A recently published systematic review and meta-analysis attempted to clarify the impact of using balanced crystalloids in sepsis; however, including these new data with previously published controlled trials and observational studies improves on those efforts (2). When prior data are considered alongside the SMART *post hoc* analysis, the benefit on short-term mortality appears less certain, although potentially still impactful (odds ratio [OR], 0.88; 95% confidence interval [CI], 0.76–1.01) (1, 3–5) (Figure 1). We have greater confidence in the decreased odds of patients developing acute kidney injury (OR, 0.67; 95% CI, 0.49–0.92) but uncertainty regarding progression to receipt of renal replacement therapy (OR, 0.85; 95% CI, 0.71–1.03) when receiving balanced crystalloids (1, 4–6). Although two of the three individual outcomes did not show significance, there was a lower incidence of major adverse kidney events in 30 days with balanced crystalloids compared with saline (OR, 0.78; 95% CI, 0.65–0.94) in the two studies that evaluated this outcome (1, 6). Differences in this composite outcome, which are not being driven by a particular intermediate clinical endpoint, are extremely encouraging for balanced crystalloid use.

When financial costs are considered, the proposition of using a balanced crystalloid rather than saline becomes even more attractive. Although Plasma-Lyte 148 is almost three times more costly than saline, lactated Ringer's is available at approximately the same purchase price as saline. The majority of patients in most published studies who were prescribed a balanced crystalloid received lactated Ringer's (1, 4–6). Given the significant costs associated with poor clinical outcomes and adverse events during critical illness, using lactated Ringer's in critically ill patients with sepsis is likely to be a substantially cost-effective intervention in most scenarios.

We hope that the fine work by Brown and colleagues will be considered favorably alongside other published evaluations of balanced crystalloids versus saline in critically ill adults (1). At this time, we believe providing fluid resuscitation with balanced crystalloids, particularly lactated Ringer's, to adult patients with sepsis is likely a more effective and cost-effective intervention than saline. ■

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Drayton A. Hammond, Pharm.D., M.B.A., M.Sc.*
Gary D. Peksa, Pharm.D.
Rush University Medical Center
Chicago, Illinois
and
Rush Medical College
Chicago, Illinois

Megan A. Rech, Pharm.D., M.S.
Loyola University Medical Center
Maywood, Illinois

ORCID ID: 0000-0002-9056-5560 (D.A.H.).

*Corresponding author (e-mail: drayton_hammond@rush.edu).

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Reply to Gueret *et al.* and to Hammond *et al.*

From the Authors:

We thank Dr. Gueret and colleagues for their interest in our study (1). They correctly point out that, although the SMART (Isotonic Solutions and Major Adverse Renal Events Trial) trial was registered before enrollment (NCT02444988, NCT02547779) and sepsis was prespecified as a subgroup of interest (2, 3), we did not separately register and publish a protocol for the current secondary analysis. Sepsis was prespecified as a subgroup of interest because we expected that patients with sepsis would be at high risk of acute kidney injury and death, receive larger-than-average volumes of intravenous crystalloid, and be physiologically susceptible to differences in crystalloid composition (4). In-hospital mortality at 30 days, a secondary outcome of the SMART trial, was selected as the primary outcome of this secondary analysis to be consistent with other clinical trials in sepsis and because mortality is a common, patient-centered sepsis outcome.

Gueret and colleagues ask which vasopressors patients received in each group. At the time of enrollment, the percentage of patients in the balanced crystalloid group and saline group, respectively, receiving norepinephrine was 33.9% versus 31.6% ($P = 0.35$), vasopressin was 4.9% versus 3.5% ($P = 0.19$), phenylephrine was 2.9% versus 3.4% ($P = 0.42$), and epinephrine was 1.8% versus 1.5% ($P = 0.71$). The proportion of patients receiving each vasopressor each day was similar between groups on the first 5 days after ICU admission ($P > 0.29$ for all), suggesting that differential use of vasopressors did not contribute to the differences in outcomes between groups.

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We agree that fluid administered during initial sepsis resuscitation, before ICU admission, is a crucial consideration for randomized trials of fluid management in critical illness. A strength of the current analysis is that, for patients presenting to the emergency department or operating room, choice of crystalloid was controlled from initial presentation through ICU discharge—a key difference from other randomized trials studying crystalloid composition in critically ill patients (5). Further research is needed to specifically evaluate the relative effects of crystalloid composition during initial resuscitation in the emergency department compared with fluid administration after ICU admission.

We also thank Dr. Hammond and colleagues for their meta-analysis combining the results of our SMART sepsis subgroup analysis with results from prior studies comparing balanced crystalloids to saline among patients with sepsis. In their meta-analysis, the point estimate favored balanced crystalloids over saline for all outcomes, and 95% confidence intervals demonstrated a statistically significant difference (major adverse kidney events and acute kidney injury) or approached a statistically significant difference (receipt of renal replacement therapy and death). We agree that, while awaiting additional data, using of balanced crystalloids rather than saline for adults with sepsis is reasonable. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Ryan M. Brown, M.D.
Li Wang, M.S.
Jonathan D. Casey, M.D.
Karen E. Jackson, M.D.
Wesley H. Self, M.D., M.P.H.
Todd W. Rice, M.D., M.Sc.
Matthew W. Semler, M.D., M.Sc.*
Vanderbilt University Medical Center
Nashville, Tennessee

ORCID IDs: 0000-0002-8778-026X (R.M.B.); 0000-0002-7664-8263 (M.W.S.).

*Corresponding author (e-mail: matthew.w.semler@vumc.org).

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Adrenomedullin: A Double-edged Sword in Septic Shock and Heart Failure Therapeutics?

To the Editor:

In a recent issue of the *Journal*, Filewod and Lee eloquently demystified the prospects of vascular leakage in sepsis, highlighting novel therapeutic avenues (1). The authors appropriately mentioned adrenomedullin (ADM) as a prominent example among approaches to harness vascular leakage (1). Given the interdisciplinary therapeutic potential of the ADM pathway, further focused discussion is warranted.

ADM is a vasoactive peptide synthesized by endothelial and vascular smooth muscle cells, has diverse multiorgan roles, and diffuses freely between the circulation and the interstitium (2, 3). In the circulation, it exerts endothelial barrier–stabilizing effects, thereby mitigating vascular leakage, whereas in the interstitium, it modulates vascular tone, exerting vasodilatory effects (2, 3). As a biomarker, ADM improves prognostication in heart failure and chronic obstructive pulmonary disease (3, 4).

Among the currently available therapies for heart failure, sacubitril-based therapy potentiates ADM by inhibiting its degradation by neprilysin (5). Adrecizumab is a monoclonal nonneutralizing antibody against the N terminus of ADM. Adrecizumab is bound to the blood compartment by virtue of its high molecular weight and leads to a dose-dependent increase of plasma ADM by compartmentalizing ADM in the circulation, and also potentially by increasing its translocation from the interstitium (3). Although a study of adrecizumab in hospitalized patients with heart failure is currently being prepared (3), a phase 2 study of adrecizumab in patients with early septic shock is already underway (6). Indeed, harnessing vascular leakage in inflammation is no longer science fiction, but an active focus of interdisciplinary scientific investigation. ■

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Muddassir Mehmood, M.D.*
The University of Tennessee Medical Center
Knoxville, Tennessee

ORCID ID: 0000-0002-3568-0419 (M.M.).

*Corresponding author (e-mail: mmehmood@utmck.edu).

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