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Building the Case Toward a Definitive Clinical Trial: Saline Versus Plasma-Lyte*

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Since its first reported use during the cholera pandemic in 1831, the potential pitfalls of sodium chloride (saline) as a resuscitative fluid for hypovolemic conditions have been described in numerous animal and human studies (1). Decrease in strong ion difference (SID) leading to hyperchloremic metabolic acidosis (2) and resultant effects on renal blood flow and renal insufficiency (3) and even potential immune dysfunction (4) are well-known phenomenon linked to saline-based resuscitation. Recent clinical studies have highlighted some of these deleterious effects. In a randomized, controlled, double-blinded, crossover study in 12 healthy volunteers, Chowdhury et al (5) demonstrated sustained hyperchloremia, reduced SID, and decreased mean renal artery velocity and renal cortical tissue perfusion when normal (0.9%) saline was administered compared with a more balanced crystalloid solution. In another single-center, prospective, sequential period study, Yunos et al (6) demonstrated significantly less acute kidney injury (AKI) and use of renal replacement therapy after the institution of a chloride restrictive resuscitation strategy when compared with a more liberal saline-based strategy used in the previous 6 months. Yet, despite these well-described deleterious effects, normal saline remains the most commonly used resuscitative crystalloid solution used today (7) and has often been the "control" fluid used in preclinical and clinical studies comparing resuscitation strategies. Aside from being inexpensive and compatible with many drugs and blood products, its common use likely reflects continued questions surrounding the true clinical significance of hyperchloremia.

In this issue of *Critical Care Medicine*, Zhou et al (8) present another study further highlighting the potential clinically significant effects of saline in a rat model of sepsis. In their experiment, they randomized Sprague-Dawley rats to receive normal saline resuscitation versus Plasma-lyte (PL) solution for a 4-hour duration following an 18-hour period after cecal ligation and puncture; the time symptoms appeared mimicking events requiring medical attention in septic patients. Predictably, the normal saline–treated animals had higher chloride levels and significant decreases in pH and base excess when compared with PL-treated animals. More striking were the differences observed in biomarkers (urine cystatin C and urine neutrophil gelatinase-associated lipocalin), kidney histology, and inflammatory response (interleukin-6), documenting actual injury occurring above and beyond that observed with sepsis alone. This is further corroborated with clinically significant differences seen in the rate of AKI overall (100% vs 76%, $p < 0.05$), the rate of more severe AKI (Risk, Injury, Failure, Loss and End stage kidney disease [RIFLE]-I or F: 83% vs 28%, $p < 0.001$), and 24-hour survival (55% vs 77%, $p = 0.01$) between the saline- and PL-resuscitated rats. It should also be noted that these observations occurred under a restricted crystalloid fluid resuscitation of 25 mL/kg, suggesting even greater effects of saline under a liberal resuscitation regimen. Although the exact mechanism by which directed cellular kidney injury occurs with saline is still somewhat unclear, this study appears to suggest a direct causal relationship. However, as this study used a rat model, its translation to human septic patients awaits confirmation. Nevertheless, the results appear to be consistent with known effects of normal saline on the kidney (1, 3–6).

The most current Kidney Disease: Improving Global Outcomes (9) and Surviving Sepsis Campaign (10) guidelines published do not differentiate among various crystalloids in their fluid resuscitation recommendations in sepsis. In a large registry-based study across 57 ICUs in Australia, Bagshaw et al (11) reported the prevalence of AKI to be 42.1% (using the RIFLE criteria) among 33,375 septic patients. In the same study, the in-hospital mortality was reported to be 29.7% in the population with both sepsis and AKI. Presumably, this was prior to the introduction of a chloride restrictive resuscitation strategy as instituted at one of the participating ICUs as described earlier (6). Thus, we can assume that most of the participating centers in the study by Bagshaw et al (11), like most ICUs around the world, used a saline-based resuscitation strategy in the setting of sepsis. We cannot help but wonder how many patients in ICUs around the world currently develop AKI as a direct result of our seemingly benign intervention (in the form of saline resuscitation)

*See also p. e270.

Key Words: acute kidney injury; fluid resuscitation; normal saline; Plasma-Lyte; sepsis

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above and beyond which would otherwise be present due to sepsis alone. Given the significant clinical impact of AKI on mortality in sepsis, how many patients, in turn, die as a result of the same "benign" intervention?

In a recent comprehensive review, Myburgh and Mythen (7) suggest that a definitive randomized, controlled trial examining the safety and efficacy of normal saline compared with a balance salt solution is warranted. In light of the current study by Zhou et al (8) and accumulating evidence over the last decade, we could not agree more.

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Lung Metabolism During Ventilator-Induced Lung Injury: Stretching the Relevance of the Normally Aerated Lung*

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***See also p. e279.**

Key Words: acute respiratory distress syndrome; fluorodeoxyglucose F18; positron emission tomography; ventilator-induced lung injury

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Concerns about pulmonary complications of positive pressure ventilation (1) are at least as old as the description of the acute respiratory distress syndrome (ARDS) (2). Yet, it took about a decade until experimental findings (3) shifted the focus from air leaks and oxygen toxicity to the biological effects of large excursions of the lung parenchyma (4). The demonstration that mechanical ventilation with high peak inspiratory pressures and low positive end-expiratory pressure (PEEP) could produce edema, increased alveolocapillary permeability, leukocyte infiltration, and inflammation in normal lungs established the current understanding of ventilator-induced lung injury (VILI) (4, 5). The clinical relevance of VILI was confirmed by the demonstration of a 22% decrease in mortality of ARDS patients when lung stretch was reduced through lower tidal volumes (V_T) (6). In addition to excessive lung stretch due to large V_T, it has been recognized that VILI can also be caused by low end-expiratory lung volumes, even at low airway pressures. Mechanisms proposed to explain such injury include concentration of stresses in the heterogeneously expanding lung parenchyma (7) and propagation and rupture of liquid plugs producing injurious fluid mechanical stresses during cyclic recruitment-derecruitment of distal lung units (8, 9). Mitigation of these low-volume phenomena by optimizing lung recruitment with higher PEEP levels (10) and proning (11) has been beneficial in patients with moderate and severe ARDS. However, despite the large number of experimental and clinical studies, uncertainty persists about