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Reply to Braillon

From the Authors:

We thank Dr. Braillon for his letter and comments in response to our recent publication (1). We agree that smoking cessation should be the foremost goal for pregnant smokers, as smoking during pregnancy is the largest preventable cause of perinatal morbidity and mortality (2). We share his commitment to improving the outcomes of both pregnant smokers and their offspring.

The letter's initial concern revolves around the provision of proactive treatment for cessation, including a motivational interview and psychological support plus nicotine replacement therapy (NRT). This was a randomized trial to determine the ability of vitamin C supplementation in pregnant smokers to improve their offspring's lung function, and not a smoking cessation trial. However, smoking cessation was encouraged and participants were educated about the negative effects of smoking at randomization and at each monthly prenatal visit under the guidance of Dr. David Gonzales of the Oregon Health & Science University Smoking Cessation Center (a co-author of this letter and a co-investigator on the study). The guidelines of the American College of Obstetrics and Gynecology (2) and the U.S. Public Health Service Clinical Practice Guidelines (3) for the management of smoking during pregnancy were followed and included the provision of the "5 A's" for smoking intervention (ask, advise, assess, assist, and arrange), distribution of pregnancy-specific smoking cessation pamphlets, certification of research staff in smoking cessation, and completion of monthly smoking questionnaires with education.

We did not provide a motivational interviewing–specific intervention, and instead opted for a more standard behavioral intervention that also included health education regarding the risks of smoking during pregnancy. Recent data suggest that motivational interviewing has no incremental benefit over standard behavioral support for cessation during pregnancy (4). Furthermore, there are data that suggest that a health education intervention may be more efficacious than motivational interviewing for individuals with a lower willingness to quit smoking (5). NRT was not included in the study because it is not approved in the United States by the Food and Drug Administration, the American College of Obstetrics and Gynecology, or the U.S. Preventive Services Task Force for use in pregnancy (2, 3). Ultimately, the participants in the study received more smoking cessation counseling than would have normally been provided, and 10% of randomized smokers quit smoking during pregnancy as per monthly respiratory questionnaires and biochemical markers.

The second point in the letter is in regard to the detrimental effects of carbon monoxide on fetal development and concerns about increased compensatory uptake by randomized pregnant smokers not given NRT. Although we agree that carbon monoxide and other combustibles likely have deleterious effects, we have preclinical data demonstrating that nicotine is the primary mediator of the effects of *in utero* smoke on fetal lung development (6). Serial carbon monoxide levels in the randomized pregnant smokers decreased from a median of 11 ppm at randomization to a median of 10 ppm at midgestation and a median of 9 ppm during late gestation, mirroring the general decrease in the number of cigarettes smoked per day.

Although the primary goal should always be complete smoking cessation, progress in this area may be incremental given the large societal issues underlying smoking during pregnancy in the United States. We hope our findings regarding the potentially beneficial effects of vitamin C supplementation in pregnant smokers will help establish a simple, safe, and inexpensive way (in addition to continued smoking cessation interventions) to decrease the negative effects of *in utero* smoke on fetal lung development. Future studies may combine vitamin C, cessation counseling, and NRT products. ■

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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. ■

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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

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