Background

- Frequent cause of fever in travelers to developing countries (25 to 42%)
- Huge difference in malaria risk
- First cause of mortality among travellers with fever after return

Falciparum malaria: data from ITM Fever Study 2000-2005

- 22% of fever cases
- 98% imported from Subsaharan Africa
- 91% occurring within one month after return
- 46% hospitalization rate
- 19% with severe malaria
- 1% overall mortality rate

Fever study: conclusions

Malaria is by far the most important causative pathogen, and is associated with major morbidity.

It is also the only tropical cause of mortality.

Revised criteria of severe malaria (WHO 2000): are these appropriate for disease management decision making?

Severe Malaria: revised WHO criteria

- Parasitaemia (>5% of RBC or >200 000/µl)
- Cerebral malaria or coma,
- Convulsions
- Acute renal failure (urine output <400/24h or creatinine >2.5 mg/dl)
- Respiratory failure and/or ARDS
- Circulatory collapse (RR < 80/50 mmHg)
- Spontaneous bleeding and/or PLT < 20000/µl
- Hypoglycaemia (<40 mg/dl)
- Acidosis (pH <7.25)
- Jaundice (bilirubin >3 mg/dl or >50 µmol/l)
- ALAT/ASAT >3 x UNL
- Anaemia (Hb <8 mg/dl)

Macroscopic changes in Cerebral Malaria

Perivascular hemorrhages in white matter
Early changes in Cerebral Malaria

Intravascular “sludging” of (parasitized) RBCs

Late changes in Cerebral Malaria

Perivascular hemorrhages

Imported falciparum malaria: outcome
Imported falciparum malaria
Revising criteria for clinical management

Issues:

Is uncomplicated malaria as presently defined really uncomplicated in a timeframe?

Can patients with uncomplicated malaria be safely treated as outpatients?

And, if not, what are the best criteria of truly uncomplicated malaria?

Towards a new definition of malaria severity applicable to imported malaria

Concerns for the clinician:

Risk for further complications after initiating treatment

Mortality risk

Patient management

Ambulatory treatment or hospitalization?

Medium care or intensive care?

Oral or parenteral treatment?

Follow up?

Imported falciparum malaria

Independent predictors of uncomplicated malaria in a multivariate model (n = 323)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubinemia &lt; 1.3 mg/dL</td>
<td>59.4</td>
<td>8.9-237.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Parasitemia &lt; 5%</td>
<td>13.3</td>
<td>4.6-38.2</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Fever &lt; 72 h before diagnosis</td>
<td>4.57</td>
<td>1.61-12.96</td>
<td>.004</td>
</tr>
<tr>
<td>Foreign visitor/migrant</td>
<td>1.21</td>
<td>1.01-1.48</td>
<td>.035</td>
</tr>
<tr>
<td>VFR traveler</td>
<td>1.13</td>
<td>1.01-1.27</td>
<td>.038</td>
</tr>
</tbody>
</table>

### Imported falciparum malaria

**Outcome of patients with uncomplicated malaria (n=321)**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>uncomplicated</th>
<th>severe*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pf &lt; 40,000/µL or 1% &amp; bilirubin &lt; 1.3 mg/dl</td>
<td>170 (53)</td>
<td>1* (0.3)</td>
</tr>
<tr>
<td>Nonvomiting patients only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pf &lt; 40,000/µL or 1% &amp; bilirubin &lt; 1.3 mg/dl</td>
<td>124 (39)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*WHO expanded definition
* patient already on ambulatory treatment with mefloquine (pretreatment parasitemia of 9%) subsequently hospitalized because of vomiting, but with low residual parasitemia

### Imported falciparum malaria

**Outcome of patients with uncomplicated malaria (n=321)**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>subsequent hospitalization rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N/n %</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
</tr>
<tr>
<td>Pf &lt; 40,000/µL or &lt; 1% &amp; bilirubin &lt; 1.3 mg/dl</td>
<td>6/171 4</td>
</tr>
<tr>
<td>Nonvomiting patients</td>
<td></td>
</tr>
<tr>
<td>Pf &lt; 40,000/µL or &lt; 1% &amp; bilirubin &lt; 1.3 mg/dl</td>
<td>4*/124 3</td>
</tr>
</tbody>
</table>

* one patient because of subsequent vomiting, one patient treated with Avq/Pg with persistent fever on D4, one patient with relapse 3 weeks after R/halofantrin, one patient hospitalized with nausea for comfort

### Fatal malaria:

**Signs and symptoms at hospitalisation (n=5)**

<table>
<thead>
<tr>
<th>Patients No</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>parasitemia (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT &gt; 30,000/µL</td>
<td>x</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>x</td>
</tr>
<tr>
<td>anemia &lt; 7 g/dL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>neurologic signs</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>-</td>
</tr>
<tr>
<td>jaundice</td>
<td>-</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>oliguric insuff</td>
<td>x</td>
<td>-</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>dyspnea/ARDS</td>
<td>-</td>
<td>x</td>
<td>-</td>
<td>x</td>
<td>-</td>
</tr>
<tr>
<td>hypotension/shock</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DIC</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>metabolic acidosis</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

| complication score | 7 | 5 | 3 | 5 | 5 |
Towards a new definition of malaria severity applicable to imported malaria

Our proposal: categorize patients with falciparum malaria according to practical management!

Green flag: criteria for safe ambulatory treatment
Orange flag: uncomplicated so far, but….
Red flag: criteria for severe malaria
Danger zone: criteria for high mortality risk

Towards a new definition of uncomplicated malaria applicable to imported malaria

Green flag criteria: Minimal morbidity

Definition: all criteria below have to be met!
- Parasitemia up to 1% or 40,000 trophozoites/µL
- and bilirubin < 1.3mg/dl
- and no vomiting

Management: safe ambulatory treatment

Imported falciparum malaria

Green flag: saving at least one third of the hospitalization costs…
Towards a new definition of severe malaria applicable to imported malaria

**Danger zone:** High mortality risk

**Definition:**
- Parasitemia >10% (400,000 trophozoites/µL)
- And/or at least 3 criteria of severe malaria, including at least one criterion of severe organ dysfunction.

**Management:**
- Hospitalization in ICU
- Close monitoring of above parameters, plus serum lactate levels, CPK, coagulation parameters. Circulating volume monitoring
- Artesunate IV

Towards a new definition of severe malaria applicable to imported malaria

**Red flag criteria:** High morbidity risk

**Definition:**
- Parasitemia > 5% < 10%
- At least one classical criterium of complicated malaria (except criteria from “danger zone”)

**Management:**
- Hospitalization for IV (PO) treatment, close supervision of parasitemia and critical organ function
- R/ Quinine IV or Artesunate IV???

Towards a new definition of severe malaria applicable to imported malaria

**Orange flag criteria:** Potential complications

**Definition:**
- At least one of the following criteria:
  - Parasitemia 1 to 5% (40,000 to 200,000 troph/mm3)
  - Age > 60 years, pregnancy, comorbidity
  - Vomiting
  - Total bilirubin 1.3 to 3 mg/dl
- and no other criteria of severe malaria.

**Management:**
- Hospitalization preferred, but ambulatory treatment to be allowed under certain conditions
- PO treatment or IV treatment with Quinine. No indication for IV artesunate so far
Severe falciparum malaria
Treatment recommendations: past and present

Past:
- IV Quinine (dihydrochloride): 10mg/kg tid, with loading dose 20mg/kg over 4h
- Exsanguinotransfusion if parasitemia > 10%

Present (since 2006, WHO recommendations):
- IV Quinine: 10mg/kg tid, with loading dose 20mg/kg
- IV Artesunate: if parasitemia > 10% and/or > 3 criteria of severe malaria

Severe falciparum malaria
IV Artesunate vs IV Quinine
Evidence for recommendation

SEAQUAMAT study in south east asian adults
- Substantial reduction of mortality (38%)
- Subanalysis: mortality reduction almost entirely in the high parasitemia group (> 10% parasitemia)
- Shorter parasite clearance time and fever clearance time

AQUAMAT study in african children
- Substantial reduction of mortality (23%)

Severe falciparum malaria
SEAQUAMAT Study: Survival curve of in-hospital mortality in SE-Asaan adults with severe falciparum malaria treated with either parenteral artesunate or quinine

=> Substantial reduction of mortality (38%)
Severe falciparum malaria

AQUAMAT Study: Kaplan-Meier curves comparing survival in African children with severe falciparum malaria treated with either parenteral artesunate or quinine

=> Substantial reduction of mortality (23%)

IV Artesunate vs IV Quinine in severe malaria
Meta-analysis from various studies

(SEAQUAMAT Study: mortality in subgroups of patients treated with parenteral artesunate compared to quinine)

“Patients with hyperparasitemia (admission parasitemia >10%) had a significantly greater treatment effect with artesunate than nonhyperparasitemic patients”

(QR 0.34; 95% CI 0.17–0.69; p=0.001).
Intravenous artesunate for severe malaria
Pharmacokinetics

Evolution of parasitaemia in 14 patients treated with IV artesunate

Severe falciparum malaria
IV Artesunate in imported malaria
Experience in Europe

Intravenous artesunate for severe malaria in travelers, Europe.

Kweelmeijer-Vegter AR, van Genderen PJ, Visser LG, Bierman WF, Clerinx J, van Veldhuizen CK, de Vries PJ
Treatment outcome of intravenous artesunate in patients with severe malaria in the Netherlands and Belgium.
Treatment outcome of intravenous artesunate in patients with severe malaria in the Netherlands and Belgium (Kreeftmeijer-Vegter AR et al, 2011)

Table: Indications for IV Artesunate (n=68)

<table>
<thead>
<tr>
<th>%</th>
<th>Syndrome feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>Multiple convulsions (&gt; 2 episodes/ 24h)</td>
</tr>
<tr>
<td>6</td>
<td>Respiratory distress or respiratory edema</td>
</tr>
<tr>
<td>9</td>
<td>Shock (systolic blood pressure &lt; 70 mm Hg)</td>
</tr>
<tr>
<td>3</td>
<td>Hemorrhagia</td>
</tr>
<tr>
<td>3</td>
<td>Abnormal bleeding</td>
</tr>
<tr>
<td>2</td>
<td>Hyperglycaemia (glucose &gt; 22.2 mmol/l)</td>
</tr>
<tr>
<td>4</td>
<td>Acidemia [pH &lt; 7.3]</td>
</tr>
<tr>
<td>6</td>
<td>Anuria (creatinine &gt; 100 µmol/L or 2.5% RBC)</td>
</tr>
<tr>
<td>6</td>
<td>Hyperlactatemia (lactate &gt; 5 mmol/L)</td>
</tr>
<tr>
<td>11</td>
<td>Renal impairment (creatinine &gt; 265 µmol/L)</td>
</tr>
<tr>
<td>11</td>
<td>Anemia (Hb &lt; 3.1 mmol/l or hematocrit &lt; 15%)</td>
</tr>
<tr>
<td>12</td>
<td>Jaundice (&gt; 50 µmol/L)</td>
</tr>
</tbody>
</table>

Clinical deterioration 6
Unable to take oral medication 7
Other 5

Intravenous artesunate for severe malaria in travelers, Europe. Zoller Th. et al, 2011

Table:

<table>
<thead>
<tr>
<th>Patient (gender, age)</th>
<th>%P.f</th>
<th>Treatment</th>
<th>PCT (days)*</th>
<th>Hb (mmol/l)</th>
<th>Additional diagnostics</th>
<th>Treatment</th>
<th>Hemolysis</th>
<th>Transfusion</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (♂, 50y)</td>
<td>34%</td>
<td>AS (2 gifts)</td>
<td>4 4.3 (D20)</td>
<td>Coombs: C3d+</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (♀, 50y)</td>
<td>19%</td>
<td>AS (4 gifts)</td>
<td>3 4.4 (D30)</td>
<td>Multiple in the context of an unexplained neurological disorder; coombs not performed</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (♀, 50y)</td>
<td>11%</td>
<td>AS (4 gifts)</td>
<td>3 2.8 (D13)</td>
<td>Coombs: neg; G6PD deficient (heterozygous); Shigella flexneri dysentery</td>
<td>Transfusion (4 PC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (♀, 44y)</td>
<td>37%</td>
<td>Q AS (3 gifts)</td>
<td>4 3.8 (D15)</td>
<td>Coombs: IgG+, C3d+</td>
<td>Transfusion (2 x 3 PC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (♂, 5y)</td>
<td>12%</td>
<td>AS (3 gifts)</td>
<td>(D10) 3.8 (D8)</td>
<td>Coombs: neg; hemoculture -</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 (♀, 50y)</td>
<td>30%</td>
<td>AS (5 gifts)</td>
<td>10 (FCT 17d) 4.3 (D13)</td>
<td>Coombs: IgG+, IgM+, hemoculture -</td>
<td>Transfusion (2 PC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 (♀, 50y)</td>
<td>36%</td>
<td>Q AS (5 gifts)</td>
<td>21 (FCT 71d) 4.3 (D17)</td>
<td>Coombs: IgG+, IgM+, hemoculture -</td>
<td>Transfusion (2 PC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment outcome of intravenous artesunate in patients with severe malaria in the Netherlands and Belgium (Kreeftmeijer-Vegter AR et al, 2011)
Intravenous artesunate for severe malaria in travelers, Europe. Zoller T et al, 2011


A) Patient 6 with sudden hemolysis at D14.
B) Patient 9 with persisting hemolysis from D1.

# Blood transfusion

Pitting after IV Quinine
Pitting after IV Artesunate

The sequestration of plasmodia from infected RBC in the splenic sinusoids: "pitting"

In patients with high parasitemia, artesunate treatment induces a large proportion of "pitted" RBC to survive with reduced lifespan: hemolysis

Severe falciparum malaria

Procedures in preparation to assure reimbursement of IV Artesunate in imported malaria in Belgium

This procedure will be implemented from early 2014

Rationale for the procedures:
IV artesunate is (relatively) expensive
It is superior to IV Quinine in patients with high parasitemia
There are concerns about severe posttreatment anemia

Procedure outline:
Criteria for severe malaria (see next)
Follow-up of patients
Reporting treated cases after complete follow-up
Severe falciparum malaria

Accepted criteria of severe malaria to be treated with IV Artesunate in Belgium

- Parasitemia >10% (400,000 trophozoites/µL)
  and/or at least 3 criteria of severe malaria, including at least one criterion of severe organ dysfunction.
- Cerebral malaria (even with < 3 criteria of severe malaria)
- Contra-indication for IV Quinine

Severe falciparum malaria

IV Artesunate in imported malaria: follow-up & reporting

- Risk of (sudden) severe anemia is highest from D10 to D20 after start of IV Artesunate
- Follow-up of patients, with full blood count is done at D7, D14, D21, and D28 (or D42) after start of IV Artesunate
- A specific reporting form will be made available at the itg.be website in due course.
  This case reporting form will be sent after completion of the patient follow-up to the ITMA for compilation, as a post-marketing surveillance