Malaria

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Outline

- Overview of malaria epidemiology
- Malaria pathophysiology and clinical features
- Recognition of severe malaria
- Management
Malaria: introduction

- 3.3 billion at risk
- Estimated 250 million cases per year
- Nearly 1 million deaths per year
- Huge advances in malaria control over the past 5–10 years
- Huge increase in international funding (US$1.8 billion 2009)
- ↑ in coverage mosquito nets
- ↑ in spraying
- ↑ access to ACT
- Many countries moving towards malaria elimination
Shrinking the malaria map

Feachem et al. Lancet 2010
Malaysia now in the pre-elimination phase of malaria control

- Majority of cases occur in Sarawak and Sabah
- Incidence in West Malaysia < 0.1/1000
- Control strategies:
  - ↑ use of mosquito nets
  - ↑ spraying
  - ↑ use of ACT

No. of cases ↓ from 12,705 in 2000 to 7010 in 2009

Major species: P. falciparum, P. vivax, P. knowlesi
Challenges for Sabah...

- Vivax malaria
- Knowlesi malaria
Vivax malaria

- Up to 390 million cases annually
- Accounts for at about half of malaria outside Africa
- Represents an increasing public health problem:
  - More difficult to eliminate than Pf
  - ↑ resistance to chloroquine
  - Increasingly recognized as a cause of severe disease
Vivax malaria: challenges for elimination

- Relapses
  - Regional variation

- Gametocytes appear earlier in infection
  - 50 – 80% of patients have gametocytes on presentation, compared to 10 – 40% with Pf

- Gametocytes more effectively transmitted to mosquitoes
Malaria on the Thai-Myanmar border

Infections/ person/ 6 mths

P.f
P.v
Mixed

'91 '92 '93 '94 '95

Malaria in Brazil

Oliveira-Ferreira et al. Malaria Journal 2010, 9:115
Chloroquine resistant P. vivax
Demographic Risk Factors for Severe and Fatal Vivax and Falciparum Malaria Among Hospital Admissions in Northeastern Indonesian Papua

Mazie J. Barcus,* Hasan Basri, Helena Picarima, C. Manyakori, Sekartuti, Iqbal Elyazar, Michael J. Bangs, Jason D. Maguire, and J. Kevin Baird

Plasmodium vivax and Mixed Infections Are Associated with Severe Malaria in Children: A Prospective Cohort Study from Papua New Guinea

Blaise Genton¹, Valérie D’Acremont¹, Lawrence Rare², Kay Baea², John C. Reeder², Michael P. Alpers², Ivo Müller²

Multidrug-Resistant Plasmodium vivax Associated with Severe and Fatal Malaria: A Prospective Study in Papua, Indonesia

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Vivax complications

- Severe anaemia
- Respiratory distress
- ARDS
- Jaundice
- Splenic rupture
- Acute renal failure
- Pancytopenia
- Cerebral malaria
Plasmodium knowlesi: The Fifth Human Malaria Parasite

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Plasmodium knowlesi
new parasite on the block

Monkey malaria in man
Balbir Singh and colleagues (Mar 27, p 1017) report interesting data on the occurrence of Plasmodium knowlesi in a human population in Malaysian Borneo. Cross-species transmission of M knowlesi from monkeys to humans is well documented.

Macaca fascicularis
Macaca nemestrina
Background: *Plasmodium knowlesi*

- Knowles, R. DasGupta BM. *Indian Medical Gazette* 1932
  - demonstrated infection of humans by inoculation of blood from infected monkeys
- Used as a pyretic agent for treatment of neurosyphilis - 24 hr asexual replication cycle
- Chin, W et al. *Science* 1965
  - First naturally acquired case of human knowlesi malaria
1999 – 20% of malaria cases in Kapit identified as *P. malariae*

*P. malariae* infections noted to be atypical

PCR performed on 5 isolates – neg for *P. malariae*

2000 – 2002: 120 (58%) of 208 malaria cases diagnosed with *P. knowlesi* by PCR

No cases of *P. malariae*
 PCR performed on 960 malaria blood films from Sarawak 2001 – 2006: 28% *P. knowlesi*

- Sabah: 41/49 (84%) *P. malariae* blood films positive for *P. knowlesi*
- West Malaysia: 4/4 *P. malariae* blood films positive for *P. knowlesi*

- 4 fatal cases of knowlesi malaria
  - High parasitemia, multi-organ failure
Prospective study

152 adult malaria cases in Kapit, Sarawak
- 107 (70%) *P. knowlesi*

Most (93.5%) had uncomplicated malaria that responded well to CQ and PQ

8 (7.5%) had severe infection

2 patients died (case fatality 1.8%)
24/41 (59%) of all childhood malaria

Children with Pk older than those with Pf (mean age 8.9 vs. 5.2 years, P<0.002)

Anaemia common
- all had Hb<11 on admission
- median Hb nadir 9.7
- 1 child had Hb 6.4

All were thrombocytopenic (mean Plt nadir 76, lowest 28)
Severe knowlesi malaria at QEH

- Retrospective study from Dec ‘07 - Nov ’09
- 56 patients with knowlesi malaria
- 22 (36%) had severe malaria, 6 (10.7%) deaths
- Complications included respiratory distress (59%), acute renal failure (55%), shock (55%)
- Risk factors for severe disease:
  - Older age

William et al, Emerg Inf Dis 2011
Knowlesi malaria: points to remember

- Nearly all reports of *P. malariae* are actually *P. knowlesi*
- *P. knowlesi* can be severe and potentially life-threatening
- Can present very similar to dengue
- May not appear severe on first presentation
- Older age group at ↑ risk of severe disease
- Thrombocytopenia is universal, and can be severe
- Resp complications common in severe disease
- Treatment the same as for *P. falciparum*
Pathophysiology

- Invasion of RBCs
  - → Haemolysis
  - → Release of cytokines

- Cytoadherence, rosetting, autoagglutination, reduced deformability
  - → sequestration
  - → microvascular obstruction
  - → ischaemia
  - → organ dysfunction
Clinical features

- Fever
- Headache, dizziness
- Arthralgias, myalgias, back ache
- Abdominal pain
- Nausea, vomiting
- Diarrhoea
- Cough, breathlessness
- Abnormal bleeding
- Jaundice
- Pallor
- Hepatosplenomegaly
- Petechiae, brusing
- Tachypnoea, hypoxia
- Acute abdomen
Biochemical features

- Anaemia
- Thrombocytopenia
- Hypoglycemia
- Hyperbilirubinemia
- ↑ ALT/AST (usually mild)
- Renal failure
- Metabolic acidosis
Management

- Severe malaria
  - Malaria with any feature of severity

- Uncomplicated malaria
  - Malaria without any feature of severity
WHO Criteria for severe malaria

Clinical features:
- Impaired consciousness
- Prostration (severe weakness)
- Failure to feed
- Multiple convulsions
- Respiratory distress
- Shock
- Jaundice + other organ failure
- Abnormal spontaneous bleeding
- Pulmonary oedema

Biochemical features:
- Hypoglycemia (BSL<2.2)
- Severe anaemia (<7g/dL)
- Lactate >5
- Renal impairment (Cr>265)
- Metabolic acidosis (HCO3<15)
- Haemoglobinuria
- Hyperparasitemia (>100,000/µL)

Reference: 2010 WHO Guidelines for the treatment of severe malaria
Approach to treatment of malaria

Do they have severe malaria?

- No
- Are they vomiting?
  - Yes
    - Give iv artesunate
  - No
    - Pf or Pk
      - Yes
        - Riamet
      - Pv
        - CQ + PQ
Severe malaria: drug treatment

- iv artesunate 2.4mg/kg stat, 12 hrs, 24 hours, then daily
- Change to Riamet when able to tolerate oral meds (usually after 3 doses of artesunate)
- consider empirical antibiotics (eg. Ceftriaxone)
  - Always take blood cultures first
  - Cease Abs if blood cultures negative
Severe malaria: supportive management

- Consider HDU/ICU referral
- iv fluids
- O2
- Blood transfusion
- Dialysis
- Monitoring –
  - BP, O2Sats, RR
  - Daily BSMP, daily FBC (platelets usually recover quickly, but Hb usually falls)
Treatment of uncomplicated Pf / Pk

- All patients should be given combination therapy
  - More effective
  - Prevents development of resistance

- Recommended treatment for uncomplicated Pf
  - Artemisinin Combination Therapy
    - Riamet (artemether/lumefantrine)
    - Artequine (artesunate/mefloquine)
Artemisinin derivatives

- Rapid clearance of parasites
  - reduce parasite density by a factor of 10,000 in each 48 hr asexual cycle
- Rapidly eliminated, so need to be combined with longer acting partner drug
  - 3 day course of artemisinin derivative will clear ≥90% of parasites
  - Remaining 10% of parasites will be cleared by partner drug
- Reduce gametocyte carriage
Practice points: Riamet

- **Riamet**: 20mg artemether + 120mg lumefantrine
- **Dosage**: 4 tabs stat, followed by 4 tabs 8 hrs later, then 4 tabs bd 2/7 (total of 6 doses)
- **For children**
  - 25 – 34kg: 3 tabs, 15 – 24kg: 2 tabs, 5 – 14kg: 1 tab
- **Must be given with ≥ 1.2g fat to increase absorption**
Riamet alternatives

- Alternatives:
  - An alternative ACT (eg. artesunate/mefloquine)
  - Artesunate + doxycycline for 7 days
  - Quinine + doxycycline for 7 days
Treatment of uncomplicated Pv

- Chloroquine still 1st line treatment for P. vivax in Malaysia
- Dose: 25mg base/kg over 3 days
  - 10mg/kg stat, 5mg/kg 6hrs, 5mg/kg day 1 and 2
  - 10mg/kg stat, 10mg/kg 6 hrs, 5mg/kg day 1
- Dosage refers to CQ base, not CQ Phosphate
- Commence PQ as soon as possible, if G6PD normal
Primaquine for preventing relapses

- Only drug available

- 15mg daily for 14 days initially adopted as standard regimen, but treatment failures common

- Recommended dose in Sth East Asia
  - 40 – 70kg: 30mg daily 14/7
  - Otherwise, 0.5mg/kg/day (total 6mg/kg)
  - If >90kg, 0.5mg/kg/day until total dose reached
Toxicity of Primaquine

- Abdominal discomfort, nausea, vomiting
  - Usually resolved if primaquine taken with food
  - Can given in divided doses

- Haemolytic Anaemia
  - Occurs in people with G6PD deficiency
  - Begins 24 – 72 hours after commencing primaquine
  - Severity depends on degree of enzyme deficiency
  - Haemolysis less severe or absent using primaquine 45mg or 60mg weekly for 8 weeks
Preventing relapses in pregnant women and patients with G6PD deficiency

- **Moderate G6PD deficiency:**
  - 45mg weekly for 8 weeks

- **Severe G6PD deficiency:**
  - Chloroquine prophylaxis for 6 – 8 weeks

- **Pregnancy**
  - Chloroquine prophylaxis until delivery
  - Primaquine post-delivery
Malaria in pregnancy

- Associated with low birth weight, increased risk of anaemia, increased risk of severe malaria and death

1st trimester:
- Current data indicates no adverse effects of ACT, but more data required
  - Pf – quinine + clindamycin 7/7

2nd trimester
- ACT
Case study: Mr KK

- 55 year old man, previously well
- Presented with 3/7 fever, headache, myalgias
- No vomiting, no abdo pain, no diarrhoea
- No resp symptoms, no bleeding tendencies
- BSMP at Tamparuli: Pv 3+, platelets 35

- Seen in ED - vital signs stable, hepatomegaly and jaundice noted – referred to medical MO
- Seen by MO – “uncomplicated Pv” – plan: chloroquine
Progress

- Admitted to MMW
- Repeat BSMP at QEH: Pm/Pk 4+
- BP overnight – 70/50, minimal improvement with fluid resuscitation
- Transferred to ICU later the following day
Additional blood results on admission:
- Platelets 20
- Bilirubin 189
- Na 127
- Cr 120
- Parasite count: 1.8 million

Subsequent blood results day 1 - 3:
- Bilirubin peaked at 290
- LDH ~2000
- Hb dropped to 7.3, transfused 2 units
Lessons...

- Microscopy reports can be wrong –
  - Assessing the patient is more important than looking at the BSMP report
- Carefully assess for *any* feature of severity (eg. Jaundice)
- Remember older patients are more at risk of severe disease
- Treat all **severe** malaria with iv artesunate – regardless of species
- Think about early ICU referral
Summary: things to remember

- **P. knowlesi**
  - in Sabah, “P. malariae” is nearly always P. knowlesi
  - can be severe and potentially life-threatening
  - Older age group at increased risk of severe disease

- **Severe malaria**
  - Know the features and complications of severe malaria
  - iv artesunate as soon as possible
  - Close monitoring for complications

- **Uncomplicated malaria**
  - Riamet for Pf and Pk
  - CQ + PQ for Pv