6. Proskocil BJ, Sekhon HS, Clark JA, Lupo SL, Jia Y, Hull WM, *et al*. Vitamin C prevents the effects of prenatal nicotine on pulmonary function in newborn monkeys. *Am J Respir Crit Care Med* 2005;171:1032–1039.

Balanced Crystalloid versus Saline Solution in Critically Ill Patients: Is Chloride the Villain?

To the Editor:

Semler and Kellum present a thorough and scholarly review of studies (theirs and others) comparing saline and balanced crystalloid solutions for intravenous fluid therapy in critically ill patients, and make a good case for the superiority of balanced crystalloid solutions over saline with respect to mortality and adverse renal events (1). This issue will hopefully be definitively settled by the results of two large randomized controlled trials in almost 20,000 patients that are currently underway and hopefully will involve the administration of larger volumes than the 1–2 L studied to date. In large part, Semler and Kellum highlight the deleterious effects of hyperchloremia and associated mild metabolic acidosis arising from saline administration. However, the argument that modest elevations in serum chloride after saline administration are entirely responsible for these worse outcomes is too simplistic. Much of the putative blame attached to chloride rests on the widely cited experiments of Wilcox (2), which involved isolated blood perfusion of dog kidneys with various hypertonic fluids at a chloride concentration of 126 mM. The kidney's sudden exposure to an instantaneous almost 20-mM rise in chloride (and the resulting hypertonicity) led to a degree of vasoconstriction and release of thromboxane that Semler and Kellum and others cite as the cause for chloride's vasoconstrictive and proinflammatory effects in patients requiring fluid resuscitation. This rationale, however, does not necessarily carry over to far lesser and more slowly developing 2- to 4-mM plasma chloride elevations as the cause of renal injury and increased mortality among critically ill patients given saline. It is important to note that Wilcox did no dose-response experiments within the range of chloride elevations that are more typically found in saline-treated critically ill patients. Other differences in the composition of balanced crystalloids beyond changes in chloride concentration could be playing a protective role in the outcomes that appear to be consistent across multiple trials. Semler and Kellum do suggest that there may be benefits to the provision of lactate or other metabolized anions in balanced solutions, as there is emerging evidence that lactate functions as an important fuel in the central nervous system and heart under stressed conditions. Likewise, small changes in potassium and calcium concentrations might also be beneficial. One way to potentially absolve or condemn chloride would be to test "normal" saline against saline with a one-to-one replacement of 24-mM bicarbonate for chloride. Given the present lack of equipoise regarding chloride, this experiment is unlikely to be performed, but until such time, chloride should be presumed innocent and not yet guilty as charged. In analogy to the arguments that arose concerning the original goal-directed bundled therapy for sepsis resuscitation proposed by Rivers and colleagues (3), balanced crystalloid solutions are a "bundle," and we do not know which element(s) is the most critical—less chloride or its replacements. Although one sometimes hears the casual statement that saline may kill, millions of patients saved might otherwise disagree. ■

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

Erik R. Swenson, M.D.*
University of Washington
Seattle, Washington

*Corresponding author (e-mail: eswenson@uw.edu).

References

1. Semler MW, Kellum JA. Balanced crystalloid solutions. *Am J Respir Crit Care Med* 2019;199:952–960.
2. Wilcox CS. Regulation of renal blood flow by plasma chloride. *J Clin Invest* 1983;71:726–735.
3. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, *et al*.; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–1377.

Reply to Swenson

From the Authors:

We appreciate the thoughtful letter from Dr. Swenson regarding our recent concise clinical review on balanced crystalloid solutions (1). Dr. Swenson notes that much of the recent research comparing balanced crystalloids with saline has examined clinical outcomes (2), leaving major questions about mechanism unanswered. Balanced crystalloids and saline differ in their concentrations of chloride, organic anions (e.g., lactate and acetate), potassium, and divalent cations (e.g., magnesium and calcium). Although saline-induced hyperchloremic metabolic acidosis has been the focus of most preclinical research comparing these solutions (3), which differences in composition cause the observed differences in clinical outcomes remains unknown.

We agree with Dr. Swenson's interest in mechanism. We would be thrilled if ancillary studies to ongoing trials (4, 5), research in animal models, and future trials examining sodium

Originally Published in Press as DOI: 10.1164/rccm.201904-0806LE on May 1, 2019

M.W.S. was supported in part by the NHLBI (K23HL143053). J.A.K. received grant support from Baxter and Grifols.

Author Contributions: Drafting of the manuscript and critical revision of the manuscript for important intellectual content: M.W.S. and J.A.K.

Originally Published in Press as DOI: 10.1164/rccm.201904-0859LE on May 1, 2019

bicarbonate in acute illness and comparing different formulations of balanced crystalloids could delineate the respective contributions of each cation and anion to organ function and clinical outcomes. Someday the evidence may allow a verdict on whether the chloride anion is individually guilty of worsening patient outcomes, a contributing accomplice, or an innocent bystander.

Mechanism aside, for the 30 million patients treated with intravenous fluid each year, we believe the weight of the current evidence favors balanced crystalloids over saline. Saline's innocence can no longer be presumed. The burden of proof now lies with those who would defend saline's safety. ■

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

Matthew W. Semler, M.D., M.Sc.*
Vanderbilt University Medical Center
Nashville, Tennessee

John A. Kellum, M.D.
University of Pittsburgh
Pittsburgh, Pennsylvania

*Corresponding author (e-mail: matthew.w.semler@vanderbilt.edu).

References

1. Semler MW, Kellum JA. Balanced crystalloid solutions. *Am J Respir Crit Care Med* 2019;199:952–960.
2. Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, *et al*.; SMART Investigators and the Pragmatic Critical Care Research Group. Balanced crystalloids versus saline in critically Ill adults. *N Engl J Med* 2018;378:829–839.
3. Kellum JA, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest* 2004;125:243–248.
4. Hammond NE, Bellomo R, Gallagher M, Gattas D, Glass P, Mackle D, *et al*. The Plasma-Lyte 148 v Saline (PLUS) study protocol: a multicentre, randomised controlled trial of the effect of intensive care fluid therapy on mortality. *Crit Care Resusc* 2017;19:239–246.
5. Zampieri FG, Azevedo LCP, Corrêa TD, Falavigna M, Machado FR, Assunção MSC, *et al*.; BaSICS Investigators and the BRICNet. Study protocol for the Balanced Solution versus Saline in Intensive Care Study (BaSICS): a factorial randomised trial. *Crit Care Resusc* 2017;19:175–182.

Promoting Neutrophil Apoptosis to Treat Acute Lung Injury

To the Editor:

We read with great interest the recently published work of Harris and colleagues in the *Journal* (1). Harris and colleagues explored the significance of neutrophil activity in acute lung injury (ALI) through thoughtful *in vitro* and *in vivo* experiments that aptly demonstrated the potential for therapeutically abrogating disproportionate neutrophilic inflammation by promoting apoptosis. We believe the implications of this study are significant and as such, we also appreciated the accompanying editorial by Summers (2), which deftly relayed why the strategy of abating overzealous neutrophil activity without placing excessive restraint on the host response holds great promise for advancing treatment of ALI. Our position is that of a lab that has devoted decades of research to neutrophil biology in inflammatory disorders, as well as one that has unfortunately often seen neutrophils overlooked, underappreciated, or not considered as viable targets of intervention.

Our pioneering studies agree with the notion that limiting neutrophil activity in the lung is beneficial in the context of ALI. Previous work in our lab used a two-hit mouse model of lung injury (LPS/immune complex) to, for the first time, diminish excessive activation of alveolar neutrophils by specific silencing of Btk (Bruton's tyrosine kinase). Targeted delivery of treatment to alveolar neutrophils *in vivo* elicited a dramatic protective effect by, among other things, ameliorating delayed neutrophil apoptosis and enhancing clearance of apoptotic neutrophils (3). Additionally, MMP-9 (matrix metalloproteinase-9) expression was reduced in neutrophils. This led us to neutrophil-specific silencing of MMP-9, which was observed to dampen proinflammatory neutrophil activity in our two-hit model. Likewise, the mice were protected from ALI. This work was predicated on earlier work that identified Btk as an important regulator of proinflammatory neutrophil activity, including cells from patients with ALI (4). Recently, we used a murine model of influenza-induced ALI to rescue animals from an otherwise lethal infection, and in parallel experiments we observed a significant drop in alveolar neutrophils as well as total white blood cells and multiple proinflammatory cytokines and chemokines present in the lung 7 days after infection (5). This was accomplished via intranasal delivery of the Btk inhibitor ibrutinib/PCI-32765, and because of the essential role of neutrophils in the early stages of infection, in these experiments treatment was administered 48 hours after infection. In addition, silencing of Btk in alveolar neutrophils enhanced neutrophil apoptosis (our unpublished results) and significantly decreased the formation of neutrophil extracellular traps (5). As Harris and colleagues noted in their Discussion, neutrophil inflammation is also an important component in chronic inflammation disorders such as chronic obstructive pulmonary disease. We have also used an atherosclerosis/chronic obstructive pulmonary disease comorbidity mouse model of apolipoprotein E–deficient mice that were regularly exposed to cigarette smoke and/or fed a proatherogenic diet, and whose treatments included ibrutinib or neutrophil-targeted siRNA to MMP-9, which we observed to have a dramatic protective effect (6, 7). Targeting either Btk or MMP-9 reduced arterial plaque growth and increased plaque stability, and furthermore ameliorated alveolar airspace enlargement as well as alveolar wall integrity and airway collagen deposition.

Evidence continues to mount supporting neutrophil apoptosis through targeted intervention as a means of treating inflammation-driven pathology. Harris and colleagues have again shown the instrumental aspects of promoting alveolar

Originally Published in Press as DOI: 10.1164/rccm.201903-0707LE on May 2, 2019