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Reply to Martelli *et al.*

From the Authors:

We thank Dr. Martelli and colleagues for their interest in our study of home symptom and spirometric monitoring for individuals with cystic fibrosis (CF), termed the eICE (Early Intervention in Cystic Fibrosis Exacerbation) study (1). A study of this nature is complicated and poses many challenges that are not encountered in a typical drug trial. Blinding is certainly one aspect that we debated when designing our study, but as Dr. Martelli and colleagues noted, we did not believe it would be ethical to have patients perform home monitoring without study personnel acting on the results.

Their letter raises concerns that certain study design factors may have biased the study toward a negative result. We agree with many of the issues raised in the letter, but they are primarily related to study conduct, which in many cases is beyond the control of investigators, rather than design. For example, the authors note that the population had relatively mild disease. The study entry criteria were much broader than those used in many CF trials and included patients with FEV₁ as low as 25% predicted. Also, as we note in our paper, the study population was very similar to the general CF population in the United States.

Martelli and colleagues note that adherence with the study intervention was suboptimal. We concur, but supplemental analyses failed to demonstrate any differences in outcomes, whether or not individuals were adherent with the intervention. They also suggest that some alarms in the early-intervention arm may have been due to poor spirometry technique rather than pulmonary exacerbations. Although this is possible, patients with CF are generally very experienced in performing spirometry, and we have pilot data for individuals with CF that demonstrate good agreement between home spirometry and spirometry performed in a pulmonary function testing lab (2).

We agree with Martelli and colleagues that differential loss to follow-up was problematic. More subjects in the early-intervention arm dropped out than in the usual-care arm. This may have been due to challenges with the technology we used for the study and the burden it placed on patients. Nevertheless, we performed several different sensitivity analyses and did not see differences in outcomes if we excluded subjects who withdrew early, or if we compared outcomes at the time subjects withdrew. Contrary to the author's viewpoint, we did not use the last observation carried forward approach for missing data. Rather, our primary analysis of the

intention-to-treat population used a standard likelihood-based longitudinal approach (mixed effects model) to estimate treatment differences between groups (3). All other univariate results were based on an available-case analysis, which uses all available nonmissing data and yields unbiased estimates under the more restrictive assumption of missing completely at random.

Dr. Martelli and colleagues suggest that differential treatment, beyond that dictated by the research protocol, may have affected outcomes, and that measurement of various treatments (such as adherence with airway clearance or dietary interventions) would have been useful. This was designed to be a pragmatic study, and although care consistent with published guidelines was encouraged, clinicians had freedom to treat patients as they saw fit. It would have been extremely hard to dictate all aspects of care over a 52-week study. Also, we entered the study with the hypothesis that our intervention would differentially impact care. We believed that feedback to patients from home spirometry would encourage better adherence with therapies. To assess this possibility, we measured self-reported adherence with recommended therapies. We did not see differences in adherence with airway clearance or inhaled antibiotics between the study arms, but we did see a decline in nebulized mucolytic use in the early-intervention arm, which was statistically significant (4).

One potential reason for a negative primary outcome that we believe deserves more consideration is how exacerbations are treated. Clinicians have a fairly limited number of options for treating exacerbations, and they are applied rather generically. We propose that more attention should be given to personalizing exacerbation treatments based on biomarkers and objective responses to therapy. The ongoing STOP2 (Standardized Treatment of Pulmonary Exacerbations 2) trial (5) (ClinicalTrials.gov identifier: NCT02781610) and the Canadian study "Prednisone in CF Pulmonary Exacerbations" (ClinicalTrials.gov identifier: NCT03070522) will contribute to our knowledge of how CF pulmonary exacerbations should be treated, but we believe adding health technologies such as home spirometry may allow for further tailoring of exacerbation treatment. ■

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The Impact of Therapeutic Hypothermia on Pulmonary Hemodynamics of Meconium Aspiration Syndrome

To the Editor:

We read with interest the findings of De Luca and colleagues (1), in which the authors suggest that therapeutic hypothermia (TH) reduces respiratory requirements and length of stay for infants with meconium aspiration syndrome (MAS). Although their findings are interesting, and the basic literature cited by the authors is compelling, there are important limitations that merit further consideration. The pathophysiological contributors to hypoxia for infants with MAS are multiple, including impact on surfactant and lung inflammation, which are contributors to pulmonary parenchymal disease, as described by the authors. For many infants, however, there may also be significant implications for the pulmonary vasculature, with a high concurrent incidence of acute pulmonary hypertension (aPH) related to impaired ventilation-to-perfusion matching (2). In choosing a comparator group of infants with both hypoxic-ischemic encephalopathy (HIE) and MAS, the implications of HIE for the cardiovascular system become important. HIE confers an additional risk of aPH and is associated with transient myocardial ischemia, which may further impair pulmonary blood flow (PBF). In addition, the phenotypic spectrum of aPH in the setting of HIE, MAS, or both is quite variable, as are the effects of induced hypothermia. The subpopulation of patients with impaired right ventricular performance may be at greater risk of hypothermia-related deterioration. Specifically, the impact of elevated afterload as characterized by the stress-velocity relationship is known to have a greater impact on the right heart. Poor PBF may be associated with hypoxia and hypercarbia in the absence of pulmonary parenchymal disease. Typically, this

degree of cardiovascular dysfunction would also be associated with poor systemic blood flow, hypotension, and acidosis. Although the authors report a difference in SNAPPE-II (Score for Neonatal Acute Physiology [SNAP] and SNAP Perinatal Extension), the absence of specific data regarding concurrent cardiotropic therapies, aside from the use of nitric oxide, makes it difficult to determine the comparability of cardiovascular disease severity. The lack of echocardiography to diagnose aPH, quantify right ventricular (RV) performance, and/or characterize pulmonary and systemic blood flow represents a gap in understanding the actual physiology of MAS both among patients and between groups.

TH has several relevant effects on the cardiovascular system that may prove disadvantageous. In an animal model, a 1°C reduction in temperature produces a 1% increase in pulmonary vascular resistance (PVR) (3), suggesting infants with preexisting aPH may be at risk for decompensation. In neonates with HIE, thermoregulatory vasoconstriction related to TH has been associated with exacerbation of oxygenation failure (4). It is unclear whether the infants were matched for disease severity before or after reaching target temperature, which may introduce an additional source of bias. In addition to its impact on PVR, TH is associated with a 67% reduction in cardiac output, related predominantly to reduced heart rate (5). Little is known about the impact of low cardiac output, either due to impaired PBF or bradycardia, on brain perfusion and neurological outcomes.

Given both the potential benefits and the paucity of effective options to treat the parenchymal component of MAS, further exploration of the role of TH in this population may be warranted. Reduction in metabolic rate and therefore reduced oxygen consumption may represent an additional protective mechanism, and rewarming data may be informative. We agree with the authors' comment that a randomized trial would be exceptionally challenging; however, any clinical use of TH for MAS remains experimental and should be used with extreme caution, and close echocardiography monitoring is advised. As infants with RV dysfunction are at greater risk of afterload-mediated deterioration, the design of future studies should consider subanalysis of infants with normal versus abnormal RV function and also investigate the relationship between incremental reductions in temperature and both PVR and RV performance. Further study demonstrating the safety and efficacy of cooling in this population with a focus on delineating the physiological changes in patients with and without aPH is necessary before clinical implementation is warranted. ■

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