challenge. A phase 3 randomized controlled trial to assess efficacy of TLD would require selecting the appropriate patient population (either frequent exacerbators and/or potentially those with severe respiratory symptoms), as well as the appropriate primary outcome (perhaps frequency of exacerbations). We recommend that the Global Initiative for Chronic Obstructive Ling Disease 2019 treatment strategy be followed before classifying an individual patient as having an increased risk for exacerbations despite optimal therapy (6). This includes long-acting β agonist/long-acting muscarinic antagonist or long-acting β agonist/long-acting muscarinic antagonist/inhaled corticosteroids pharmacotherapy plus consideration of roflumilast and azithromycin based on established criteria. Acquired immunoglobulin deficiency should also be excluded as a cause for repeated chest infections before trial enrolment (7).

What's the bottom line? New effective treatments for COPD are desperately needed. Patients with moderate and severe COPD continue to suffer from unresolved symptoms of breathlessness, activity limitation, and risk for exacerbation. Pharmacologic treatments for symptomatic COPD have not significantly evolved since the introduction of long-acting anticholinergic bronchodilators in 2003. A treatment with a novel therapeutic device, such as TLD, would be most welcome if treatment could be shown to improve patient-reported outcomes such as symptoms, quality of life, and activity limitation in patients with advanced COPD. A therapeutic breakthrough for treatment of COPD would be enthusiastically welcomed by patients and healthcare professionals. ■

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References

1. Slebos D-J, Shah PL, Herth FJF, Pison C, Schumann C, Hübner R-H, *et al.*; AIRFLOW-2 Study Group. Safety and adverse events after targeted lung denervation for symptomatic moderate to severe chronic obstructive pulmonary disease (AIRFLOW): a multicenter randomized controlled clinical trial. *Am J Respir Crit Care Med* 2019;200:1477–1486.
2. Lulling J, Delwiche JP, Ledent C, Prignot J. Controlled trial of the effect of repeated administration of ipratropium bromide on ventilatory function of patients with severe chronic airways obstruction. *Br J Dis Chest* 1980;74:135–141.
3. Hummel JP, Mayse ML, Dimmer S, Johnson PJ. Physiologic and histopathologic effects of targeted lung denervation in an animal model. *J Appl Physiol (1985)* 2019;126:67–76.
4. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL, *et al.*; AIR2 Trial Study Group. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med* 2010;181:116–124.
5. Slebos D-J, Klooster K, Koegelenberg CFN, Theron J, Styen D, Valipour A, *et al*. Targeted lung denervation for moderate to severe COPD: a pilot study. *Thorax* 2015;70:411–419.
6. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2019 report). 2019 [accessed 2019 Aug 12]. Available from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf.
7. Leitao Filho FS, Ra SW, Mattman A, Schellenberg RS, Criner GJ, Woodruff PG, *et al.*; Canadian Respiratory Research Network (CRRN). Serum IgG subclass levels and risk of exacerbations and hospitalizations in patients with COPD. *Respir Res* 2018;19:30.

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Balanced Crystalloids or 0.9% Saline in Sepsis
Beyond Reasonable Doubt?

Intravenous fluid therapy with crystalloid solutions is one of the most common interventions for patients with sepsis. Both 0.9% saline and balanced crystalloids are widely used (1). However, with respect to mortality risk, the comparative effectiveness of these fluids is uncertain (2).

In this issue of the *Journal*, Brown and colleagues (pp. 1487–1495) report a *post hoc* analysis of SMART (Isotonic Solutions and Major Adverse Renal Events Trial) (3). SMART was a single-center, open-label, cluster-randomized, multiple-crossover trial (4). A total of 15,802 patients were enrolled in five ICUs at Vanderbilt University Medical Center in under 2 years. This remarkable feat was possible because of the study's novel design. Random assignment to balanced crystalloids or 0.9% saline occurred at the level of the ICU, rather than at the level of the individual patient, and each ICU "crossed over" to use each fluid multiple times over the duration of the study. All patients who were admitted to an ICU during the study were included in the study by default. All data were obtained from the electronic health record, and a waiver of consent was granted. This novel methodology represents a major breakthrough for comparative effectiveness research in critical care and has resulted in a tremendously useful dataset that can now be

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used for hypothesis-driven exploratory analyses. Here the authors report one such analysis evaluating 30-day in-hospital mortality among the 1,641 trial patients who were admitted to the medical ICU with sepsis. Their hypothesis was that balanced crystalloids would reduce in-hospital mortality at day 30.

The primary finding of the current analysis was that 217 patients (26.3%) in the balanced crystalloids group died in-hospital within 30 days compared with 255 patients (31.2%) in the saline group (adjusted odds ratio, 0.74; 95% confidence interval, 0.59–0.93; $P = 0.01$) (3). Based on the observed point estimate of treatment effect, this corresponds to a number needed to treat with balanced crystalloids instead of saline to prevent one death of just over 20.

Although the investigators' findings were robust in a number of sensitivity analyses, as they themselves have highlighted, caution is required in interpreting these findings. One methodological issue of potential concern is that the comparison between treatment groups undertaken was not truly randomized because patients were categorized as having sepsis based on International Statistical Classification of Diseases and Related Health Problems, 10th Revision codes. These codes were determined after randomization had already occurred. Although it seems unlikely that assignment to balanced crystalloids or 0.9% saline affected such coding, it might have, and in doing so, could have introduced bias. According to the findings of previous research, the mechanism of harm from 0.9% saline was hypothesized to be via hyperchloremic metabolic acidosis and renal injury (5, 6). However, the mortality effect in the current analysis was not altered by either the baseline chloride or bicarbonate concentrations, and there was no apparent effect of study treatment on serum creatinine. Although these findings led the authors to conclude that the observed mortality effect might be explained by the hemodynamic effects of the fluids used, an alternative explanation is that the findings in relation to day 30 in-hospital mortality represent a false positive. In general, the volumes of fluids that patients received were very small. In both groups, the median volume of study fluid received in the emergency department was 1,000 ml (interquartile range [IQR], 0–2,000 ml). Between ICU admission and Day 30, patients allocated to 0.9% saline received a median of 2,000 ml (IQR, 500–4,830 ml) of 0.9% saline in total, and patients allocated to balanced crystalloids received a median of 1,500 ml (IQR, 0–4,000 ml) in total. Given the small volumes of fluid administered, one can only conclude either that 0.9% saline is extraordinarily toxic to patients with sepsis or that the mortality effect observed is a result of the play of chance. In favor of the latter explanation, it is notable that the 95% confidence intervals for the odds ratio for in-hospital mortality at Day 60 cross one (i.e., encompass no effect). Moreover, as there was no statistically significant heterogeneity of treatment effect for patients with and without sepsis either in the original SMART study (4) or in the current analysis of medical ICU patients (6), the available data do not support the conclusion that patients with sepsis respond differently to other patients when given 0.9% saline as compared with balanced crystalloids.

Based on these considerations, it is clear that the findings of this *post hoc* analysis do not constitute proof beyond reasonable doubt that balanced crystalloids reduce in-hospital mortality compared with 0.9% saline in patients with sepsis. Because millions of patients around the world with sepsis receive intravenous crystalloid fluid therapy every year, such proof is desirable to inform healthcare decision-making on a global scale. Although randomized controlled trials that are being conducted in Australia and New Zealand (7) and in Brazil (8), respectively, may provide such proof, despite the caveats outlined here, the current data are already actionable by clinicians. This analysis includes data from 1,641 trial participants with sepsis, and the treatment groups appear very similar at baseline. Differences in outcomes observed could well be a result of differences in exposure to the fluids studied. Moreover, for trials that evaluate the comparative effectiveness of standard treatments, my view is that clinicians should not wait for proof beyond a reasonable doubt before they implement trial findings. Instead, the appropriate burden of proof to consider should be based on the balance of probabilities. Logically, given that in many countries both 0.9% saline and balanced crystalloids are available and widely used, clinicians should ask themselves, "On the basis of all of the available evidence (and considering the costs), is it more probable that 0.9% saline or a balanced crystalloid is the best choice for this patient?"

On the balance of probabilities, the data presented by Brown and colleagues (3) suggest that balanced crystalloids are likely to be the best choice. Although these data do not represent proof beyond a reasonable doubt, they add to a growing body of evidence suggesting that balanced crystalloid fluids are preferred to 0.9% saline for intravenous fluid therapy (4, 9). Although the results of ongoing trials are awaited, clinicians can reasonably use balanced crystalloids in preference to 0.9% saline. Doing so might well reduce the risk for death in critically ill patients with sepsis and potentially in other patients as well. ■

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References

1. Hammond NE, Taylor C, Finfer S, Machado FR, An Y, Billot L, *et al*.; Fluid-TRIPS and Fluidos Investigators; George Institute for Global Health, The ANZICS Clinical Trials Group, BRICNet, and the REVA research Network. Patterns of intravenous fluid resuscitation use in adult intensive care patients between 2007 and 2014: an international cross-sectional study. *PLoS One* 2017;12:e0176292.
2. Myburgh J. Patient-centered outcomes and resuscitation fluids. *N Engl J Med* 2018;378:862–863.
3. Brown RM, Wang L, Coston TD, Krishnan NI, Casey JD, Wanderer JP, *et al*.; SMART Investigators and the Pragmatic Critical Care Research Group. Balanced crystalloids versus saline in sepsis: a secondary analysis of the SMART clinical trial. *Am J Respir Crit Care Med* 2019;200:1487–1495.
4. 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.
5. Yunos NM, Kim IB, Bellomo R, Bailey M, Ho L, Story D, *et al*. The biochemical effects of restricting chloride-rich fluids in intensive care. *Crit Care Med* 2011;39:2419–2424.
6. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid

administration strategy and kidney injury in critically ill adults. *JAMA* 2012;308:1566–1572.
7. 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.
8. 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.
9. Self WH, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, *et al*.; SALT-ED Investigators. Balanced crystalloids versus saline in noncritically ill adults. *N Engl J Med* 2018;378:819–828.

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Identifying Biomarkers in Pediatric Rare Lung Disease
chILD Grows Up

Children's interstitial and diffuse lung disease (chILD) has been recognized as distinct from adult interstitial lung diseases for nearly 2 decades after the first descriptions of disorders of surfactant metabolism and neuroendocrine cell hyperplasia of infancy (NEHI) (1, 2). In that interval, advances in clinical phenotyping, histopathology, genetic testing, and imaging have improved diagnostic capabilities and led to the discovery of novel chILD disorders (3). However, although blood- or airway-derived biomarkers can be informative in adult ILD (4, 5), similar biomarkers do not exist in chILD, and lung biopsy is often still required to make a definitive diagnosis. In recognition of these limitations, a recent National Heart, Lung, and Blood Institute workshop to advance chILD identified a "lack of validated biomarkers or outcome measures suitable for use in infants and young children" as a key gap (6). In this issue of the *Journal*, Deterding and colleagues (pp. 1496–1504) help to address this gap through the use of aptamer-based proteomics to identify proteins and related pathways in BAL fluid that distinguish two of the most common chILD disorders (NEHI and disorders of surfactant metabolism) from each other and from control individuals without chILD (7). Although this was a single-center study on a relatively small population, these findings represent a significant step forward in the study of these rare lung diseases.

The identification of unique protein signatures for both NEHI and surfactant protein deficiency could have substantial diagnostic value. Both disorders typically present similarly, with tachypnea, crackles, and hypoxemia starting before 1 year of age (8). Although findings on chest computed tomography (CT) are often diagnostic, nearly a quarter of patients with biopsy-proven NEHI have atypical findings on chest CT (9), and there are reported cases of a NEHI pattern on chest CT that were ultimately found to be caused by surfactant dysfunction (10). Genetic testing can also be informative, although approximately 25% of patients who have lung biopsy consistent with surfactant dysfunction have negative genetic studies (8). Reliance on genetic studies can also delay diagnosis and treatment, as current testing often requires up to 4 weeks for completion. This delay has meaningful treatment implications, as surfactant dysfunction is typically treated with multiple medications such as hydroxychloroquine, azithromycin, and corticosteroids (1), whereas the therapy for NEHI is supportive care. Thus, a validated BAL proteomic signature could improve diagnostic accuracy, allow more rapid intervention in critically ill children, and reduce the need for lung biopsy in those patients in whom radiologic and genetic studies are indeterminate.

The protein signatures identified in this study also offer exciting potential insights into disease mechanisms and possible new therapeutic targets. This is particularly important for NEHI, which, although relatively common (by chILD standards), is poorly understood from a mechanistic standpoint. Lung biopsies performed on patients with NEHI show increased pulmonary neuroendocrine cells, which function as innervated sensory cells within the lungs (11). However, it is unclear how abnormalities within this cell type lead to hypoxemia, as the lung parenchyma in patients with NEHI is almost normal on biopsy (2). The cell signaling and metabolic pathways identified in this study offer new pathways to investigate and may provide mechanistic insight. Interestingly, the proteomic signatures suggested two distinct endotypes in NEHI. This may indicate that NEHI represents two separate disorders, although both had similar clinical outcomes. In surfactant protein deficiency, the identification of pathways involved in fibrosis offers hope that work in adult inflammatory-fibrosis lung models may be relevant to these rare disorders. This is particularly important, as many patients with surfactant dysfunction, particularly those with pathologic variants in *ABCA3* (ATP-binding cassette subfamily A member 3), have significant mortality (12), and therefore medications that slow progression are needed. Also, most patients with surfactant dysfunction that present in childhood have progressive disease, so antifibrotic medications developed for adult ILD may be beneficial.

Although the findings of this study represent an exciting advance in chILD, the conclusions must be viewed with some caution, as the study was small (understandable, given the low prevalence of chILD) and lacked an independent validation cohort. Although the authors used appropriate statistical methods to minimize bias, the relationships between the identified pathways and disease pathophysiology will remain uncertain until validated through independent study. Furthermore, many of the markers elevated in the surfactant dysfunction group have also been associated with neutrophilic airway inflammation in other diseases (13), which was elevated in this cohort. Further investigation will be needed to identify which are specific to surfactant dysfunction.

Overall, this study by Deterding and colleagues offers an exciting first step toward developing biomarker-based evaluation of chILD. Although bronchoscopy and BAL is not without risk, it offers a significant benefit over lung biopsy, particularly in critically ill children. With appropriate validation, this study could represent a critical first step toward developing improved biomarker-based diagnostic and treatment strategies for pediatric rare lung disease. ■

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