Fluid Resuscitation in Acute Illness — Time to Reappraise the Basics
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Fluid resuscitation is a fundamental intervention in the treatment of critically ill patients. However, there is little conclusive evidence to guide clinicians about the best type of resuscitation fluid; the appropriate timing, volume, and rate of fluid administration; and the optimal way to adequately monitor the efficacy and safety of fluid resuscitation in various clinical conditions.

Although the complications associated with excessive volume of resuscitation fluid — such as pulmonary and interstitial edema — are well recognized, an emerging body of evidence suggests that the type of resuscitation fluid may adversely affect the outcomes in specific clinical conditions; for example, albumin is associated with increased mortality in patients with traumatic brain injury,2 and high-molecular-weight preparations of hydroxyethyl starch are associated with acute kidney injury in patients with severe sepsis.3 Conversely, improved outcomes associated with the use of albumin for resuscitation have been shown in children with severe malaria4 and in a subgroup of adults with severe sepsis in the Saline versus Albumin Fluid Evaluation study (SAFE; Current Controlled Trials number, ISRCTN76588266).5,6 However, these reports were not sufficiently conclusive to justify the adoption of strong clinical recommendations.

The results of the Fluid Expansion as Supportive Therapy (FEAST) trial,7 reported in this issue of the Journal, are an important contribution to the literature. This remarkable, pragmatic, randomized, controlled trial, conducted in six hospitals in Kenya, Tanzania, and Uganda, assessed the effects of bolus-fluid resuscitation with albumin or saline as compared with no bolus fluid in children with febrile medical illness and impaired perfusion. Children with severe hypotension, or decompensated shock, received boluses of either albumin or saline for resuscitation. The trial centers had no access to intensive care units, and the trial included a comprehensive education program aimed at optimizing early case recognition and training in emergency pediatric life support. The primary outcome was 48-hour mortality — a relevant patient-centered outcome in regions in which the high prevalence of severe sepsis in children, often due to malaria, is associated with high early mortality.8

The trial was powered to determine a plausible absolute risk reduction in 48-hour mortality (as derived from power calculations described in the Methods section in the article) of 5 percentage points and was conducted with high standards of internal validity — excellent randomization procedures, a high rate of adherence to the protocol, concealment of the treatment assignments, a minimal loss to follow-up, the use of the intention-to-treat principle for the analyses, and performance of analyses according to prespecified subgroups. The sample size was appropriately increased from 2800 patients to 3600 patients after an interim analysis showed that the rate of death was lower than predicted in the intervention groups. However, the trial was stopped after the recruitment of 3141 patients when bolus-fluid resuscitation with albumin or saline was shown to increase the absolute risk of death at 48 hours by 3.3 percentage points and the risk of death, neurologic sequelae, or both at 4 weeks by 4 percentage points. No difference in mortality was observed in patients with decompensated shock, although these patients were few in number and had significantly higher mortality. The excess mortality associated with bolus-fluid resuscitation was consistent across all prespecified subgroups, which included subgroups according to age, lactate level, base deficit, presence or ab-
sence of severe anemia, and status with respect to coma and malaria.

These results will have an immediate effect on the way children presenting with febrile illness due to medical causes and with associated hypotension are treated in resource-poor settings. In conjunction with a program of education and training, discontinuation of the practice of bolus-fluid resuscitation in patients with febrile illness due to medical causes and impaired perfusion or compensated shock must be recommended. Given that 2 million children die from this condition each year in sub-Saharan Africa, the potential impact is enormous. Extrapolating these results to children with other hypotensive conditions, such as severe dehydration from gastrointestinal and malnutrition, burns, and surgery, is not justified on the basis of these data; further research would be required.

The results of the FEAST trial, as with those of other trials that generated results contrary to clinical opinion and practice,9,10 make it imperative that we reappraise the fundamentals. Early identification of shock, basic life support, and early antimicrobial therapy remain at the forefront of the clinical care of young patients with severe infection and shock. It is highly probable that education, training, and participation in a high-quality, randomized, controlled trial itself had a substantive positive effect on the overall rate of death, although these factors were not directly assessed in this trial. However, the entrenched practice of fluid-bolus resuscitation in patients with compensated shock remains highly questionable.

We can only speculate about the mechanisms by which bolus-fluid resuscitation had adverse biologic effects in these patients. Potential mechanisms may include the interruption of genetically determined catecholamine-mediated host defense responses by the rapid increase in plasma volume, which might result in a reperfusion injury. Similarly, transient hypervolemia or hyperosmolarity might exacerbate capillary leak in patients who are susceptible to intracranial hypertension2 or pulmonary edema, with fatal consequences.

How should clinicians who work under circumstances different from those in this trial—that is, in high-income countries with access to intensive care units—or clinicians who care for adult patients interpret the results of this important trial? It seems clear that the results of this trial indicate that bolus-fluid resuscitation with either crystalloids or colloids in patients with compensated shock who do not have a clinical fluid deficit must be practiced with much greater caution than is now the case and with increased vigilance.

Fluid resuscitation is such a fundamental intervention in acute medicine that these results indicate that further high-quality research is urgently required to define appropriate practice for fluid resuscitation, including a study of the timing and rates of fluid administration and ways to monitor its effects. Similarly, a careful assessment of the safety, efficacy, and cost-effectiveness of various resuscitation fluids is mandatory before their incorporation into clinical practice.

The courage and dedication of the FEAST investigators and attending clinicians must be acknowledged, not only because of the quality of the research they conducted in this vitally important area of acute medicine, but also because they conducted a landmark trial in such challenging economic conditions in sub-Saharan Africa.

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