MALARIA: DISEASE, HISTORY AND TREATMENT

K. Pavenski, MD FCRCPC
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Disclosures

- I have no relevant conflicts of interest to disclose.
- I am an adult clinical hematologist and a medical director of the apheresis unit.
Learning Objectives

- Discuss prevalence of malaria and clinical presentation of severe malaria
- Discuss pathophysiology of malaria
- Discuss malaria as a driver of human evolution
- Discuss treatment of malaria
  - Antimalarial medications
  - Exchange transfusion
Malaria

- Infection of RBC caused by protozoan parasite *Plasmodium* and transmitted by a bite of an infected female Anopheles mosquito
- Endemic throughout most of the tropics and subtropics
- Nearly all severe disease caused by *Plasmodium falciparum*
  - 225 million cases of malaria and nearly 1 million deaths
    - most deaths in children <5 years old and pregnant women
- In USA, commonest cause of serious imported infection
  - 1688 (0.55 per 100,000) cases per year; 10% of cases are severe

Crompton et al 2014; Marks et al 2014; Mali et al 2011
Life cycle of Plasmodium
Clinical Manifestations: Severe Malaria

- **Clinical features**
  - Cerebral malaria (impaired LOC, seizures)
  - Acute respiratory distress syndrome
  - Circulatory collapse
  - Jaundice in the setting of other organ dysfunction
  - Hemoglobinuria
  - Abnormal spontaneous bleeding

- **Laboratory features**
  - Hypoglycemia (<2.2mmol/L)
  - Severe anemia (Hb<5g/dL)
  - Metabolic acidosis (plasma bicarbonate <15mmol/L, pH<7.35)
  - Hyperparasitemia (>2-5%)
  - Acute kidney injury (Cr>265 umol/L)
Clinical Manifestations:
Three Distinct Pediatric Syndromes
Pathogenesis: Sequestration

- Major actor: *P. falciparum* erythrocyte membrane protein 1 (PfEMP-1)
  - Highly variable protein encoded by parasite genome and expressed on the outer surface of infected RBC (iRBC)
  - Binds to ligands on endothelial cells, platelets, RBC (ex. CD36, ICAM-1, PECAM, CR1, heparan sulphate, etc.)
- iRBC stick to uninfected RBC ("rosettes"), as well as platelets and endothelium leading to
  - Obstruction of microvascular blood flow and endothelial dysfunction → tissue damage due to thrombosis and hemorrhage
  - Evasion of splenic clearance
Pathogenesis: Inflammation

- *P. falciparum* induces systemic inflammatory response
  - Upregulation of vascular adhesion molecules (eg ICAM-1) leading to further exacerbation of iRBC sequestration
  - Increased production of proinflammatory cytokines (ex. TNFα, IFNγ, IL-1, IL-6, IL-8)
Malaria as a Driver of Evolution

Plasmodium species
- P. falciparum (human)
  - P. reichenowi (chimp)
  - P. malariae
  - P. ovale
  - P. vivax

Mammals
- Hominoids diverge from chimpanzees
- Homo sapiens emerge in Africa
- Hominid group O mutation from A
- Human emigrations out of Africa
- Dawn of agriculture
- Hb S; Hb C
- G6PD
- Thalassemia
- Hb E
- Membranopathies

Cserti & Dzik 2007
Plasmodium falciparum malaria and carbohydrate blood group evolution

C. M. Cserti-Gazdewich

Department of Laboratory Hematology, Blood Transfusion Medicine Laboratory & Department of Medicine (Hematology), University Health Network/
Toronto General Hospital, Toronto, Ontario, Canada

<table>
<thead>
<tr>
<th>Study</th>
<th>A</th>
<th>Non-A</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fischer, 1998 (coma)</td>
<td>9/104</td>
<td>11/385</td>
<td>3.22 (1.30, 8.00)</td>
</tr>
<tr>
<td>Lell, 1999 (SM)</td>
<td>27/38</td>
<td>73/162</td>
<td>2.99 (1.39, 6.44)</td>
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<tr>
<td>Pathirana, 2005 (SM)</td>
<td>26/66</td>
<td>54/177</td>
<td>1.48 (0.82, 2.67)</td>
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<tr>
<td>Loscertales, 2006 (PM)</td>
<td>24/38</td>
<td>92/160</td>
<td>1.27 (0.61, 2.63)</td>
</tr>
<tr>
<td>Fry, 2007 (SM)</td>
<td>554/979</td>
<td>1538/3016</td>
<td>1.25 (1.08, 1.45)</td>
</tr>
<tr>
<td>Rowe, 2007 (SM)</td>
<td>52/95</td>
<td>111/247</td>
<td>1.48 (0.92, 2.38)</td>
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<tr>
<td><strong>Summary</strong></td>
<td></td>
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<td>1.34 (1.17, 1.52)</td>
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<th>O</th>
<th>Non-O</th>
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</tr>
</thead>
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<tr>
<td>Fischer, 1998 (H/CNS)</td>
<td>3/26</td>
<td>10/27</td>
<td>0.22 (0.05, 0.93)</td>
</tr>
<tr>
<td>Lell, 1999 (SM)</td>
<td>54/118</td>
<td>46/82</td>
<td>0.66 (0.38, 1.16)</td>
</tr>
<tr>
<td>Pathirana, 2005 (SM)</td>
<td>19/97</td>
<td>51/146</td>
<td>0.34 (0.19, 0.62)</td>
</tr>
<tr>
<td>Loscertales, 2006 (PM)</td>
<td>57/102</td>
<td>59/96</td>
<td>0.79 (0.45, 1.40)</td>
</tr>
<tr>
<td>Fry, 2007 (SM)</td>
<td>898/1828</td>
<td>1196/2167</td>
<td>0.78 (0.69, 0.88)</td>
</tr>
<tr>
<td>Rowe, 2007 (SM)</td>
<td>37/123</td>
<td>126/219</td>
<td>0.32 (0.20, 0.51)</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td></td>
<td></td>
<td>0.71 (0.63, 0.79)</td>
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</table>

- A or AB in death vs UM: 23/48 (48%) vs 302/1077 (28%), p 0.005
- OR for death vs UM for A/AB vs O: 2.27 (1.21 – 4.28)

ABO severity gradient effect
A (A1 vs A2) dose effect
A more harmful than HbS trait beneficial

Risk Factor OR (95% CI) P-value
Age 0.83 (0.79-0.88) P<0.001
Female 0.91 (0.73-1.14) P=0.43
HB S 0.82 (0.49-1.37) P=0.46
WBC count 1.12 (1.05-1.19) P<0.001
Platelet count 1.04 (0.93-1.16) P=0.20
Hyper parasitaemia 1.95 (1.54-2.48) P<0.001
Group A or AB 1.62 (1.29-2.53) P<0.001
Group B 1.24 (0.94-1.66) P=0.13
Ln Mono CD54 0.44 (0.36-0.53) P<0.001
Ln Mono CD36 0.77 (0.65-0.91) P=0.002
Ln PII CD36 1.16 (0.97-1.37) P=0.055

Uncomplicated Severe or Fatal
The importance of ABO

- Group A RBC are more likely to be invaded *in vitro* by *P. falciparum*
- PfEMP-1 contains 2 types of adhesive domains, one of which (DBL-1α) binds primarily to cells bearing A and B oligosaccharides
- Group O RBC form weaker rosettes and are less likely to form rosettes
- Macrophage mediated phagocytosis is enhanced for group O iRBC
- Group O individuals have lower levels of VWF

Cserti & Dzik 2007; Wolofsky et al 2012
# Treatment: Antimalarial Drugs

## Table 1. Key Strengths and Weakness of the Major Available Antimalarials (Excluding ACTs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Key Strengths</th>
<th>Key Weaknesses</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine</td>
<td>• Kills the sexual stages of <em>P. vivax</em>, <em>P. malariae</em>, and <em>P. ovale</em></td>
<td>• Does not kill the pre-erythrocytic stages of malaria parasites or the mature gametocytes of <em>P. falciparum</em>. Difficult to administer in severe malaria</td>
<td>• Uncomplicated <em>P. falciparum</em>, <em>P. vivax</em>, or unidentified malaria</td>
</tr>
<tr>
<td></td>
<td>• Low cost</td>
<td></td>
<td>• Safe in pregnancy</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>• It maintains efficacy for the treatment of <em>P. vivax</em>, <em>P. ovale</em>, and <em>P. malariae</em> infections. Low cost</td>
<td>• Widespread drug resistance has made it almost useless for the treatment of <em>P. falciparum</em> in most of the world</td>
<td>• Chloroquine-sensitive <em>P. falciparum</em> or unidentified malaria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• It does not produce radical cure of <em>P. vivax</em> and <em>P. ovale</em></td>
<td>• Uncomplicated <em>P. vivax</em>, <em>P. ovale</em>, <em>P. malariae</em>, and <em>P. knowlesi</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Low safety margin and very dangerous if overdosed</td>
<td>• Can be used in pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Used for prophylaxis</td>
</tr>
<tr>
<td>Artemether</td>
<td>• Effective against some chloroquine-resistant strains of <em>P. falciparum</em></td>
<td>• There is some cross resistance with chloroquine</td>
<td>• Uncomplicated <em>P. falciparum</em> malaria</td>
</tr>
<tr>
<td></td>
<td>• Low cost</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mefloquine</td>
<td>• Effective against all species of malaria</td>
<td>• Associated with adverse neurological side effects such as mood disturbance and dizziness, and GI side effects</td>
<td>• Uncomplicated <em>P. falciparum</em>, <em>P. vivax</em>, or unidentified malaria</td>
</tr>
<tr>
<td>(Lariam™)</td>
<td>• Long half-life of around 21 days</td>
<td>• High cost</td>
<td>• Used for prophylaxis -- proposed for IPTp</td>
</tr>
<tr>
<td>Primaquine</td>
<td>• Effective against the hypnozoite and so provides radical cure of <em>P. vivax</em> and <em>P. ovale</em></td>
<td>• Hemolytic side effects in G6PD-deficient patients</td>
<td>• Uncomplicated <em>P. vivax</em> and <em>P. ovale</em>, anti-gametocyte activity in other species</td>
</tr>
<tr>
<td></td>
<td>• Low cost</td>
<td>• Must be taken daily for 14 days to be effective</td>
<td></td>
</tr>
<tr>
<td>Sulfadoxine-pyrimethamine</td>
<td>• One-dose cure</td>
<td>• Resistant strains in East Africa</td>
<td>• Used for IPTp and proposed for use in IPTi</td>
</tr>
<tr>
<td></td>
<td>• Can be used in pregnancy</td>
<td>• Rare severe adverse effects: Stephen Johnson Syndrome</td>
<td>• Can be used in pregnancy</td>
</tr>
<tr>
<td>Intravenous artesunate</td>
<td>• Intravenous formulation</td>
<td>• No GMP formulation available. Need to compare intravenous and intramuscular delivery (and potentially intra-rectal)</td>
<td>• Used for prophylaxis</td>
</tr>
<tr>
<td>Atovaquone-proguanil</td>
<td>• Administration: once per day for 3 days</td>
<td>• High cost</td>
<td>• Uncomplicated <em>P. falciparum</em> or unidentified malaria</td>
</tr>
<tr>
<td>(Malarone™)</td>
<td>• Active against all species of Plasmodium</td>
<td>• GI side effects</td>
<td>• Used for prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• Inhibits pre-erythrocytic development in the liver and oocyst development in the mosquito</td>
<td></td>
<td></td>
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</tbody>
</table>

GI: Gastrointestinal; GMP: Good manufacturing practice; G6PD: Glucose-6-phosphate dehydrogenase; IPTp: Intermittent preventative treatment in pregnancy; IPTi: Intermittent preventative treatment in infants; WHO: World Health Organization.
Treatment: Antimalarial Drugs for Severe Falciparum Malaria

- **Quinine**
  - Derived from Cinchona plant
  - Used since 16th century
  - Parasite clearance time (PCT) for IV quinine – about 50 hrs

- **Artemisinins (artesunate)**
  - Derived from Artemisia (aka Qinghaosu or wormwood) plant
  - Used since 200 BC
  - PCT for IV artesunate – about 20 hrs
  - Compared to quinine, reduces MR in severe malaria by >30%
  - Since early 2000’s, first line therapy for severe malaria

Tan et al 2013
Treatment: Exchange Transfusion (ET)

- 1st reported use in 1974 in a patient with cerebral tropical malaria with blackwater fever
- Adjunct ET became standard of care and recommended for severe malaria with hyperparasitemia by
  - CDC until 2013
  - ASFA guidelines (Grade 2B recommendation, 2013 edition)
- What is “ET”?
  - Manual vs. automated (differences in efficacy and safety)
  - Whole blood vs. RBC + FFP vs. erythrocytapheresis (+/-plasmapheresis)
  - Partial vs. 1 red cell volume vs. 1 whole blood volume vs….
Exchange Transfusion: Biologic Rationale

- Removes parasite load
  - ET + IV quinine halves the volume of parasites within 2-6 hrs
- Removes parasite derived antigen load reducing sequestration and improving rheology
  - Removal of less deformable/sticky iRBC -> improved microcirculatory flow
  - (Ability to change patient’s blood group thus significantly altering cytoadherence)
- Replenishes ADAMTS13
- Removes hemolytic metabolites (free hemoglobin, other RBC proteins)
- Removes cytokines and pro-inflammatory mediators
- Corrects anemia and coagulopathy

Powell & Grima 2002; Miller et al 2013
Does it work?

Summary of 8 studies showing ORs for survival after ET compared with antimalarial chemotherapy (quinine) alone

Mark S. Riddle et al. Clin Infect Dis. 2002;34:1192-1198

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Exchange Transfusion: Efficacy

- Case-control study of US patients with severe malaria (26 yrs experience)
  - Matched for age, completion of appropriate prophylaxis, antimalarial regimen, ARDS, cerebral malaria, renal failure, *P. falciparum* infection, type of hospital, immune status, and parasite

<table>
<thead>
<tr>
<th></th>
<th>Cases (adjunct ET)</th>
<th>Controls (no ET)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of patients</td>
<td>101</td>
<td>314</td>
</tr>
<tr>
<td>MR</td>
<td>17.8%</td>
<td>15.9%</td>
</tr>
</tbody>
</table>

- No statistically significant association between ET and survival outcome (OR 0.84, 95% CI 0.44-1.60)
- Adjunct ET cannot be recommended
Exchange Transfusion: Safety

- Very little data
- Complications of ET may mimic complications of malaria or antimalarial treatment
- Dependent on type of procedure, type of replacement and its safety, local resources
  - Automated RBC exchange is safe (van Genderen et al 2010, Auer-Hackenberg et al 2012)
Exchange Transfusion: The problem with evidence…

- The problem with current evidence is a lack of good quality evidence
  - 73 case reports and case series, 12 comparative studies
  - Mostly retrospective
  - No appropriate controls, no adjustment for confounders
  - Small numbers of patients, low mortality
    - Underpowered to detect differences in survival
    - Effect on other clinically significant outcomes?
- Heterogeneous patient population
  - Different severity of disease (sicker patients more likely to have had ET), immunity status
- Heterogeneous treatments
  - “ET” – ex. manual ET is not as effective and not as safe as automated exchange (Kreeftmeijer-Vegter 2013)
  - Antimalarial treatments

Tan et al 2013; Riddle et al 2002
Exchange Transfusion:
Getting more evidence may be very difficult

- To perform RCT, need a huge number of patients
- Resource and patient mismatch
  - Small numbers of patients where capacity exists (equipment, trained personnel and adequate amounts of safe blood components) and where there is no immunity
  - Large numbers of patients where no capacity exists
Exchange Transfusion: Forget it?

- There is a biological rationale for efficacy
- The existing data are not helpful
  - RBC exchange may be effective in a patient subgroup (non-immune travelers, elderly with cerebral malaria, etc.)
  - RBC exchange may impact morbidity (ICU stay, permanent organ damage or disability)
- Automated RBC exchange is safe
- The current treatment does not save all with severe malaria (cerebral malaria or acidosis)
  - On artesunate, 15% mortality rate in (mostly) adults (SEAQUAMAT RCT) and 8.5% mortality rate in children (AQUAMAT RCT)
- Artesunate resistance is emerging

Dondorp et al 2005; Dondorp et al 2010
Decision?

- Do not perform adjunct RBC exchange
- or
- Perform adjunct RBC exchange in select patients with severe malarial manifestations despite administration of appropriate drugs
Current State

- I practice in one of the two adult apheresis centres in the Greater Toronto Area (catchment population: over 6.1 million)

- The last time either of our centres have performed automated RBC exchange on a patient with severe malaria was 2012
Conclusion

- Malaria is a devastating disease
- Effective drug therapy exists but unable to save all
- There is a compelling biological rationale for performing an exchange transfusion
- The evidence on exchange transfusion (as it exists) is unhelpful
- More studies are necessary but may not be feasible