Malaria diagnostics, clinical presentation and treatment

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Malaria epidemiology

• Globally (WHO report 2014):
  – 200 million cases
  – 600 000 deaths

• Europe (ECDC report 2014):
  – 5 161 cases
  – 1/100 000/year
  – Imported cases 99%
Malaria Lithuania and Norway

Malaria life cycle

- Anopheles
- Sporozoites
- Liver schizont
- Gametocytes multiply in mosquito
- Parasites multiply in red cells
- Merozoite invade red cell
Five species infect humans

Potentially severe malaria:
• *P. falciparum*
• *P. knowlesi*
• *(P. vivax)*

Benign malaria:
• *P. vivax* (usually)
• *P. ovale curtisi* and *wallikeri*
• *P. malariae*
Uncomplicated malaria – clinical presentation

- Unspecific fever

- Headache, myalgia, nausea, vomiting, diarrhoea
Severe malaria clinical presentation

- Coma (cerebral malaria)
- Severe anaemia
- Kidney failure
- Acidosis
- Pulmonary oedema
- Hypoglycaemia
- Spontaneous bleeding
- Shock
- Haemoglobinuria
- Hyperparasitaemia (>2-4%)
Diagnostics

- Giemsa stained blood slides
- Rapid diagnostic tests
- PCR
P. falciparum
P. vivax
Rapid diagnostic tests

- Detects
  - Histidine rich protein-2 (*P.falciparum* specific)
  - *Plasmodium* specific aldolase (pan-malaria)
  - *Plasmodium* associated LDH (pan-malaria)
WHO quality assurance reports

Figure S1: Malaria RDT performance in phase 2 of rounds 2–5 against wild-type (clinical) samples containing *P. falciparum* at low (200) and high (2000–5000) parasite density (parasites/μL) and clean-negative samples.

Panel detection score: A sample is considered detected only if all RDTs from each kit read by the first technician, at the minimum specified reading time, are positive.

Clean-negative: blood samples from healthy volunteers with no known current illness or blood abnormality.

Indicates tests that also detect other non-*P. falciparum* parasites.
PCR

- Detects parasite DNA
- Most sensitive method
- Not available in routine diagnostics
PCR versus microscopy
Bergen – Norway

Ref: Haanshus, Mohn, Mørch et al. Malaria journal 2013.

<table>
<thead>
<tr>
<th>Samples (n = 135)</th>
<th>New single-round amplification mitochondrial (PCRpgMt19 F3 &amp; B3 [21])</th>
<th>Modified single-round amplification 18S PCR (rPLU 6 &amp; 5 [9])</th>
<th>Genus-specific nested 18S PCR [10]</th>
<th>Microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>28</td>
<td>27</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Negative</td>
<td>107</td>
<td>108</td>
<td>108</td>
<td>109</td>
</tr>
</tbody>
</table>
PCR versus microscopy globally

• Meta analysis:
  – 70 paired microscopy and PCR estimates from endemic areas (Africa, Asia, Americas)

• Microscopy detected 50.8% of malaria cases detected by PCR

Okell et al. JID 2009
Artesunate compared to quinine efficacy

- Artesunate reduces mortality in endemic areas:
  - Relative risk 0.61 in adults
  - Relative risk 0.75 in children

Treatment

• **Severe**
  – Artesunate i.v.
  – Quinine i.v.
  – Change from i.v. to a full course of oral drug when condition allows

• **Uncomplicated *P. falciparum***
  – Artemether-lumefantrine
  – Atovaquone-proguanil
  – Mefloquine

• **P. vivax, P. ovale**
  – Chloroquine + primaquine

• **P. malariae**
  – Chloroquine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Artesunate</td>
<td>2.4 mg/kg intravenously immediately and after 12 and 24 hours, then once daily, normally for up to 3 days. Change to peroral drug as with uncomplicated falciparum malaria when the patient can swallow tablets and parasitaemia &lt; 1%</td>
</tr>
<tr>
<td>Quinine</td>
<td>1200 mg (20 mg/kg) infused over 2–4 hours as saturation dose, then 600 mg (10 mg/kg) at 8-hour intervals. The total dose per day should not exceed 1800 mg. Change to peroral medication as for uncomplicated falciparum malaria when the patient can swallow tablets and parasitaemia &lt; 1%</td>
</tr>
<tr>
<td>Artemether-lumefantrine (artemether 25 mg, lumefantrine 120 mg)</td>
<td>4 tablets at 0, 8, 24, 36, 48 and 60 hours. Should be taken with fatty food</td>
</tr>
<tr>
<td>Dihydroartemisinin-piperaquine (dihydroartemisinin 40 mg, piperaquine tetraphosphate 320 mg)</td>
<td>36–75 kg: 3 tablets once a day for three days. 75–100 kg: 4 tablets once a day for three days. To be taken between meals</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>Initially 750 mg (3 tab.), after 6–8 hours 500 mg (2 tab.) and for patients &gt; 60 kg after a further 6–8 hours 250 mg (1 tab.). To be taken with food</td>
</tr>
<tr>
<td>Proguanil-atovaquone (proguanil 100 mg, atovaquone 250 mg)</td>
<td>4 tablets once a day for three days. Should be taken with fatty food</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Initially 600 mg (4 tab.), after 6 hours 300 mg (2 tab.). Then 300 mg daily for 2 days. To be taken with food</td>
</tr>
<tr>
<td>Primaquine</td>
<td>15 mg per day for 14 days. If acquired in areas with primaquine resistance (see text) or in areas where relapses have been recorded after normal dosage: 22.5 mg or 30 mg or 0.5 mg/kg per day for 14 days. Primaquine is contra-indicated during pregnancy or in cases of G6PD deficiency.</td>
</tr>
</tbody>
</table>

Side effects

• Artesunate: Post treatment heamolysis
  – May require repeated blood transfusions
  – Hgb should be monitored 2–4 weeks after treatment

• Quinine: Arrythmia, hypoglycaemia, cinchonism
  – Infusion slow (2–4 hours)
  – Cardiac monitoring during infusion
Preparedness for severe malaria in a non-endemic country

- Among all hospitals in Norway
  - 40% (19/48) not artesunate or quinine available
  - 6% no diagnostic methods available

- In Lithuania?

Malaria patient

• Previously healthy doctor

• Did not turn up at work as usual

• Colleges alarmed the police who found him in his home; confused

• Admitted to department of neurology with tentative diagnosis cerebral stroke
Findings

• Dysphasia

• Awake but confused

• RF 40, puls 120, temperature 39

• Sent for MRI
The nurse received information saving the patient
Test results

- Malaria rapid test: *P. falciparum* positiv
- Lactate: 10
- Platelets: 11
- Creatinine: 120
- Bilirubin: 121
- LD: 522
- INR 1.4, APTT 46, D-dimer > 20 (DIC)
Blood smear
Blood smear two hours later
Treatment

- Artesunate
- Exchange transfusion
Thank you for your attention
Klausimai?