood cells in each microscopy until 200 WBC was counted. Continue counting of a total 500 WBC if < 10 asexual parasite are counted

Light microscopy

- Thick film: stained without methanol fixing, allow red cells but not parasite to lyse
  - High sensitivity to detect low number of parasite

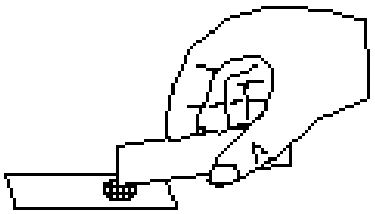
- Thin film: monolayer of red cells dried and fixed with methanol
  - Intensity of parasitaemia
  - Species identification
  - Parasite maturity
  - Neutrophil containing malarial pigment (haemozoin)
  - Monitor the effect of treatment

FIGURE A-2. Preparation of a thin and thick blood film on the same slide



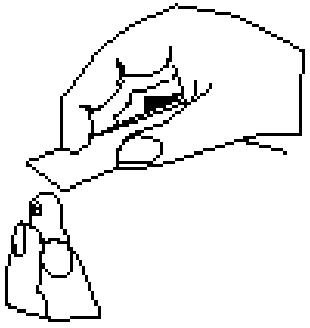
1

Touch the blood drop with a clean slide.



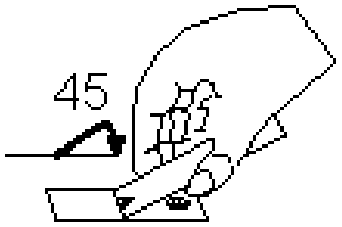
2

Using the corner of another slide, spread the blood drop into the shape of a circle or square of ~1 cm^2.



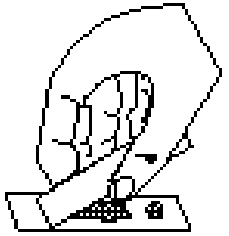
3

Gently squeeze the patient's finger again, and touch the edge of a clean slide to the newly formed blood drop.



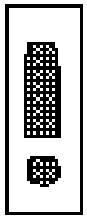
4

Take this slide and hold the edge that has the blood drop at an ~45 angle against the surface of the first slide. Wait until the blood completely spreads along the edge of the second slide.



5

While holding the second slide at the same angle, rapidly and smoothly push the slide forward.



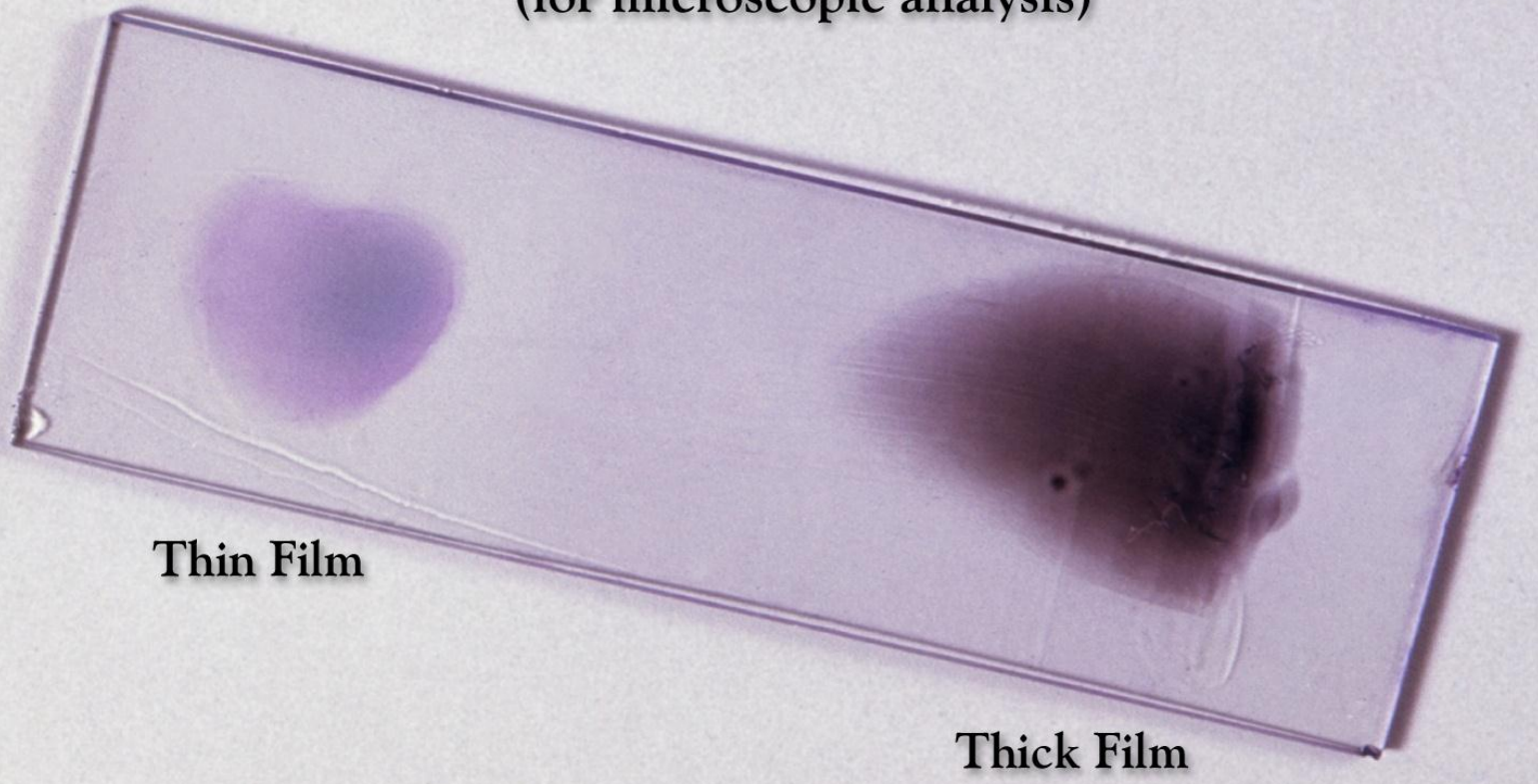
6

Write the identification number on the slide. Wait until the thick film is completely dry before staining it.

Blood Films

Properly Prepared Smears

(for microscopic analysis)



Rapid diagnostic test

- Detect parasite antigens: histidine-rich protein 2 (HRP2) [for falciparum], plasmodium LDH (pLDH) and aldolase
- Provide qualitative information only
- Cannot distinguish new infection and persistent infection in HRP2 antigenaemia
- Accuracy affected by various factors
- Inadequate negative predictive value in endemic areas
- Used outside endemic areas when expert diagnosis is not readily available and should be confirmed with microscopy

Molecular tests

- PCR assays targeting genus-specific and species-specific sequences of the 18S small-subunit ribosomal RNA, circumsporozoite surface protein and cytochrome b gene
- Detects low-density malaria or viability of parasite
- Gold standard in efficacy studies for anti-malarial drugs, vaccines and evaluation of other diagnostic agents
- Offered by CDC for confirmation of species and identification of drug resistance mutations in the US

Pathogenesis

- Plasmodium sporozoites transmitted via bite from an infected anopheles mosquitos
- Invades hepatocytes and divide > 1000 folds until mature tissue schizonts formed – exoerythrocytic stage
- Liver schizonts rupture after 6 to 30 days, releasing thousands of merozoites into bloodstream
- Invades RBC and mature red cell schizonts formed over 48 hours (for P falciparum) – erythrocytic stage
- Haemoglobin is digested by parasite and non-toxic metabolic haemozoin is formed

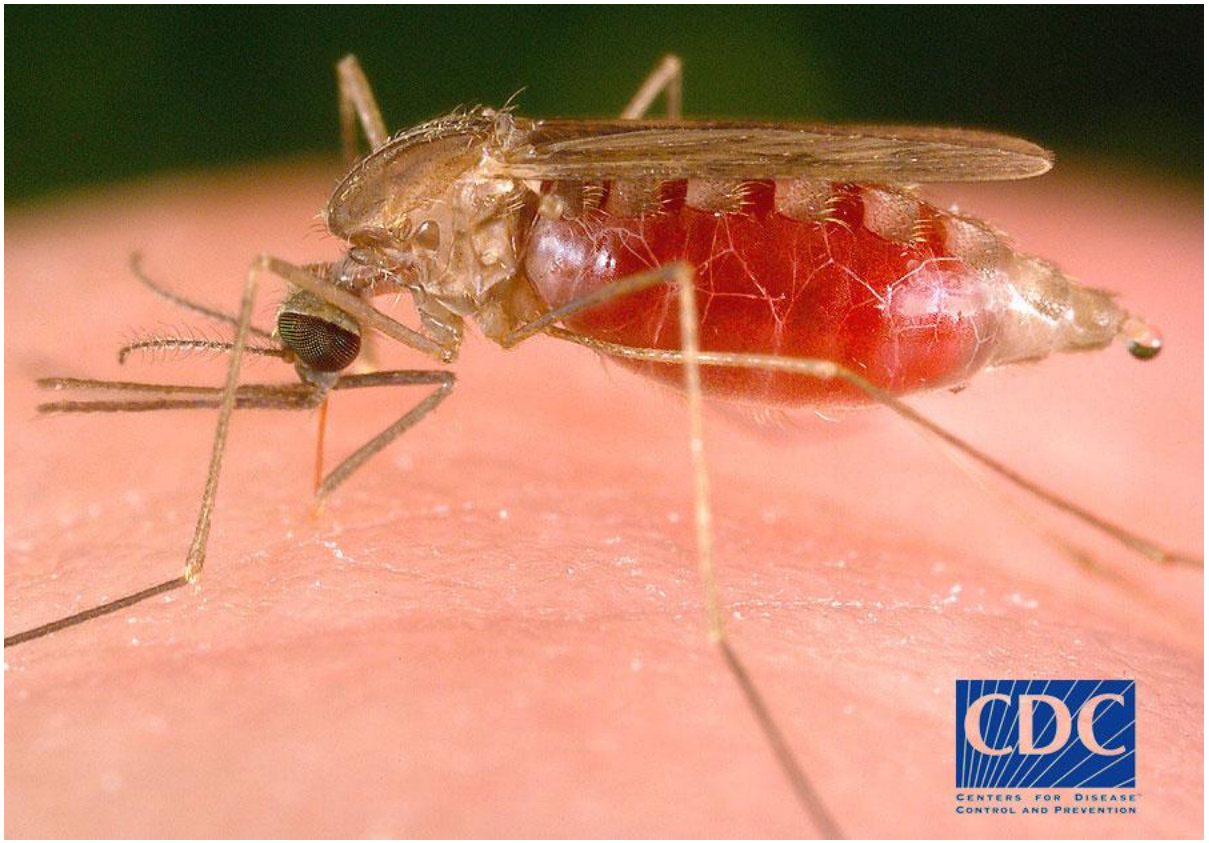
Pathogenesis

- Intracellular parasites derive energy from anaerobic glycolysis of glucose to lactic acid, contributing to hypoglycaemia and lactic acidosis
- Reduce red cell membrane deformability, resulting in haemolysis and accelerated splenic clearance
- Alters membrane of uninfected red blood cells
- Immune cascade activated when haemozoin are phagocytized by circulating macrophages
- Red cell lysis stimulates cytokines including TNF which further suppress haematopoiesis

Pathogenesis

- A few merozoites differentiate into gametocytes (sexual forms), which leave bloodstreams and develop in bone marrow over 3-4 days
- Ingested by blood-feeding anopheles mosquito and life-cycle completed in midgut
- Develop into sporozoites and migrate to salivary glands
- Reinfect humans through another bite

Anopheles mosquito – the deadly vampire



Anopheles mosquito is pumping blood on the skin

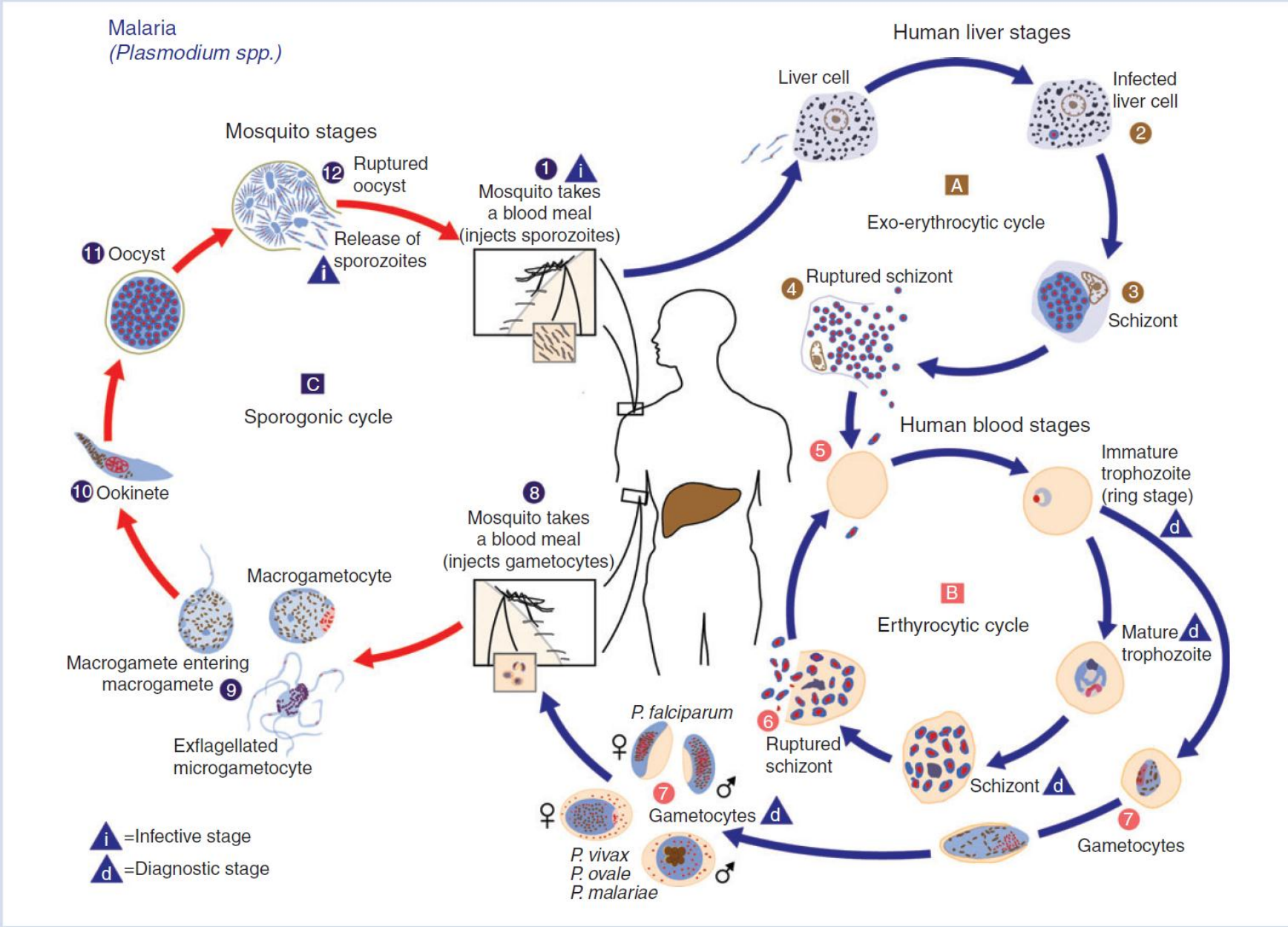
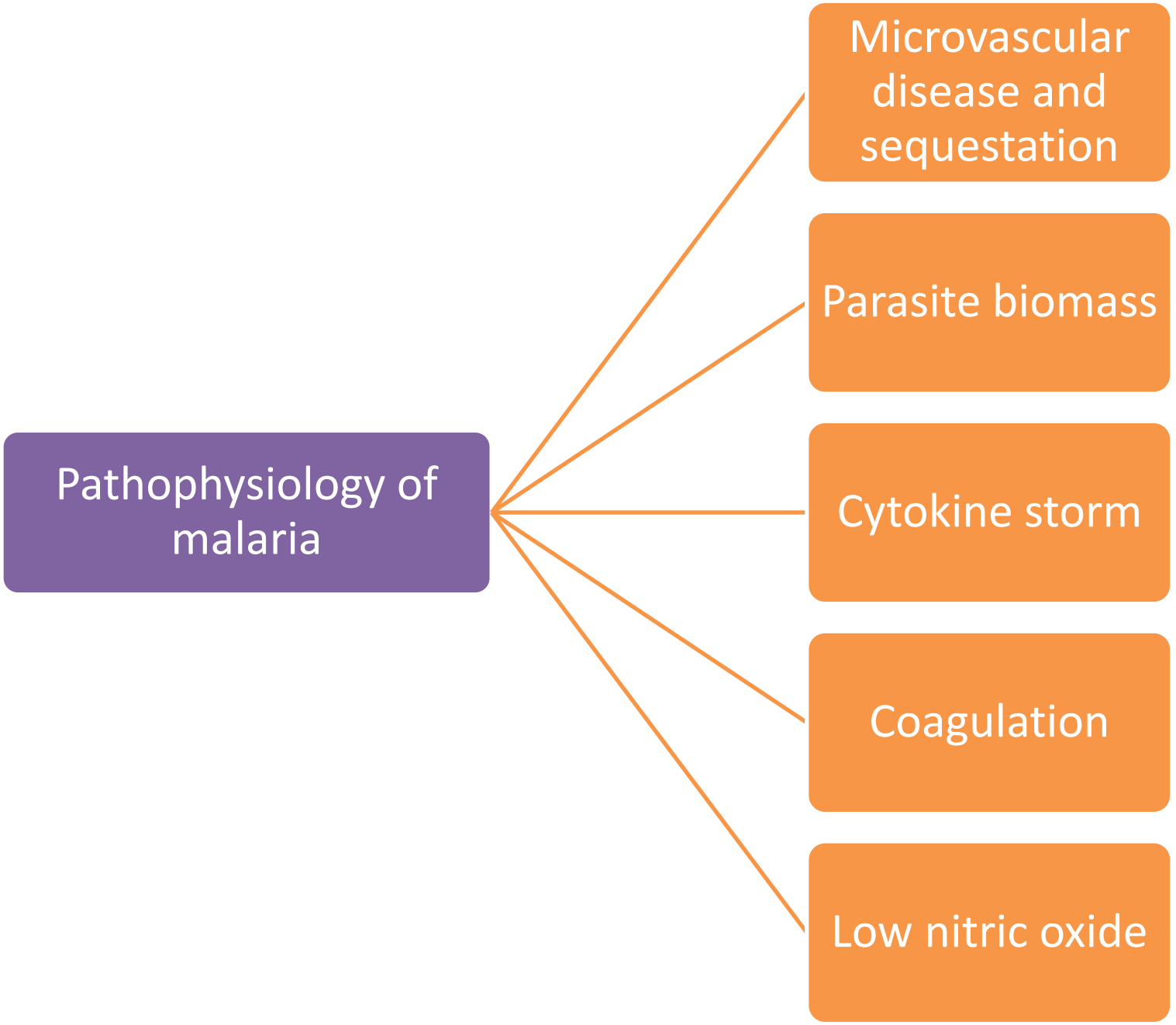
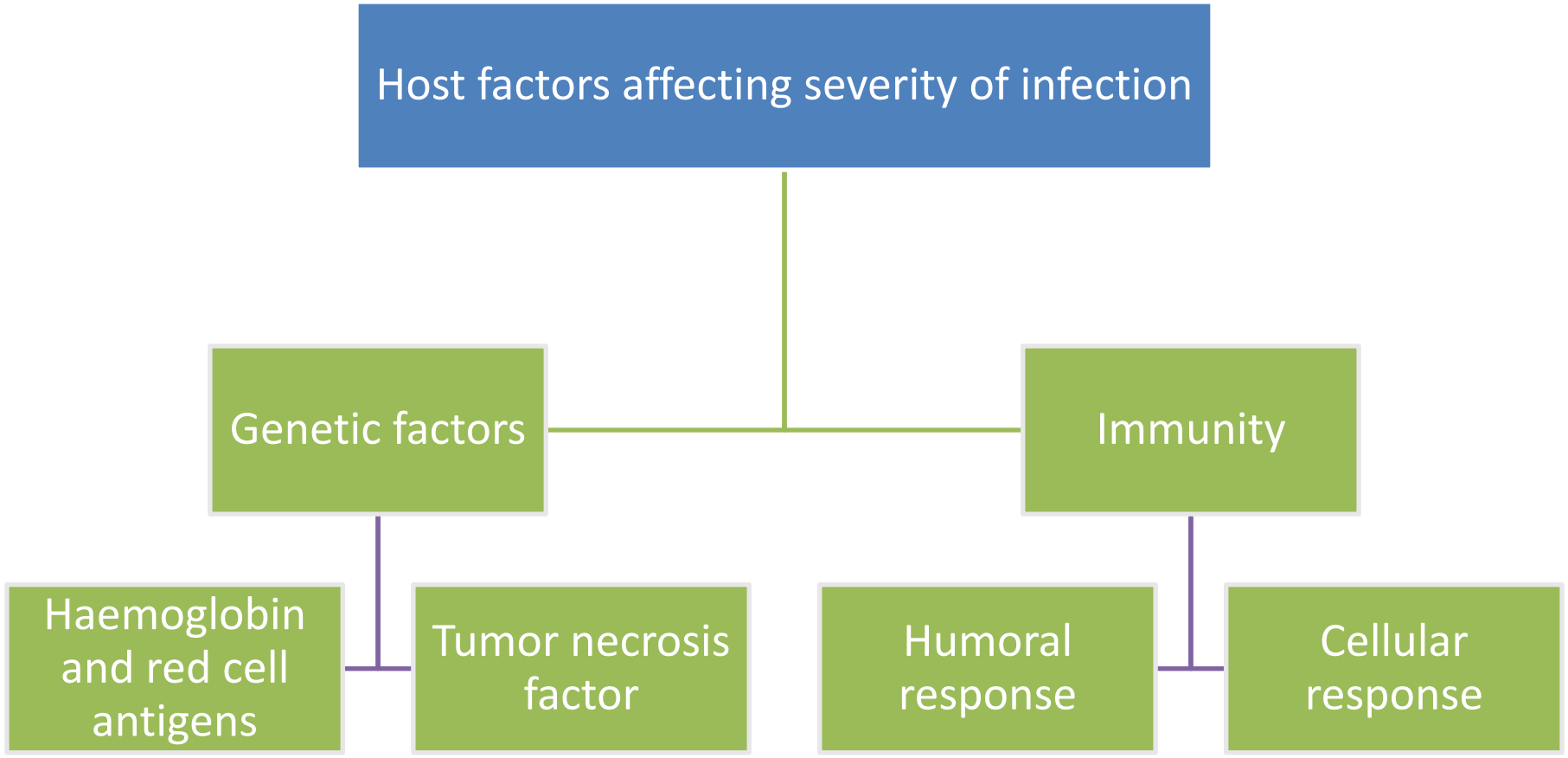


Fig 2 Life cycle of *Plasmodium*. Image from the Centers for Disease Control and Prevention (www.cdc.gov). Image produced by CDC — DPDx/Alexander J. da Silva, Melanie Moser.


Pathophysiology of malaria
Microvascular disease and sequestation
Parasite biomass
Cytokine storm
Coagulation
Low nitric oxide


Host factors affecting severity of infection
Genetic factors
Immunity
Haemoglobin and red cell antigens
Tumor necrosis factor
Humoral response
Cellular response

Clinical features

- Initial symptoms are non-specific
- Fever every 48 hours (72 hours for P. malariae)
- Tachycardia, tachypnoea, chills, malaise, fatigue
- Headache, sweating, cough, anorexia
- Nausea, vomiting, abdominal pain, diarrhoea
- Arthralgia, myalgia

Table 1 Criteria for severe malaria. Adapted from WHO Guidelines for the treatment of malaria, 2nd Edn.[27] http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html. Reproduced with permission of the World Health Organisation

Clinical features of severe falciparum infection
Cerebral malaria as characterized by impaired consciousness or coma, convulsions, or both
Acute respiratory distress syndrome
Circulatory collapse
Jaundice in the setting of other organ dysfunction
Haemoglobinuria
Abnormal spontaneous bleeding
Laboratory features of severe falciparum infection
Hypoglycaemia [<2.2 mmol litre^{-1} (<40 mg dl^{-1})]
Severe anaemia (Hb <5 g dl^{-1}, packed cell volume $<15\%$)
Metabolic acidosis (plasma bicarbonate <15 mmol litre^{-1} or pH <7.35)
Hyperparasitaemia ($>2\%/100\,000$ μl^{-1} in low-intensity transmission areas or $>5\%$ or $250\,000$ μl^{-1} in areas of high stable malaria transmission intensity)
Hyperlactataemia (lactate >5 mmol litre^{-1})
Acute kidney injury (serum creatinine >265 μmol litre^{-1}).

Cerebral malaria

- Encephalopathy presenting with impaired consciousness, delirium and seizures
- Clinical case definition
  - Impaired consciousness / blantyre coma score < 2
  - Falciparum malaria
  - No alternative identifiable cause of coma (e.g. hypoglycaemia, meningitis or post-ictal state)
- Cerebral edema and elevated ICP may lead to fatal outcome
- 30-40% had retinal haemorrhage, other findings include retinal opacification, papilloedema, cotton wool spots or decolourization of retinal vessels

Cerebral malaria

- Mean opening pressure in lumbar puncture is 16cmH_2O with normal or slightly elevated total protein level and cell count
- Neurological sequelae more common in children than adults (15% versus 3%)
  - Hemiplegia, cerebral palsy, cortical blindness, deafness, epilepsy, language deficit or impaired cognition
- Risk factors include age, pregnancy, poor nutritional status, HIV infection, host genetic susceptibility and immunity and history of splenectomy

Hypoglycaemia

- Diminished hepatic gluconeogenesis
- Depletion of liver glycogen storage
- Increased consumption of glucose by host
- Quinine-induced hyperinsulinaemia

- Common and carry poor prognosis particularly in children and pregnant women

Acute kidney injury

- Cytoadherence of parasitized erythrocytes to glomerular and tubular vascular beds
- Cytokine release
- Immune complex deposition
- Hypovolaemia
- Haemolysis

- Histopathological findings include acute tubular necrosis (common), intersitial nephritis and glomerulonephritis

Metabolic acidosis

- Anaerobic glycoglysis in host tissue
- Parasite lactate production
- Hypovolaemia
- Insufficient hepatic and renal lactate clearance
- Acute kidney injury

Acute respiratory distress syndrome

- Endothelial dysfunction and altered capillary permeability
- Parasitized erythrocyte adherence and sequestration
- Exaggerated host immune and inflammatory response, particularly TNF-alpha, IL-1, IL-6 and IL-8
- May reflect persistence of inflammatory cytokines in the absence of any infected erythrocytes

Cardiac dysfunction

- Elevated circulating level of cardiac enzymes including BNP in patients with severe malaria
- Low nitric oxide causes increased pulmonary pressures and myocardial wall stress

Anaemia

- Blackwater fever - massive intravascular haemolysis and haemoglobinuria in some patients particularly if semi-immune
- Associated with G6PD deficiency
- Worse prognosis when associated with renal impairment
- WHO defines severe anaemia when Hb < 5 g/dL
- Commonly seen in endemic areas, especially among children and pregnant women

Anaemia

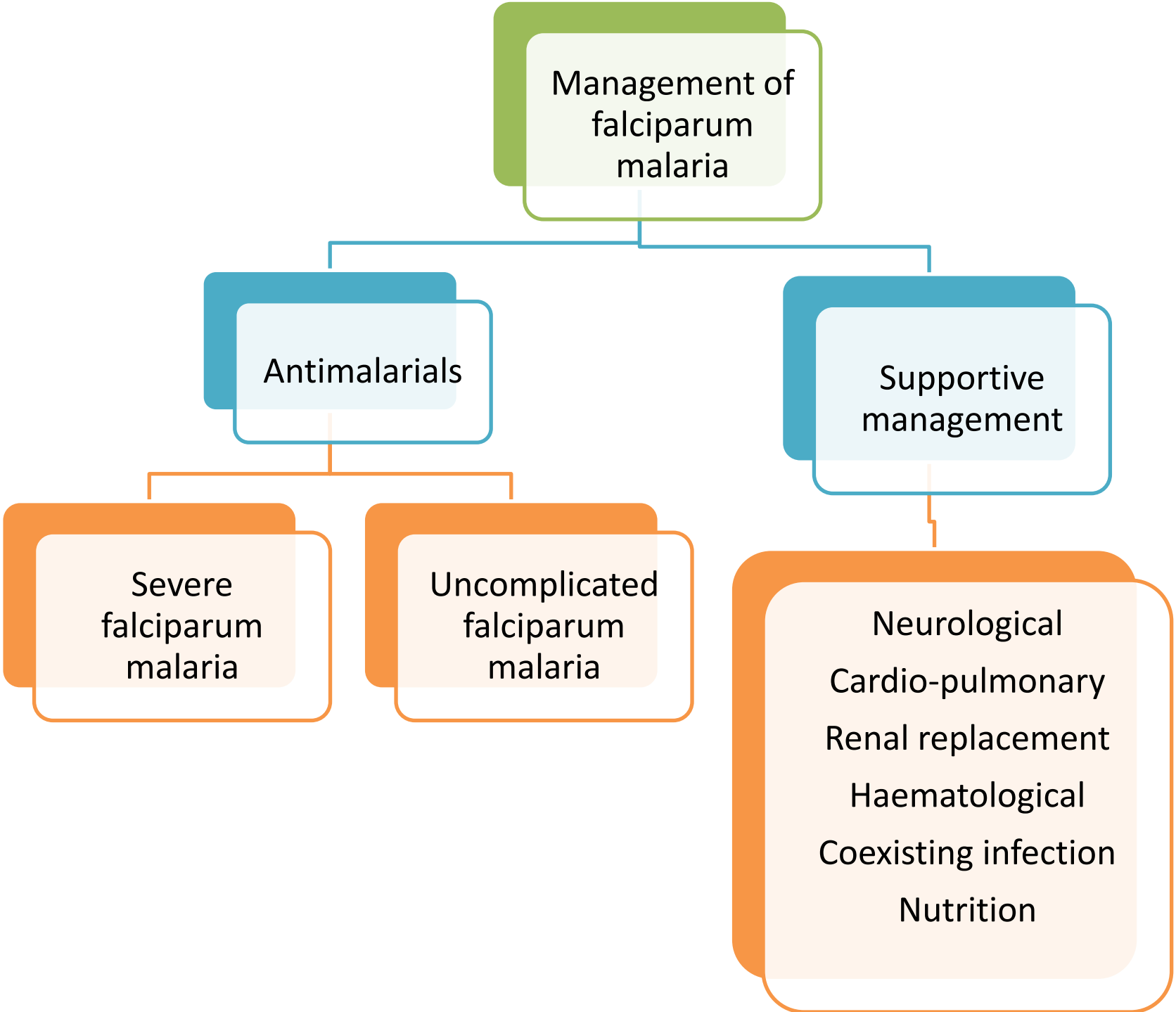
- Haemolysis of parasitized red cells
- Increased splenic sequestration and clearance of erythrocytes with diminished deformability
- Cytokine suppression of haematopoiesis
- Shortened erythrocyte survival
- Anaemia of chronic illness – repeated infections and ineffective treatments

Liver dysfunction and coaguloapthy

- Mild jaundice due to haemolysis
- Severe jaundice also due to hepatocyte injury and cholestasis
- Liver dysfunction results in coagulopathy
- DIC occurs in 5-10% of severe imported malaria
- Thrombocytopenia caused by increased platelet consumption and splenic sequestration

Coexisting infection

- Non-typhoidal salmonellae in 5-12% of children with malaria
- Heme-oxygenase-1 mediating tolerance to malaria-induced haemolysis results in reduced resistance to such infection
- High rates of co-infection with HIV reported in some series
- Ventilator assoicated pnuemonia
- Catheter related sepsis


Management of falciparum malaria
Antimalarials
Supportive management
Severe falciparum malaria
Uncomplicated falciparum malaria
Neurological
Cardio-pulmonary
Renal replacement
Haematological
Coexisting infection
Nutrition

Antimalarials – severe P. falciparum

- IV or IM **artesunate** 2.4mg/kg at time zero, then at 12 h and 24 h, then once daily for a total of 7 days
- Plus doxycycline 100mg po bd for 7 days or mefloquine 1000mg base po on day 2 then 500mg po on day 3

- Quinine dihydrochloride 20mg/kg loading dose in D5 infused over 4 hours, maintainence dose 10mg/kg infused over 2-4 hours every 8 hours. Change to oral dose when feasible to complete a 7-day course

Artesunate (青蒿琥酯)

- Derived from Qinghausu (青花素) or wormwood
- IV form of reliable quality not available in many countries
- In 2011 WHO recommends **IV artesunate as 1st line treatment** for severe malaria in both adults and children
- Not approved by US FDA but is available for use under investigational protocol

Evidence

- **Lower mortality** in artesunate group versus quinine **(15% versus 22%)** in open-label RCT of 1461 patients with severe falciparum in Bangladesh, India and Indonesia
  - *Dondorp A, Nosten F, Stepniewska K, et al. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial* Lancet 2005; 366: 717-725

- **Lower mortality** in artesunate group versus quinine **(8.5% versus 10.9%)** in open-label RCT of 5425 children < 15 years in nine African countries
  - *Dondorp A, Fanello CI, Hendriksen IC, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial* Lancet 2010; 376: 1647-1657

Evidence

- **IV Artesunate was superior** to quinine in terms of mortality (overall odds ratio 0.69, 0.57-0.84, p<0.00001) in a meta-analysis of seven randomised trials
- **Delayed haemolysis** is common (7-23% in two prospective trials) in both travellers and young African children with severe malaria
  - *Thierry R, Tsiri A, Sanjeev K, et al. Delayed haemolysis after artesunate treatment of severe malaria – Review of the literature and perspective* Travel Medicine and Infectious Disease (2015) 13, 143-149
- Artesunate still remained the **treatment of choice**

Monitoring

- Monitor Hb up to four weeks after treatment of artesunate
- No dosage adjustment for artesunate
- If quinine is used, monitor blood glucose, QT interval and renal function (adjust dose in renal failure)
- Look for cinchonism – tinnitus, visual blurring and nausea

- Parasite density should be monitored every 12 hours during first two to three days and then daily until negative to monitor treatment response of severe malaria

Antimalarials – uncomplicated P. falciparum

- Artesunate 200mg po daily for 3 days + mefloquine as above
- Atovaquone-proguanil (malarone) 4 tabs (1000mg atovaquone/400mg proguanil) po daily for 3 days
- Quinine 600mg every 8 hours for 7 days + doxycycline 100mg BD for 7 days
- Mefloquine + doxycycline (dosing as above)
- Chloroquine 600mg stat, 300mg 6 hours later and daily for 2 more days OR hydrochloroquine 620mg stat, 310mg 6 hours later and daily for 2 more days (chloroquine sensitive or other malaria species)

Supportive management – neurological

- No role for routine EEG monitoring and seizure prophylaxis
- Benzodiazepine remains first-line agents for seizure treatment
- Subsequent management follows the protocol for status epilepticus
- Supportive care to avoid elevation of ICP
- Dexamethasone fails to improve mortality, but also lengthen duration of unconsciousness and increase the risk of infection and gastrointestinal bleeding in two studies
- Adjunctive treatments including mannitol, aspirin, NAC, anti-TNF, heparin, deferoxamine fail to show clinical benefit

Supportive management

- **Meticulous fluid control** to strike a balance between intravascular volume depletion resulting in tissue hypoperfusion and fluid overload
- Use inotropes and vasopressors as indicated
- Respiratory support
  - Low tidal volume ‘protective’ ventilation and moderate PEEP
  - Fluid restrictive strategy
  - Cerebral edema and high ICP may limit the use of permissive hypercapnia and high PEEP
  - Use of ECMO has been reported
  - Monitor VAP and manage accordingly

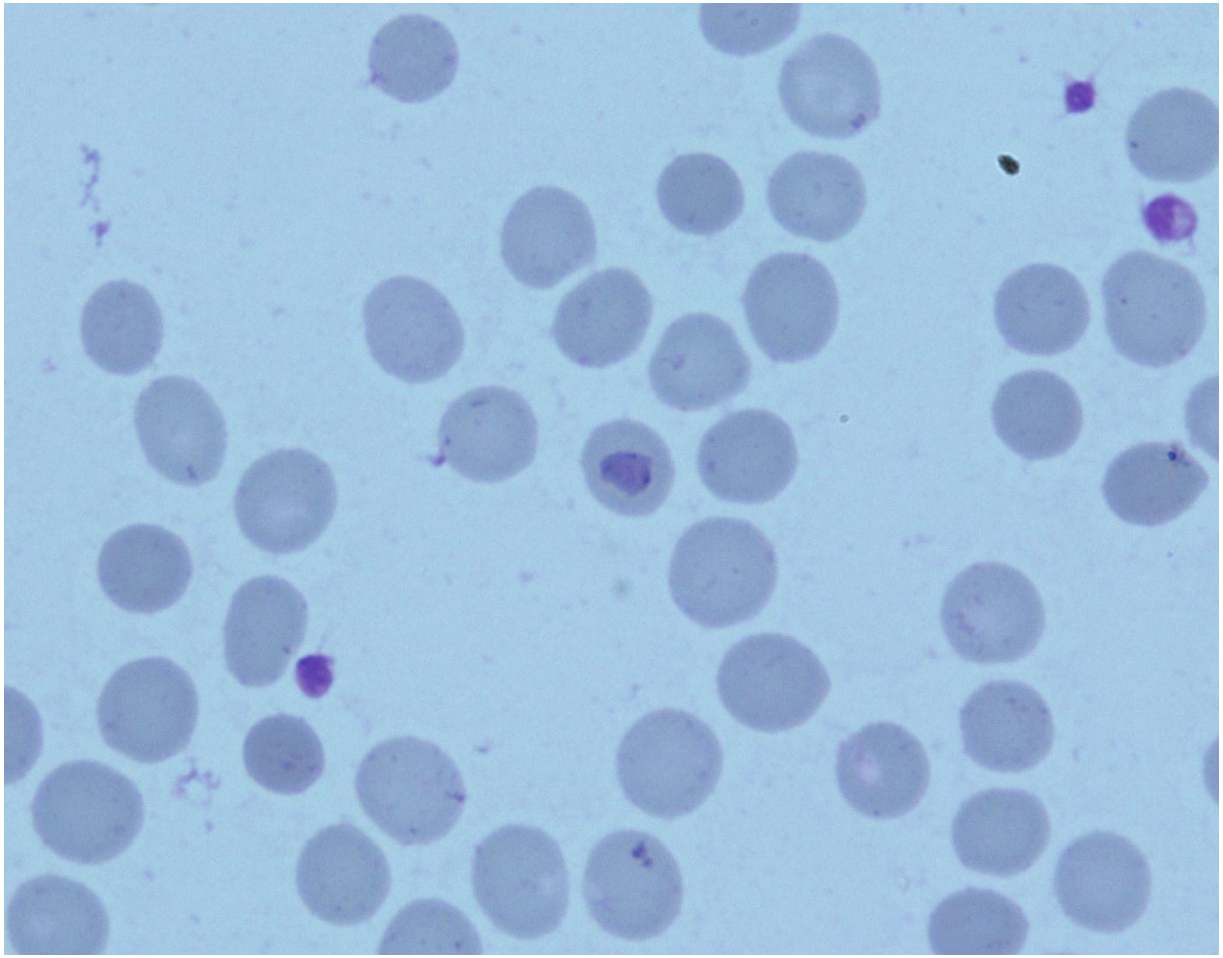
Supportive management

- Renal support
  - Maintenance of appropriate fluid balance and electrolytes
  - Avoid and adjust dosage of nephrotoxic drugs
  - Renal replacement therapy as indicated
- Early enteral feeding and correct hypoglycaemia
- Supportive blood product transfusion
- Treat secondary infection and ICU-related complications
- Surgical intervention for possible splenic rupture

Exchange transfusion

- Theoretically removes parasitized red cells, toxic products, harmful metabolites, cytokines and uninfected red cells and corrects anaemia
- Erythrocytapheresis has the advantage of speed, efficiency, haemodynamic stability and retention of clotting factors
- No evidence to support the efficacy and clinical benefit
- CDC and WHO not longer recommend currently

Back to our patient



Patient’s blood film after four days of IV artesunate and doxycycline

Our patient

- The density and sizes of trophozoites (ring form) were much reduced – estimated parasitaemia **<0.05% of RBC**
- **IV artesunate** was given for **10 days** and IV rocephin was given for 1 week
- IV doxycycline was changed to oral form
- In 2nd week of admission, there is still a **rare tiny ring form after prolonged examination of thick film (>100HPF)**
- Started another one week course of quinine (on top of doxycycline) after discussion with microbiologist
- Malaria smear becomes negative after three days of treatment

Our patient

- Fever resolved
- Inotropes were gradually weaned off on Day 7 ICU
- Enteral feeding was resumed and H'stix was stable
- Hb **7-8** platelet **385** LFT **9/217/30** INR **1.2**
- No more blood product transfusion required
- **Three** sessions of CRRT and **five** sessions of haemodialysis were delivered
- Urine output regained and serum creatinine gradually improved

Our patient

- GCS **E2VTM1-2**
- On low dose midazolam occasionally
- Repeat CT brain normal
- EEG on 24/8: severe diffuse encephalopathic state, no epileptic activities
- Limbs are flaccid – likely **critical illness polyneuropathy**
- Tracheostomy was done for prolonged mechanical ventilation

Our patient

- EEG on 8/9: Improved encephalopathic state with more delta waves seen
- MRI brain on 10/9: Non-specific signal changes at bilateral globus pallidus only
- Tolerates tracheal mask and ventilator was discontinued
- GCS further improved – **E2-4VTM4**
- Transferred to HDU for tracheostomy care and monitoring

Prognosis

- 5-29% mortality for patients with imported malaria requiring ICU admission
- Old age, reduced GCS and high parasitaemia at ICU admission associated with high mortality
- Coma-acidosis-malaria score derived from SEAQUAMAT data
  - 0-2 points for GCS and 0-2 points for base deficit
  - Total score < 2 identified patients who survived
- Malaria score for adults (MSA)
  - Anaemia (1), AKI (2), respiratory distress (3), cerebral malaria (4)
  - Score of 5 reported sensitivity of 89.9% and specificity of 94.1%
  - Score < 5 had good predictive power for survival

Prognosis – neurological

- Meta-analysis in 2015 (8 studies with 842 cases and 1163 controls) suggested survivors in cerebral malaria are at **increasing risk of long-term neurological adverse outcome**
- Epilepsy, IQ impariment, neuro-disabilities and behavioural disorder
- Cortical blindness, cerebellar ataxia and peripheral nerve palsy were also reported
- Acute disseminated encephalopathy (ADEM) responding with high-dose prednisolone was also reported

Prognosis – neurological

- **Post-malaria neurological syndrome (PMNS)** –self-limiting post-infective encephalopathy of varying severity that occurred within 2 months after an episode of P. falciparum
- Acute confusional state, convulsion, ataxia, ophthalmoparesis and tremor
- Possible immunological cause
- Normal blood film, CSF and neuroimaging
- May have extensive multi-focal white matter abnormalities on MRI brain during acute phase

Prevention

Scientific Committee on Vector-borne Diseases

Guidelines on Malaria Chemoprophylaxis for Travellers from Hong Kong

http://www.chp.gov.hk/files/pdf/guidelines_on_malaria_chemoprophylaxis_for_travellers_from_hong_kong_r.pdf

- Awareness of risk of malaria among travellers
- Preventing mosquito bites (physical and chemical)
- Proper use of chemoprophylaxis with good drug compliance
- High index of suspicion for breakthrough infection

Chemoprophylaxis

- Chloroquine
  - One week before and throughout journey, then continue for 4 weeks
  - 5mg base/kg once a week
  - Adverse effects: headache, dizziness, skin eruption, blurred vision, pruritis, impaired hearing, convulsion, blood disorder
  - Contraindications: psoariasis, epilepsy, G6PD deficiency
- Proguanil
  - One day before and throughout journey, then continue for 4 weeks
  - 3mg/kg daily
  - Adverse effects: nausea, diarrhoea, mouth ulcers, haematuria, hair loss
  - Contraindications: severe renal impairment

Chemoprophylaxis

- Mefloquine
  - One week before and throughout journey, then continue for 4 weeks
  - 5mg/kg once a week
  - Adverse effects: dizziness, headache, syncope, insomnia, diarrhoea, severe neuropsychiatric syndrome
  - Contraindications: aircrew, epileptic, psychiatric disorder , first 3 months of pregnancy, allergy to quinine
- Doxycycline
  - One day before and throughout journey, then continue for 4 weeks
  - 1.5mg salt/kg daily
  - Adverse effects: nausea, diarrhoea, candida vaginitis, skin photosensitivity
  - Contraindications: pregnancy

Chemoprophylaxis

- Atovaquone-proguanil (malarone)
  - One day before and throughout journey, then continue for 7 days
  - 40kg / 1 tab daily
  - Adverse effects: abdominal pain, nausea, vomiting, headache, diarrhoea, mouth ulcers, hair loss, haematuria
  - Contraindications: severe renal impairment

- **Individual risk assessment and counseling beforehand:** endemicity, predorminant strains, visiting areas, climate and seasonlity, altitude, pattern of activities, duration of stay and individual characteristics

Special considerations

- **Stand-by emergency treatment** in:
  - Those who elect not take chemoprophylaxis
  - Those travelling to areas with low level of transmission
  - Those receiving suboptimal chemoprophylaxis due to underlying medical conditions and possible drug interactions
  - Those taking effective chemoprophylaxis but with difficult access to appropriate medical care

- **Special groups:** young children, pregnant women, breast-feeding mothers, immunocompromised, long term or frequent travellers, those returning to endemic areas after staying in malaria free area for long time

Conclusions

- Malaria is a potentially lethal disease
- We can still see **severe falciparum malaria with multi-organ failure** in this locality nowadays although uncommon
- Chemoprophylaxis and advice for potential travellers to endemic areas of malaria is of utmost importance
- Be vigilant for fever in returning travellers even they have taken appropriate precautions and chemoprophylaxis