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Check for updates

🔓 New Imaging Tools Allow Bronchopulmonary Dysplasia to Enter the Age of Precision Medicine

Bronchopulmonary dysplasia (BPD) is the most common complication of prematurity, and best estimates suggest it affects roughly 20,000–30,000 infants annually in the United States alone (1, 2). According to the "classical" National Institute of Child Health and Human Development definition (3), about 13,000 infants/yr in the United States are affected by severe BPD requiring positive pressure support at 36 weeks corrected gestational age, with an estimated mortality of 1,000–2,400 deaths annually (4, 5). This is a substantially higher annual incidence than all of childhood cancer with similar or worse survival. Unfortunately, despite decades of preventative efforts, rates of BPD have not improved and indeed seem to be increasing steadily as our abilities to save extremely preterm infants improve. The International Neonatal
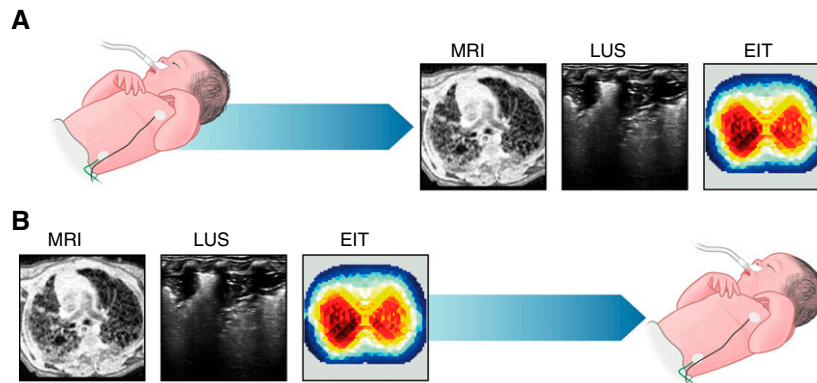
Figure 1. New imaging tools that may be useful to provide precision medicine for neonates with chronic pulmonary insufficiency of prematurity evolving toward different types of bronchopulmonary dysplasia. Quiet-breathing magnetic resonance imaging, semiquantitative lung ultrasound, and electrical impedance tomography all have the potential to give useful information of pulmonary physiopathology and carry different advantages and disadvantages. (*A*) So far, in neonates with evolving bronchopulmonary dysplasia, they have been mainly used to give a snapshot of the patient's situation. (*B*) Nonetheless, they might be used much earlier to direct patients toward a more personalized therapeutic approach or tailored ventilatory strategy. EIT = electrical impedance tomography; LUS = lung ultrasound; MRI = magnetic resonance imaging.

Consortium started a discussion between clinicians, regulatory bodies, and industries to identify the main issues to be addressed in this area (6). Some of them are represented by the need for new therapeutic strategies and recognize that preterm infants may be affected by chronic pulmonary insufficiency of prematurity on a continuum over time, starting well before the 36-week time point. This clearly entails a need for a more personalized approach, including early selection of high-risk patients and long-term outcomes.

We believe that the lack of this approach led to markedly variable differences in clinical care and outcomes that are difficult to compare across centers. One recent study of infants with severe BPD cared for at 21 Children's Hospital Neonatal Database centers, for instance, demonstrated that the rate of the combined outcome of tracheostomy placement and/or death occurred in between 2% and 45% of patients, depending on center, despite no measurable differences in patient characteristics (4). Therefore, we are heartened to see the study by Gouwens and colleagues (pp. 1024–1031) in this issue of the *Journal*, examining regional V_T measured by magnetic resonance imaging (MRI) in infants with severe BPD (7).

The authors investigated the utility of MRI in 17 nonsedated, quiet-breathing infants with severe BPD compared with 3 term infants without lung disease at end inspiration and end expiration to determine the relative contribution of "cystic" versus "normal" lung tissue to V_T. Interestingly, they found that the cystic areas contributed significantly more to V_T than healthy areas when normalized for total lung volume. A second notable finding was that this contribution to V_T was not uniform, and some cystic areas of the lung had negative V_T, suggesting that they actually expanded during exhalation. The authors investigated potential correlations between a variety of ventilatory parameters and did not find robust associations between most of these and cystic V_T.

Though the number of patients involved in this study is small (particularly for the control group), we must commend the authors on the infrastructure they have developed to provide advanced diagnostics in this fragile patient population. Clearly, the ability to obtain accurate and reliable quiet-breathing MRI in intubated neonates gated for end inspiration and expiration has the potential to provide precision medicine. It would be very helpful to the clinician, for instance, to be able to identify patients with a high burden of cystic lung tissue. These patients could then be further classified into those with positive versus negative V_T, which likely would allow more effective ventilator manipulations. This represents a much more detailed definition than those based on pure clinical appearance, such as need for oxygen and respiratory support.

Though we are grateful for the data within this manuscript, we must note some substantial limitations. First, and most obviously, this is a very small study with a limited number of patients. Second, the approach to ventilation within this group was not standardized, which limits the applicability of the comparisons between the ventilator settings and V_T. We assume that all of these settings were chosen by experienced neonatologists with expertise in ventilatory care to achieve overall stability; however, a more comprehensive physiological monitoring (including, for instance, saturation, transcutaneous blood gas, and end-tidal CO_2 measurements) and the titration on ventilatory settings based on MRI results would have allowed a deeper understanding of severe BPD physiopathology. Third, none of the patients were receiving high-frequency oscillatory ventilation, which is regularly used in several neonatal ICUs (8), and, finally, easy access to on-unit MRI facilities is not common. Thus, we caution that this approach may not be easily generalizable.

Perhaps the most important contribution of this study, however, is that it helps us envision a future in which we can begin to apply precision medicine to this growing pediatric patient population. We can imagine a time when infants with serious lung disease are no longer classified simply as having "severe BPD," but are further and earlier subclassified into one or more of the following categories based on appearance on MRI, semiquantitative lung ultrasound (9), electrical impedance tomography (10), or other diagnostic tools. Patients could be divided between those with substantial cystic component, with or without positive V_T; those with and without pulmonary hypertension, with or without satisfactory pulmonary vascular bed development; those with or without high airway resistances and more or less good lung aeration; and so forth. Each subgroup may clearly correspond to a

"different" BPD from a pathobiological point of view, as some of these patients may have been invasively ventilated, whereas some others may have experienced an impaired lung development without the ventilation-induced inflammatory trigger (11). Each of these subclassifications can then be managed more precisely to match their physiology, and data on outcomes can be more accurately portrayed and compared. In the commented study, MRI was performed when severe BPD was already established; however, the aforementioned diagnostic tools might be used much earlier in infants with chronic pulmonary insufficiency of prematurity to direct them toward a particular therapeutic approach or a more tailored ventilation rather than just give snapshots of the patients' situation (Figure 1). This would match with the main issues identified by the International Neonatal Consortium statement (6).

We believe that innovative diagnostic tools and a new mindset are critically necessary to provide precision medicine to our most vulnerable patients and improve our ability to care for and learn from them. ∎

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∂ Bubble Trouble in COVID-19

In training, we learn that there are five causes of hypoxemia: V̇/Q̇ mismatch, right-to-left shunt, diffusion impairment, hypoventilation, and low F_{IO_2}. Right-to-left shunts may be intracardiac or intrapulmonary and are characterized by a reduced or absent response to supplemental oxygen. Frontline healthcare workers witness this shunt physiology on a regular basis while caring for hospitalized patients with coronavirus disease (COVID-19). Gattinoni and colleagues initially described this unique phenomenon of large shunt fractions and severe hypoxemia in patients with COVID-19 as compared with "typical" acute respiratory distress syndrome (ARDS) (1). Hypoxemia in COVID-19 can also be disproportionate to the degree of symptoms and impairment in lung mechanics. In a study by Guan and colleagues, only 18.7% of 1,099 hospitalized patients with COVID-19 reported dyspnea despite the majority having abnormal chest imaging (2). Although both intrapulmonary and