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. ■

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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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Reply to Mehmood

From the Author:

I thank Dr. Mehmood for his comments. I agree that the pathological importance of vascular leakage extends far beyond sepsis and acute lung injury (acute respiratory distress syndrome) to include diverse syndromes such as heart failure (1, 2), renal failure (3), and connective tissue diseases (4). In my opinion, this reflects the fact that increased endothelial permeability is usually maladaptive, given the detrimental effects of tissue edema. Furthermore, severe vascular leakage may be difficult for the body to remediate, given the limited ability of the mature endothelium to proliferate (5).

As we enter the era of clinical trials for agents that stabilize the vascular barrier (6), it is important to remember that multiple cellular and molecular mechanisms exist for vascular leakage. These include endothelial apoptosis (7), pyroptosis (8), and remodelling of endothelial cell–cell junctions and the cellular cytoskeleton (9). The success of drugs aimed at reducing vascular leakage in clinical trials may therefore depend on the cause of the leakage and the mechanism of action of the drug. Nonetheless, given its ubiquity in clinical medicine, the prospect of either harnessing (10) or counteracting vascular leakage without impairing the immune response (11) is an intriguing prospect for clinicians. ■

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Importance of Occupational Exposure Data: A National Idiopathic Pulmonary Fibrosis Registry Perspective

To the Editor:

We read with interest the insightful opinion provided by Nett and colleagues regarding the importance of gathering