Challenging fluid resuscitation for critically sick children in Africa

The problem of shock in children
Shock affects around one in 10 children admitted to African hospitals. Malaria and septicaemia (a bacterial bloodstream infection) can both lead to shock. Despite having effective medicines which directly treat the illnesses they are suffering from, around 11-22% of children admitted to hospital with shock die within hours of admission.

How is shock treated?
Rapid fluid resuscitation is the standard treatment for shock in many parts of the world. It was initially developed for use when it was obvious that the body had lost a great deal of fluids, for example through diarrhoea or severe bleeding. It was extended to shock in severe infections like septicaemia, where rather than fluid being lost, blood flow is diverted to vital organs in order to stave off death.

The aim of fluid resuscitation is to rapidly increase perfusion to all organs and limbs, and revive the sick child. However, not every case treated this way responds adequately. In high-income countries, these patients are admitted to an intensive care unit so that they can receive other supportive treatment such as ventilation.

What is shock?
Shock is a term used to describe a group of symptoms and signs in critically sick patients. Shock occurs when there are changes in the way that blood is distributed around the body. This happens either because of fluid losses (as in severe diarrhoea, burns or acute blood loss) or severe infections when blood is concentrated in the vital organs. Shock results in impairment of blood flow (also called poor perfusion) to non-vital tissues such as the skin and limbs. This is why children in shock look pale, their limbs feel cool, and their heart rate increases. In children, blood pressure only falls at a late (often pre-terminal) stage. Different criteria have been used for defining shock. The World Health Organisation (WHO) definition is the strictest.

Key Points
- Shock caused by severe infections is a major killer of children in Africa.
- The use of rapid fluid resuscitation (giving a large emergency dose of fluids through an intravenous drip) to combat shock is standard practice in high-income countries, but the evidence for it is weak. It has been unclear whether this approach should be used in Africa.
- Fluid resuscitation (or ‘boluses’) given to African children with shock caused by severe infections (but not from fluid losses such as diarrhoea, burns or trauma) actually increased mortality when compared to low volume fluids given slowly to maintain normal fluid levels (maintenance fluids).
- Emergency triage of the sickest children coming to hospital and appropriate treatment appeared to reduce mortality among all the critically ill children in the FEAST trial.
- Emergency guidelines on fluid resuscitation for sick children with shock suffering from conditions such as sepsis and malaria need to be reviewed in the light of the FEAST trial results.
It has been suggested that fluid resuscitation would be a low cost option for saving lives. The WHO has developed guidelines for identification and management of shock (including children with malaria and septicaemia). These recommendations however only apply to children with the most severe form of shock (WHO definition) owing to concerns about the safety of fluid resuscitation. Few African hospitals have the backup of intensive care equipment (such as ventilators) to support children if they receive too much fluid.

What is the evidence that fluid resuscitation works for treatment of infections associated with shock?

Randomised trials are the best form of evidence. Prior to the FEAST trial, no randomised controlled trials in children or adults have looked at whether fluid resuscitation helps in shock. The current guidelines in high-income countries, which have been in place for many years, are largely based on observational studies. The trials which have been undertaken in adults with sepsis and children with dengue fever and malaria only examined which type of fluid was better and not whether giving fluid boluses was better than no bolus (control). In malaria, previous small trials suggested a beneficial outcome with albumin compared to any other type of fluid.

The FEAST trial

The FEAST (Fluid Expansion As Supportive Therapy) trial tested the safety and effectiveness of giving rapid fluid resuscitation in the first hour to children in Africa with febrile illness and shock compared with maintenance fluids only. The trial was carried out in 6 hospitals in Kenya, Tanzania and Uganda. Children were divided randomly into three arms. Two arms were to receive emergency boluses of fluid, between 20-40 mls per kg of bodyweight, in the first hour of arriving in hospital: one arm albumin boluses and the other normal saline boluses; children in the third arm, or control arm, were given maintenance fluids (3-4ml/kg) but no bolus. After this all children received maintenance fluids until they were able to drink. The maintenance fluids given were those that were routinely available, which was generally dextrose saline.

When children present to hospital with a severe life threatening illness, frontline doctors do not have time to make a specific diagnosis before they initiate emergency treatments. The FEAST trial was therefore designed as a practical trial that represented the realities of emergency care and therefore included a range of infectious diseases.

The main outcome was how many children survived after forty-eight hours in hospital. Children were then followed up for the next month to check there were not more deaths or long term effects on the quality of life, especially neurological disability.

What were the results?

Who were the children enrolled in the FEAST trial?

3141 children took part in the FEAST trial. They were aged between 60 days and 12 years (average age 24 months). All had fever and one or more features of poor perfusion (half had 2 or more), with either impaired consciousness or respiratory distress, or both. Severe acidosis (Ph <7.2 and/or lactate levels >5mmol per litre) was present in over half the children. 57% of the children had malaria parasites; 12% had a blood infection (bacteraemia); 32% had severe anaemia; 3% had meningitis; 42% had respiratory conditions...
including respiratory infections or ‘panting’ due to their acidosis, and 4% had HIV.

Children with shock caused by diarrhoea, burns or traumatic injuries, where substantial losses of fluids from the body had taken place were not included. Children with acute malnutrition were also excluded and only a few (2%) had a mid upper arm circumference <11.5cm.

What was the effect of fluid resuscitation on mortality?

The trial results showed that 89.4% of those given boluses survived the first 48 hours in hospital. But those given only maintenance fluids did better: 92.7% of them survived. This is a statistically significant difference. This means that compared to maintenance fluids, boluses cause more than 3 children (3.3%) to die out of every hundred treated. The death rates were no different between children receiving boluses of albumin compared with boluses of saline. For all of the illnesses described above children treated with boluses were more likely to die within 48 hours. None of the common conditions studied in the trial benefited from boluses.

The use of boluses increased mortality among children with shock regardless of which definition of shock was used, including the strict criteria used by the WHO (See Table 1). The results were similar in all six trial centres in the three African countries taking part in the trial.

Side effects of fluids

The main side-effects which could occur with boluses are pulmonary oedema (fluid in the lungs) and cerebral oedema (fluid in the brain) causing increased intracranial pressure. Very few children experienced side effects and in even fewer was either of these two side effects thought to contribute to death. The occurrence of pulmonary oedema and increased intra-cranial pressure were not statistically different between the arms.

Why did the use of boluses lead to more deaths?

While the results of the trial are very clear, it is unclear why boluses are harmful for critically sick children in Africa. Throughout the FEAST trial there was strict safety monitoring of the data by experts to look for any signs of fluid over-load. Very few children seemed to develop these side effects. In particular, the effect of fluids was if anything worse in children with more normal levels of oxygen in their blood (i.e. less hypoxaemia) before boluses. Those who received boluses did not have a worsening of oxygen levels in their blood.

One theory is that shock itself may be an important defence mechanism, which is unbalanced by giving fluid boluses. If this were found to be true, it could herald a complete re-evaluation worldwide of how shock works in children and how it should be treated.

Emergency triage and treatment

Encouragingly, the death rate in the FEAST trial (under 10%) was around half that seen generally in shocked children in Africa (up to 20%). This maybe because the trial doctors and nurses had been given training in emergency care to rapidly identify very sick children (triage) and promptly deliver treatments such as oxygen, glucose, antibiotics, and antimalarial drugs. This reinforces other evidence showing the potential benefits of training in emergency triage assessment and treatment (ETAT), as in the ETAT course which is promoted by WHO.

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### Table 1: Risk of death among participants in the FEAST trial with different definitions of shock

<table>
<thead>
<tr>
<th>Shock definition</th>
<th>Overall (all arms)</th>
<th>Mortality (%)</th>
<th>Absolute risk difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEAST inclusion criteria</td>
<td>297/3141 (9.5%)</td>
<td>221/2097 (10.6%)</td>
<td>76/1044 (7.3%)</td>
</tr>
<tr>
<td>ACCM-PALS</td>
<td>194/2030 (10%)</td>
<td>150/1389 (11%)</td>
<td>44/641 (7%)</td>
</tr>
<tr>
<td>Surviving Sepsis Campaign</td>
<td>230/1419 (16%)</td>
<td>167/950 (18%)</td>
<td>63/469 (13%)</td>
</tr>
<tr>
<td>WHO</td>
<td>27/65 (42%)</td>
<td>24/50 (48%)</td>
<td>3/15 (20%)</td>
</tr>
</tbody>
</table>

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IMPLICATIONS AND RECOMMENDATIONS

For Africa

As fluid boluses are not commonly used in Africa for children with the conditions covered by the FEAST trial, the results do not mean big changes in fluid management. Only small numbers of children in the FEAST trial fulfilled the strict WHO definition of shock. However, there was clear evidence of harm in this group, so this guidance should be reviewed.

Boluses are used in Africa to treat diarrhea and other conditions where children lose fluids. It is important that this continues as fluid resuscitation is a vital life saving treatment for these conditions. It is also important that children who cannot drink for themselves are given fluids to maintain normal levels.

The FEAST trial demonstrates the importance of testing interventions, used in high-income countries, in low and middle-income countries, to check for effectiveness and feasibility in the very different settings. It also shows that high quality trials can be conducted in normal hospitals in Africa.

- Children with shock caused by infections (and not loss of fluid) should not be given boluses
- All sick children who cannot drink for themselves need fluids through a drip to maintain normal levels in the body
- Hospital staff should be trained in pediatric emergency triage and treatment as it may help to reduce mortality

For high-income countries

Boluses may not carry the same risks in high-income countries because children are healthier, and in particular are not exposed to recurrent infections, chronic infestation and poor nutrition. Fluid boluses could still be beneficial in this setting, when given with the other components of intensive care which are not available in Africa. However, further research is now important to understand whether the results of FEAST may be relevant to treatment of critically ill children in high-income countries. The only way of answering these questions in high-income countries is through a fully randomized clinical trial. In the meantime, paediatric emergency care guidelines should be reviewed, particularly with regard to boluses given outside intensive care units, or where there may be no immediate access to intensive care.

Recommended reading


Credits

This policy brief was written by Annabelle South, Kath Maitland and Di Gibbon behalf of the FEAST trial team.

The FEAST trial was carried out at six sites in three different countries:

- **Kenya**: Kilifi District Hospital
- **Uganda**: Makerere University and Mulago Hospital National Referral Hospital; Mbale Regional Referral Hospital; Soroti Regional Referral Hospital; St Mary’s Hospital, Lacor
- **Tanzania**: Tuele Hospital, Muheza

Overall trial co-ordination was carried out by KEMRI-Wellcome Trust Research Programme, Clinical Trials Facility Kilifi, Kenya in collaboration with the Medical Research Council Clinical Trials Unit, London who also undertook the statistical analysis. The trial was designed by KEMRI-Wellcome Trust Research Programme in collaboration with the MRC Clinical Trials Unit and the Department of Paediatrics, Imperial College London. The London institutions also provided technical and scientific support, advice and training.

The trial was funded by the Medical Research Council (provided through the MRC DFID concordat) and the trial sponsor was Imperial College London. Baxter Healthcare Corporation generously donated the resuscitation fluids for the trial, but was not involved in any other way. In Uganda Logistics and co-ordination were carried out by Malaria Consortium Africa, Kampala.

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