the in vitro arm of the publication, the authors found that albumin inhibited HBP-induced increase in human endothelial cell permeability, which may provide a mechanism of action for a beneficial role of albumin in the pathophysiology of AKI (2).

In contrast to the presumption and findings of Fisher et al (2) that, in patients with sepsis, albumin levels alone are not predictive of AKI development, there is evidence from observational studies that this may not be the case. In an EMBASE search for the period from January 1, 2010, to October 31, 2018, the terms ("sepsis"/exp OR sepsis) AND ("acute kidney failure"/exp OR "acute kidney failure") AND ("albumin"/exp OR albumin) revealed a total of 442 entries, among them five study reports that confirmed the association of albumin levels with AKI development also in patients with sepsis (3–7). The association was significant in univariate analyses in three of them (5–7); in two of the reported study cohorts, hypoalbuminemia was confirmed as an independent risk predictor for the development of septic AKI by multivariate analyses (3, 4).

The reported lack of association between albumin levels and AKI development in patients with septic shock by Fisher et al (2) may be due to certain characteristics of the VAAST trial such as the randomized controlled study design with inclusion and exclusion criteria determining disease severity and comorbidities rather than a particular mechanism of albumin in the pathophysiology of septic AKI. Hence, the reported HBP-dependent effects of albumin would need to be investigated in other cohorts of patients with sepsis, where the association with AKI development may be seen not only for circulating levels of HBP but also with hypoalbuminemia. Strengths of associations and risk prediction as reported for the two markers by Fisher et al (2) may then be capable of better assessment.

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The authors reply:

We thank Dr. Wiedermann (1) regarding his discussion on our recent article (2) published in *Critical Care Medicine* and for highlighting publications that evaluate hypoalbuminemia versus outcomes of critically ill patients. Key differences between those studies and the Vasopressin And Septic Shock Trial (VASST) cohort might explain the lack of association of serum albumin with acute kidney injury (AKI) in VASST.

Of the five publications, two include ICU patients (not specifically sepsis). Of the sepsis publications (3, 4), two (3, 4) describe the same cohort in which albumin was associated with AKI in unadjusted analysis, but not after adjustment for variables associated with AKI, notably, septic shock. The other study (postoperative patients with sepsis and septic shock) reports a significant association of serum albumin with AKI even when adjusted. A recent meta-analysis found that hypoalbuminemia was associated with AKI (5), but most of these studies did not include patients with sepsis and most used unadjusted analyses.

The relationship between hypoalbuminemia and AKI in sepsis is unclear (i.e., there is equipoise), partially also because hypoalbuminemia identifies sicker patients. Therefore, the presence of hypoalbuminemia is usually confounded by variables that are independently associated with development of AKI. Indeed, adjusted analyses are preferable for evaluations of the prognostic biomarker serum albumin vis-à-vis AKI.

Similarly, as Dr. Wiedermann (1) states, the association between hypoalbuminemia and AKI could also have been confounded by characteristics (measured and unmeasured) unique to the VASST cohort. One key characteristic of VASST is that all patients had septic shock upon enrollment. Hypoalbuminemia is common in septic shock; the mean baseline plasma albumin level in VASST was quite low, 25.4 g/L. It is therefore conceivable that, in patients with septic shock, differences between subgroups (such as AKI vs no AKI) with such low serum albumin levels may be too small to detect an association of albumin with AKI.

We crisply differentiate serum albumin as a prognostic biomarker (e.g., for development of AKI) and as a predictive biomarker (e.g., for response to albumin infusion to mitigate frequency and severity of AKI). We agree with Dr. Wiedermann (1) that a prospective cohort study designed to test the prognostic accuracy of albumin (and heparin-binding protein) would facilitate discovery and validation of prognostic AKI biomarkers in sepsis. Perhaps a cohort of sepsis patients that includes septic patients with less severe illness (and so higher albumin levels at baseline than in more severely ill patients) might facilitate detection of small differences in albumin levels between patients who do or do not develop AKI.

However, association studies do not prove causation. Only randomized controlled trials of albumin infusion (e.g., Albumin Italian Outcome Sepsis [ALBIOS] [6]) can determine whether correction of hypoalbuminemia with albumin infusion decreases frequency and severity of AKI in sepsis.

The ALBIOS trial of albumin versus crystalloid in sepsis permits evaluation of serum albumin as a predictor of response

TABLE 1. Serum Albumin Versus Endpoints in Albumin Italian Outcome Sepsis Trial (5)

Analysis	*p*
Serum albumin vs 90-d mortality (all patients; $n = 1{,}609$)	< 0.001
Serum albumin vs 90-d mortality (septic shock subgroup; $n = 1{,}004$)	0.004
Serum albumin vs AKI (renal SOFA score > 1) (all patients; $n = 1{,}634$)	0.39
Serum albumin vs AKI (renal SOFA score > 1) (septic shock subgroup; $n = 1{,}018$)	0.63
Serum albumin vs need for CRRT (all patients; $n = 1{,}516$)	0.32
Serum albumin vs need for CRRT (septic shock subgroup; $n = 923$)	0.22
Serum albumin interaction with albumin vs crystalloid treatment (all patients; $n = 1{,}511$)	0.85
Serum albumin interaction with albumin vs crystalloid treatment (septic shock subgroup; $n = 919$)	0.92

AKI = acute kidney injury, CRRT = continuous renal replacement therapy, SOFA = Sequential Organ Failure Assessment.

to albumin versus crystalloid (6). Serum albumin was significantly associated with 90-day mortality (7) but not with AKI or the need for renal replacement therapy, nor to response to albumin versus crystalloid infusion in sepsis and in the subgroup of septic shock (**Table 1**).

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Airway Pressure Release Ventilation as a Rescue for Acute Respiratory Distress Syndrome But Use Early to Prevent It!

To the Editor:

I enjoyed the well done article by Fielding-Singh et al (1) in a recent issue of *Critical Care Medicine* but would like to comment on the authors failing to include the use of airway pressure release ventilation (APRV). It has been used for over 30 years most commonly as a rescue ventilator mode for severe hypoxemia and acute respiratory distress syndrome (ARDS). Multiple clinical trials have shown improvements in oxygenation (reduced A-a gradient and increased Po_2/Fio_2 ratio), reduction in peak inspiratory pressures (PIP) but increased lung compliance, decreased need for sedation, paralytics, and vasopressors, and improved cardiac index and renal blood flow (2–4). A recent trial using APRV early in ARDS confirmed these older studies by finding much improved Po_2/Fio_2 ratios (280.3 vs 180.5), reduced PIP (26.2 vs 28.5 cm H_2O), successful extubation rate (66.2% vs 38.8%), reduced days on MV (8 vs 15), decreased need for