Mortality after Fluid Bolus in African Children with Sepsis

TO THE EDITOR: The Fluid Expansion as Supportive Therapy (FEAST; Current Controlled Trials number, ISRCTN69856593) Trial Group (June 30 issue) performed a meticulous study of fluid resuscitation in children with sepsis. We note that the excess mortality in the intervention group was most pronounced among severely anemic children but not statistically significant among children with a hemoglobin level of 5 g per deciliter or more (Fig. 3 of the article). This finding suggests that acute hemodilution in children with preexisting anemia may have caused the increased mortality in the resuscitation group. Assuming a circulating blood volume of 80 ml per kilogram of body weight, a child with a hemoglobin level of 5 g per deciliter on admission would undergo hemodilution to 4 g per deciliter. The most comprehensive pediatric literature on anemia in children with sepsis and in pediatric intensive care unit (ICU) populations has studied a transfusion threshold hemoglobin level of 7.0 g per deciliter. Below this level, evidence is anecdotal. The physiological effect of severe dilutional anemia is predictable and detrimental: impaired oxygen delivery leading to organ failure.

This is not a criticism of the trial per se, but it is a possible mechanism for the apparent harm of fluid resuscitation with an agent other than blood in children with anemia and sepsis seen in this study.

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TO THE EDITOR: Maitland et al. report increased 48-hour mortality among African children with severe febrile illness without hypotension after fluid resuscitation as compared with no resuscitation. Although the authors report the exclusion of children with severe malnutrition and gastroenteritis, among other clinical conditions, it is not clear what criteria were used to determine nutritional status and the relevance of moderate undernutrition among the groups. We deem that these criteria are relevant, given the different car-
diovascular and inflammatory responses that are adaptive manifestations of the nutritional status of an ill child. Second, the authors describe malaria as the cause of febrile illness in 57% of the children, but they do not describe the causes of the other cases of febrile illness. We believe it is important to discriminate among the three groups other causes known to alter host vascular permeability, such as dengue, and the differences in the inflammatory response triggered by different types of pathogens. The results presented are innovative, but in some aspects in conflict with the higher volume of fluids recommended by current guidelines, which are based on studies that have shown lower mortality among children mainly in developing countries.

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No potential conflict of interest relevant to this letter was reported.


TO THE EDITOR: Maitland et al. expand our deficient knowledge about fluid resuscitation, since they established that fluid boluses containing albumin and saline might increase mortality among African children with severe infection. Physicians struggle worldwide with the optimal fluid-resuscitation strategy. In one study involving 391 ICUs across 25 countries, colloid was administered to more patients than crystalloid, despite the association with adverse effects. The attempt to find a truly physiological crystalloid resuscitation has been going on for 175 years, and the results have inevitably been a compromise. In the meantime, we infuse billions of liters of 0.9% saline worldwide, although this fluid is neither “normal,” nor “physiological,” because it differs markedly from plasma. Chloride-rich solutions such as 0.9% saline or albumin, when used in large volumes, can potentiate metabolic acidosis, but trading part of the chloride content with ions such as lactate (Ringer’s lactate) may be at the expense of other side effects (e.g., metabolic alkalosis). Without international studies, we may never be able to make rational choices about fluid resuscitation.

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No potential conflict of interest relevant to this letter was reported.


TO THE EDITOR: As members of UNC (University of North Carolina) Project–Uganda who provide education and pediatric emergency care in that resource-limited country, we dispute the conclusion that bolus crystalloid resuscitation is harmful in the treatment of shock. The importance of rapid fluid resuscitation in shock is supported by the World Health Organization (WHO) emergency triage, assessment, and treatment (ETAT) and the pediatric advanced life support (PALS) guidelines. In this study, 43% of all patients had severe anemia. In the “no bolus” control group, 20% of the patients received whole-blood transfusion within 1 hour. In contrast, only 2% of patients in the albumin-bolus group and 4% of patients in the saline-bolus group received this definitive therapy for severe anemia because they were receiving bolus fluid; this could have resulted in the observed 3.3 percentage-point increase in the absolute risk of death. Our first-hand experience has shown that rapid infusion of bolus crystalloid fluids followed by reassess-
ment in severe shock is highly beneficial in patients without severe anemia. This study also shows that improvements in mortality can be obtained by creating a rapid triage and treatment delivery system for children — something that is lacking in most of Africa.

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TO THE EDITOR: In 2005, the Journal published an article that said that fluid boluses were associated with nearly 100% survival among patients with previously fatal hypovolemic dengue shock syndrome in Southeast Asia. The accompanying editorial called for an evaluation of the use of fluid boluses in the sub-Saharan population because blood — not fluid boluses — is recommended in populations with isovolumic, high-output, anemic shock. The FEAST Trial Group found fluid boluses harmful as compared with maintenance fluids. Patients with hypovolemic dehydration were excluded, and fluid boluses were given for hypotension, a surrogate for hypovolemia. Patients with a hemoglobin level of less than 5 g per deciliter received transfusions of 20 ml of whole blood per kilogram over 4 hours. Blood transfusion was delayed in the “fluid-bolus” groups as compared with the “no-fluid-bolus” group (3% vs. 20% of children began to receive fluid in the first hour). Fluid boluses were most harmful in subgroups of patients who had signs that were consistent with severe anemic shock (hemoglobin level <5 g per deciliter and base deficit >8 mmol per liter, without coma). These findings provide support for two therapeutic approaches — first, use a fluid bolus in patients with hypovolemic shock who have dengue shock syndrome but no severe anemia; second, patients with severe anemic shock without hypotension should undergo transfusion with blood (do not administer a fluid bolus).

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TO THE EDITOR: The examination by Maitland et al. of resuscitation with fluids shows the rarity of early hypotension in pediatric febrile illness. Their inclusion criteria were consistent with pediatric sepsis guidelines recommending diagnosis through physical examination findings, but these are unproved in a normotensive population. Of recommended physical findings, only mental status predicted organ dysfunction in children with sepsis in U.S. emergency departments. Diagnostic criteria were adapted differently in recent studies involving children with sepsis in emergency departments, resulting in dissimilar populations.

In the study reported by Maitland et al., interpretation rests on whether the patients were in shock. The increased mortality among patients in the bolus groups may indicate that fluids harm ill patients who are not in shock. Alternatively, boluses may produce harm in patients with shock. Most likely, low-volume fluid resuscitation without critical care is insufficient for patients in shock and excessive for the remainder of this population.

Until diagnostic strategies in early sepsis in
children are refined and consensus is achieved, evaluation of therapies in the most proximal phase of illness will be limited.

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Children with acute severe malnutrition (ac

The Authors Reply: The correspondence regarding the FEAST trial raises three important issues: first, the definition of shock used in the FEAST trial; second, the effect of anemia and transfusions on results; and third, the effect of nutritional status. We address these points and include new analyses of our data.

In our trial, we compared bolus with no bolus in subgroups of children fulfilling different definitions of shock with respect to 48-hour mortality4−3 (Table 1). The FEAST criteria most closely resembled the American College of Critical Care Medicine definition of “cold shock,” which was present in 2127 participants (68%). The WHO ETAT shock criteria identified only 65 children (2%); however, even in this small subgroup, there was a significant excess risk associated with boluses, with an absolute difference in risk of 28 percentage points (95% confidence interval [CI], 3.4 to 52.5). We acknowledge problems with interobserver variation and specificity of the bedside assessment of shock that are inherent in current definitions of pediatric shock. However, objective measures such as moderate hypotension were also associated with higher mortality in the bolus groups as compared with the no-bolus group (absolute difference in risk; 9.4 percentage points; 95% CI, −2.6 to 21.4). Despite some ambiguity in interpretation of different definitions of shock, the findings are remarkably consistent and all point to the same conclusion.

The suggestion that anemia is a reason for the increased mortality among bolus-treated children is not supported in our analyses; excess mortality in the bolus groups was as apparent among children without severe anemia (hemoglobin level, ≥5 g per deciliter) as among children with severe anemia (hemoglobin level, <5 g per deciliter) (Fig. 3 of our article and Table 5 in the Supplementary Appendix). Similar results were also apparent in children with a hemoglobin level of 10 g per deciliter or more or less than 10 g per deciliter. Questions about earlier initiation of blood transfusion in the control group were also raised; however, the volume of blood received in all groups was small in the first hour (the mean [±SD] volume by 1 hour in the bolus vs. no-bolus groups was 0.05±0.7 ml per kilogram vs. 0.6±1.6 ml per kilogram) (Table 3a in the Supplementary Appendix).

Children with acute severe malnutrition (according to clinical judgment) were excluded. However, 70 children (2%) had a mid-upper-arm circumference of 11.5 cm or less (Table 1 of our article). The effect of bolus fluids was not significantly different in children with a mid-upper-arm circumference of more than 11.5 cm (absolute difference in risk, 1.2 percentage points; 95% CI, −0.5 to 3.0) or 11.5 cm or less (absolute difference in risk, 3.5 percentage points; 95% CI, −13.0 to 20.1; P=0.96 for heterogeneity).

There was little clinical evidence of dengue infection or its life-threatening complications where our trial took place. Severe dengue in-
## Table 1. Risk of Death Among Participants, According to Various Definitions of Shock in Children.*

<table>
<thead>
<tr>
<th>Definition of Shock</th>
<th>Application of Criteria to FEAST Admission Data</th>
<th>Mortality</th>
<th>Percentage-Point Difference (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEAST inclusion criteria</td>
<td></td>
<td></td>
<td>Overall (All Groups)</td>
</tr>
<tr>
<td>History of fever or axillary temperature &gt;37.4°C or &lt;36°C and impaired consciousness (prostration or coma), respiratory distress, or both; plus ≥1 of: capillary refill time &gt;2 sec; lower-limb temperature gradient; weak pulse, tachycardia (heart rate &gt;180 beats/min in children &lt;12 mo; &gt;160 beats/min in children 12 mo–5 yr; &gt;140 beats/min in children &gt;5 yr)</td>
<td>297/3141 (9.5)</td>
<td>221/2097 (10.5)</td>
<td>76/1044 (7.3)</td>
</tr>
<tr>
<td>ACCM</td>
<td></td>
<td></td>
<td>Bolus (Saline or Albumin)</td>
</tr>
<tr>
<td>Cold shock (with one sign)</td>
<td>Axillary temperature &gt;37.4°C or &lt;36°C; plus ≥1 of: prostration or coma or Blantyre coma score; &lt;5, capillary refill time &gt;2 sec, weak pulse, increased temperature gradient</td>
<td>194/2127 (9.1)</td>
<td>150/1452 (10.3)</td>
</tr>
<tr>
<td>Cold shock (with two signs)</td>
<td>Axillary temperature &gt;37.4°C or &lt;36°C; plus ≥2 of: prostration or coma or Blantyre coma score &lt;5, capillary refill time &gt;2 sec, weak pulse, increased temperature gradient</td>
<td>189/1733 (10.9)</td>
<td>147/1196 (12.3)</td>
</tr>
<tr>
<td>PALS</td>
<td></td>
<td></td>
<td>No Bolus (Control Group)</td>
</tr>
<tr>
<td>Compensated shock</td>
<td>Two of the following: tachycardia (see FEAST above), increased temperature gradient, capillary refill time &gt;2 sec, or weak pulse</td>
<td>238/1650 (13.2)</td>
<td>161/1113 (14.5)</td>
</tr>
</tbody>
</table>

* The New England Journal of Medicine

† Percentage-point difference in mortality between bolus and no-bolus groups.
Decompensated shock

Signs and symptoms consistent with inadequate delivery of oxygen to tissues (one of the following signs: pallor, peripheral cyanosis, tachypnea, mottling of skin, decreased urine output, metabolic acidosis, depressed mental status); also weak or absent peripheral pulses, weak central pulses, or hypotension (systolic blood pressure <70 mm Hg in children 1-12 mo; <70 mm Hg plus twice child’s yr of age in children 1-10 yr; <90 mm Hg in children ≥10 yr)

WHO ETAT

Cold hands or feet with both capillary refill time >3 sec and weak and fast pulse

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<tr>
<td>Cold hands or feet with both capillary refill time &gt;3 sec and weak and fast pulse</td>
<td>157/755 (20.8)</td>
<td>115/513 (22.4)</td>
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<tr>
<td>Cold hands or feet with both capillary refill time &gt;3 sec and weak and fast pulse</td>
<td>42/242 (17.4)</td>
<td>5.1 (-0.9 to 11.0)</td>
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ACCM denotes American College of Critical Care Medicine, FEAST Fluid Expansion as Supportive Therapy, PALS pediatric advanced life support, and WHO ETAT World Health Organization emergency triage, assessment, and treatment.

† Percentage-point differences are for the absolute risk of death in the bolus groups versus no-bolus groups.

‡ The Blantyre coma score is rated on a scale of 0 to 5, with 0 indicating the complete absence of any response to a painful stimulus and 5 indicating full consciousness.

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Since publication of their article, the authors report no further potential conflict of interest.


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