Respiratory problems with severe malaria: an opportunity to talk about fluid trials!!!

Kathryn Maitland
Severe malaria-the numbers

- Up to 1 million deaths in African children <5y

- In-hospital mortality unchanged ~ 20-30%

- Progress towards improving case management hampered by
  - inadequate clinical definition
  - treatment guidelines (WHO) – principally informed by adult studies
Severe malaria in African Children
different from SE Asian adults

- Fulminant disease course
  - >75% deaths < 24hr
- Jaundice, renal failure and lung damage are rare
- Brain swelling – potential complication of coma
- Respiratory distress -key feature
- Many features in common with severe sepsis/ sepsis syndrome

Maitland et al 2003
Severe malaria: central role of acidosis

• More common than previously recognised ~70% cases

• Presents as respiratory distress

• Best independent predictor of a fatal outcome

Marsh et al, 1995; English et al, 1997
Association of respiratory distress, acidosis and fatal outcome

English et al., 1996
Severe malaria in African children

- More complex than previously recognised
- Many features in common with the sepsis syndrome
- Acidosis/ respiratory distress: best predictor of a fatal outcome
- Therapies aimed at treatment of acidosis may improve outcome
Common approaches to resuscitation: saves lives

- Kinetics of the innate immune: similar range of responses to a range of pathogens
- Common and complex derangements of host physiology
- Most complications reversible by simple approaches
- Treatment of critically ill children – based on bedside assessments & without primary diagnosis
- Development of separate paediatric protocols: reduced mortality in sepsis from >60% to <10%
Acidosis: in critically ill children

- Commonest cause of metabolic acidosis in sick children is hypovolaemia
- Limited intravascular reserve of children: shock common response to acute infection
- Hypotension – pre-terminal manifestation; diagnosis overlooked
- *Standard management* – volume resuscitation
Hypovolaemia is not synonymous with dehydration
Current WHO recommendations (2006)

- Volume resuscitation = controversial and thus discouraged
- Should be given with CVP monitoring (CVP 0-5cm H$_2$O!!)
- Dehydration should be corrected – infusion tied to quinine administration (4 hours)

Consequences

- No agreed ‘standard of care’
- Some hospital continue to give frusemide to children with respiratory distress (‘heart failure’)
Aims of Kilifi programme

1) To determine whether hypovolaemia aetiologically important in the pathogenesis of severe malaria

2) Through clinical trials assess the safety and efficacy of volume resuscitation

3) To determine with is the optimum fluid for correction of volume depletion: is this more safely achieved with colloids (albumin) than crystalloids (saline).
Retrospective review admission features of children with severe malaria

<table>
<thead>
<tr>
<th>Triage</th>
<th>Clinical feature present (%)</th>
<th>Fatality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway &amp; Breathing</td>
<td>O$_2$ Saturation &lt;90% (17%)</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Tachypnoea &gt;60 (17%)</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Deep breathing (20%)</td>
<td>31%</td>
</tr>
<tr>
<td>Circulation</td>
<td>Extreme Tachycardia &gt;180 (16%)</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Hypotension (13%)</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>Capillary refill &gt;2s (32%)</td>
<td>15%</td>
</tr>
<tr>
<td>Disability</td>
<td>Impaired consciousness (78%)</td>
<td>13%</td>
</tr>
</tbody>
</table>

Lab features:
- Acidaemia pH <7.2 (22%) 36%
- Elevated creatinine >80 (19%) 26%
- Potassium >5.5 mmols (10%) 28%
- Hypoglycaemia (12%) 28%

Maitland et al, QJM 2003
Transfer of intensive care technology

Children with severe malaria & acidosis
  – Standard methodology to assess volume status
  – Haemodynamic response
  – Continuous haemodynamic monitoring over following 48 hours

Two studies:
  • Phase I trial: dose finding studies
  • Phase II trial: volume expansion saline or albumin
Physiological studies: hypovolaemia

CVP low at admission
Bolus ~ 20-40mls/kg

Maitland et al (2005)
Safety of volume expansion

Results

53 children received volume expansion: 4 deaths (8%)
No complications of pulmonary oedema/brain swelling
Trial recruitment

Severe Malaria + Deep breathing
Assessed for eligibility (n=150)

Severe Acidosis
(Base excess < -15)
n=49

- Albumin (n=23)
- Saline (n=26)

Moderate Acidosis
(Base excess -8 to -15)
n=101

- Control (n=33)
- Albumin (n=33)
- Saline (n=35)

No control arm:
Pilot data: 40% hypotension at admission
Ethical to waive consent

A priori mortality lower:
- ethical to include control arm (standard of care)
- Provision for rescue therapy

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$1^\circ$ endpoint: resolution of acidosis by 8 hours
20 endpoint: in-hospital mortality

Severe Acidosis

Moderate Acidosis

Albumin 2/56 (3.6%) vs Saline 11/61 (16%) P = 0.01

15% rescued
Phase II trial
Albumin as a targeted therapy- coma vs non-coma

Coma (cerebral malaria)
  Albumin 1/21 (5%)
  Saline 11/24 (46%)
  Relative risk: 9.6 [1.4-68]

Non-coma
  Albumin 1/35 (3%)
  Saline 0/37 (0%)

Maitland et al (2005)
# External relevance: global context

<table>
<thead>
<tr>
<th>Report</th>
<th>Year</th>
<th>Mortality</th>
<th>Clinical Sub-group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational- Blantyre</td>
<td>1993</td>
<td>28%</td>
<td>coma &amp; acidaemia</td>
</tr>
<tr>
<td>Observational- Kilifi</td>
<td>1996/1997</td>
<td>24%/28%</td>
<td>deep breathing/coma</td>
</tr>
<tr>
<td>Observational- Kumasi</td>
<td>2003</td>
<td>19%</td>
<td>deep breathing</td>
</tr>
<tr>
<td>Observational- Banjul</td>
<td>2003</td>
<td>24%/40%</td>
<td>deep breathing/coma/deep breathing</td>
</tr>
<tr>
<td>Randomised trial Kilifi</td>
<td>2004</td>
<td>4%/18% (2/56)/(11/61)</td>
<td>albumin arm/saline arm</td>
</tr>
<tr>
<td>Coma subgroup</td>
<td>2003</td>
<td>5%/46% (1/25)/(11/24)</td>
<td>albumin arm-coma/saline arm -coma</td>
</tr>
</tbody>
</table>
Albumin – relevant for Africa?

- Early evidence of improved outcome with albumin
- HAS expensive and not routinely available
- Cost effective: USD 30-40 per life saved ~ same as the cost of a blood transfusion
- Oncotic effects or due to its other beneficial properties
- Could this be achieved with a cheaper synthetic colloid?
- Aim of Phase II trial: inform the design of the next phase, and NOT to establish statistical superiority of either colloid.
# Phase II: Gelofusine Vs albumin RCT

No difference in mean volumes received  

Akech et al, 2006

<table>
<thead>
<tr>
<th>Outcome n/N</th>
<th>Sub-Category</th>
<th>Albumin</th>
<th>Gelofusine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;o&lt;/sup&gt; Resolution of shock (%)</td>
<td>0 h</td>
<td>35/42 (83)</td>
<td>37/43 (86)</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>1 h</td>
<td>12/41 (29)</td>
<td>7/37 (19)</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>8 h</td>
<td>9/41 (20)</td>
<td>5/37 (14)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital death, (%)</td>
<td>By ITT</td>
<td>1/43 (2.3)</td>
<td>7/44 (16)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>1/40 (2.5)</td>
<td>4/40 (10)</td>
<td>0.36</td>
</tr>
<tr>
<td>Neurological sequelae (%)</td>
<td>By ITT</td>
<td>3/43 (7.0)</td>
<td>17/37 (2.7)</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>3/39 (7.7)</td>
<td>1/36 (2.8)</td>
<td>0.62</td>
</tr>
<tr>
<td>Adverse events, (%)</td>
<td>Pulmonary oedema</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Raised intracranial pressure</td>
<td>0</td>
<td>2/44 (5)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Possible allergic reaction</td>
<td>0</td>
<td>1/44 (2.3)</td>
<td>—</td>
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</tbody>
</table>
# Summary of trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
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<tbody>
<tr>
<td><strong>Pilot Studies</strong></td>
<td></td>
</tr>
<tr>
<td>Established hypovolaemia</td>
<td></td>
</tr>
<tr>
<td>40% severe acidosis - hypotension</td>
<td>60</td>
</tr>
<tr>
<td><strong>RCT</strong></td>
<td></td>
</tr>
<tr>
<td>Resolution of acidosis and shock</td>
<td>150</td>
</tr>
<tr>
<td>Albumin (4%) mortality lower than saline (18%)</td>
<td></td>
</tr>
<tr>
<td><strong>Colloid trial</strong></td>
<td></td>
</tr>
<tr>
<td>Resolution of acidosis and shock</td>
<td></td>
</tr>
<tr>
<td>Albumin (2%) mortality less than Gelofusine (18%)</td>
<td>88</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>298</td>
</tr>
</tbody>
</table>
Summary estimate of the effect of albumin on mortality

Akech et al, 2006
Considerations for Phase III

• Consistently low mortality with human albumin solution: should be included despite cost
• Gelofusine no better than saline
• Current standard of care: (no resuscitation fluids) included as a control
• Definitive address whether volume expansion should be used in general management
• Should lead to general improvement in management of other childhood illnesses where benefit of volume expansion is beyond doubt
If confirmed in larger trial.....

- Management of the sick child: protocol implemented by bedside assessments
- Rationale for generic approach to management
- Dispel common misconceptions
- Demonstration that improved outcome can come through effective delivery of emergency care
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