Shifting the Paradigm in Hemolytic Uremic Syndrome

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In this issue of the journal, Ardissino et al¹ report that early volume expansion in children with hemolytic uremic syndrome associated with Shiga toxin-producing *Escherichia coli* (STEC-HUS) significantly improves clinical outcomes. The observation possesses significant clinical implications for the management of an illness that causes much morbidity and not infrequently, mortality.² The data are among the first in several decades that motivate a clinically useful change in the standard practice. The elegantly simple study design led to a relatively straightforward, yet palpably important conclusion that upon presentation, timely administration of sufficient intravenous fluids to increase the child's body weight by 10% meaningfully decreases length of stay, need for admission to a PICU, use of renal replacement therapy, and the incidence of long-term sequelae.

There is much to learn from the trial. First, and clearly most significant, treatment of STEC-HUS entails time-sensitive delivery of intravenous fluids. The trial provides compelling evidence that a less vigorous regimen of rehydration increases the risk of an unfavorable outcome. The notion that optimal treatment of STEC-HUS includes generous volume expansion, to 10% above the body weight represents an important shift in the primarily supportive care paradigm.³ Moreover, implicit in the trial is the administration of intravenous hydration immediately after diagnosis, which represents a time-sensitive proposition and is another important shift in the standard approach to children with STEC-HUS.

Although the trial design, conclusions, and implications for clinical care are important, yet straightforward, there are less readily apparent aspects of the trial that might be highly generalizable and merit our collective consideration. First, the investigators designed the trial with clear knowledge of the relevant previous literature, specifically noting the poor prognostic implications of dehydration upon presentation.⁴ The authors built upon the previous clinical observations and trials to articulate a plan for treatment that will meaningfully improve outcomes.

Second, and arguably more important, the authors were willing, and able, to effectively challenge the standard approach for treatment of STEC-HUS. Over the course of the past several decades, care providers were wary of providing intravenous fluids in the context of renal insufficiency, owing to concerns over potential for fluid overload. In general, with greater concern for renal insufficiency, more stringent fluid restrictions have been applied.³ Fortunately, the authors challenged the collective by arguing that a parsimonious approach to fluid replacement might not only be ineffective, but harmful. Certainly, the finding gives pediatricians that have been at the bedside of these children for those same decades moment to pause and will inform the approach moving forward.

Third, the trial was overwhelmingly successful despite a design and number of study subjects that many critical observers would characterize as less than optimal. In children, generating

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new and robust knowledge is notoriously difficult.⁵ The number of randomized, placebo-controlled, blinded clinical trials in infants and children is vanishingly small relative to similarly rigorous trials in adults. Doubtless, larger trials, with the highest level of rigor are preferred, but carefully undertaken, well-performed smaller trials can just as certainly provide important new knowledge to guide care even in diseases and illnesses that, fortunately, occur only infrequently. The pragmatic approach to trial design proved to be wise.

That the authors were able to demonstrate efficacy after enrolling only 38 children is remarkable. Outcomes were improved for almost every end point studied. The important end points that did not reach statistical significance, death, and central nervous system involvement likely result from a justifiable type 2 error. The significance of the trial should not be mitigated, in any way, by the use of historical controls. On

the contrary, the authors should be commended for designing a trial that permits conclusions surrounding the merits of vigorous volume expansion in the context of STEC-HUS compared with the standard approach. The study design serves the interests of the academic community by creating important new knowledge even while ensuring that study subjects get access to the treatment approach favored by the authors.

The trial “Early volume expansion and outcomes of hemolytic uremic syndrome” outlines an approach to treatment that promises to favorably inform care for children with a specific illness.¹ Creating this knowledge through the design and conduct of outstanding clinical trial is an impressive feat. By wedding careful clinical observations with the emerging literature and taking a pragmatic approach to clinical trial design and execution, the authors channeled the very best traditions of academic medicine.

ABBREVIATION

STEC-HUS: Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome

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