

In their conclusions, the authors state that early initiation of noninvasive ventilation (NIV) may have impacted patients' quality of life and survival, particularly in the rapid progressor group. This is debatable, as studies in other neuromuscular disorders (such as muscular dystrophy) have shown that "preventive" initiation of NIV was not successful in slowing or preventing progression of disease (10). In fact, patients with close to normal VC often resist the use of NIV until their VCs have decreased to low levels (<30% predicted or 1 L) or there is associated bulbar dysfunction.

The authors are to be commended for performing a thoughtful and sophisticated analysis of a feature of ALS that has been described in general terms for the last half century, namely, the variability in functional decline. Clearly, the next step would be to conduct genetic analyses in a large population of patients in an attempt to identify plasma biomarkers that predict the onset and timing of respiratory insufficiency long before patients are confronted with decisions regarding goals of care. Better yet, identification of such genetic biomarkers could lead to targeted, patient-centered therapies that would halt and perhaps even reverse the (currently) inexorable decline in respiratory function. ■

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Heart of the Matter? Early Ventricular Dysfunction in Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) represents one of the most challenging causes of respiratory failure managed in neonatal critical care. These challenges arise from the pathophysiological triad of pulmonary hypoplasia, pulmonary vascular disease, and left ventricular (LV) dysfunction associated with herniated abdominal contents, impaired fetal lung growth, and perturbations in umbilical venous return to the developing left ventricle (1). The management of CDH has evolved from a primarily surgical problem to one of

integrated prenatal, surgical, respiratory, and cardiac care, principally focusing on lung-protective approaches to support the hypoplastic lungs and reducing the burden of pulmonary hypertension (2–4). Unfortunately, mortality remains persistently high (25–30%) (5), and, in contrast to what has been observed with other causes of severe neonatal respiratory failure, the rates of extracorporeal membrane oxygenation use have not decreased with incremental improvements in ventilatory care (Figure 1). LV hypoplasia has long been recognized as a fetal manifestation of CDH (6), and resultant cardiac dysfunction has been postulated as an important and underappreciated determinant of outcome (1, 7).

Early cardiac function in CDH is poorly understood, and investigations have been limited to small observational studies (8, 9). The study presented in this issue of the *Journal* by Patel and colleagues (pp. 1522–1530) is thus timely and provides valuable insight into CDH pathophysiology (10). They report echocardiographic categorizations of LV and right ventricular function performed in the first 48 hours after delivery in 1,173 infants enrolled in the CDH Study Group Registry (59 centers) from 2015 to 2018, a period encompassing current lung-protective

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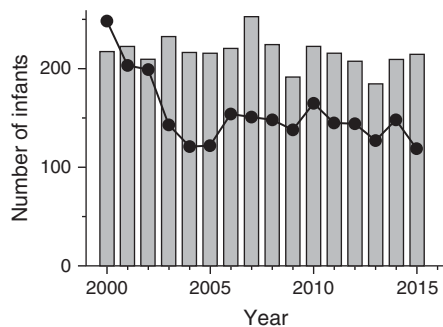


Figure 1. Use of extracorporeal membrane oxygenation for congenital diaphragmatic hernia (gray bars) and meconium aspiration syndrome (solid circles) over the 15-year period after the U.S. Food and Drug Administration approved inhaled nitric oxide for persistent pulmonary hypertension in newborns (16). The marked reduction in the use of extracorporeal membrane oxygenation for meconium aspiration syndrome contrasts with little change in its use for congenital diaphragmatic hernia over this period.

ventilatory strategies and a multimodal pharmacological approach to pulmonary hypertension. Some form of ventricular dysfunction was identified on echocardiography in 39% of the infants (15% with isolated right ventricular dysfunction, 5% with LV dysfunction, and 19% with biventricular dysfunction). Both LV and biventricular dysfunction were independently associated with mortality and extracorporeal membrane oxygenation use, with biventricular dysfunction conferring the highest risk of mortality (49%). Importantly, the mortality risks associated with LV/biventricular dysfunction were comparable to established prognosticating factors, specifically the diaphragmatic defect size, presence of liver in the chest, and need for a surgical patch (11). This study provides the first large population signal to support the complex but critical interplay between cardiac function and outcomes for infants born with CDH.

The most important finding of this study is the impact of early LV dysfunction on CDH outcomes. Pulmonary hypertension is established as a hallmark of CDH, and resultant right ventricular systolic and diastolic dysfunction well described (1). The finding that biventricular dysfunction is common in CDH (48% of all infants with any cardiac dysfunction) is thus not surprising. Patel and colleagues show that the left ventricle may also be the primary cause of cardiac dysfunction, whether from hypoplasia and a reduced ability to manage the acute increase in afterload after birth, or by directly elevating pulmonary venous pressure and pulmonary vascular resistance. An understanding of the interplay between right ventricular and LV function will allow the development of targeted therapies. Pulmonary vasodilatation to reduce right-heart afterload is often advocated (3), but in the presence of LV dysfunction this may worsen LV diastolic function and increase systemic hypoxemia and acidosis. In such situations, inotropic and lusitropic support (for example, with the use of milrinone) may be more appropriate; however, there are insufficient data to warrant routine use (12, 13).

The authors provide a strong argument for routine, early assessments of cardiac function. Their study provides the first step toward meaningful translation rather than the definitive answer. In their study, echocardiography was performed in the first 48 hours of

life, and only 37.5% of the infants had a second assessment within 14 days, so conclusions regarding balancing LV dysfunction and pulmonary hypertension are limited to the period of immediate preoperative CDH stabilization. Furthermore, echocardiography was not performed on 29% of eligible infants in the registry, highlighting the fact that it is difficult to assess cardiac function. It is also difficult to define “function.” In the study by Patel and colleagues, ventricular function was categorized semiquantitatively by experienced operators. Measures of diastolic and systolic right-sided function were used, but specific parameters for LV dysfunction were not recorded. Although quantitative methods of LV function have been suggested (1, 14), validation of these methods is lacking, and there is a pressing need for international agreement on parameters to define LV function.

In this study, large diaphragmatic defects were common in infants with ventricular dysfunction; however, it is more interesting that early ventricular dysfunction was also present in at least 25% of infants with smaller diaphragmatic defects. Clinicians are often confronted with an infant with relatively favorable prenatal measures of lung growth but a severe postnatal disease course. This highlights the limitation of prognosticating outcomes purely on the basis of antenatal markers (15).

The management of CDH is complicated by structural and functional changes in the heart, pulmonary vasculature, and lung; consequently, it is challenging to determine the optimal management strategies. The study by Patel and colleagues reinforces the need for vigilant management of cardiac function in early life and recognition of the important cardiopulmonary interactions that characterize CDH if outcomes are to improve. ■

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⊗ The Role of Xpert MTB/RIF Ultra in Diagnosing Pulmonary Tuberculosis in Children

Bacteriological confirmation of pulmonary tuberculosis in young children (<5 yr) can be challenging because of the difficulty of obtaining suitable specimens and the paucibacillary nature of the disease. Mycobacterial culture remains the reference standard for confirming tuberculosis in children. However, cultures are positive in only a minority of cases, with highly variable yields depending on the specific disease phenotype (1). Molecular epidemiology studies raised awareness that drug-resistant strains of *Mycobacterium tuberculosis* are readily transmitted within affected communities, as well as to children, with estimates that the vast majority of drug-resistant tuberculosis cases result from person-to-person transmission rather than acquisition (2). This demonstrates the dire need for not only improved bacteriological confirmation but also routine drug susceptibility testing in young children with tuberculosis.

In this issue of the *Journal*, Zar and colleagues (pp. 1531–1538) present data on the value of the new Xpert MTB/RIF Ultra (Ultra) in hospitalized children suspected of having pulmonary tuberculosis (3). Ultra on one induced sputum (IS) and one or two nasopharyngeal aspirates (NPAs) were compared with mycobacterial culture from a single IS specimen. Compared with

culture, Ultra yield from a single IS specimen (74.3%) was much better than from two NPA specimens (54.2%), but multiple specimens provided the best sensitivity: 87% for single IS plus two NPAs. The authors stress the fact that Ultra yield may have been compromised by storage of the original specimens before testing, but DNA is robust, and the expected detrimental effect of freezing at -80°C is minimal. Even if there were some detrimental effects, the results presented represent an underestimation, rather than an overestimation, of the true diagnostic performance using fresh specimens.

These findings represent an exciting advance for tuberculosis diagnostics in children, although two major caveats limit translation. The first is the fact that tuberculosis confirmation was achieved in only a small percentage of children admitted to hospital with possible tuberculosis. Among children treated for tuberculosis (confirmed or unconfirmed tuberculosis), only 40 (27.8%) of 144 tested positive on culture, which demonstrates its suboptimal yield and limitations as a reference standard. “Unconfirmed tuberculosis” is a heterogeneous group in whom the probability of tuberculosis disease is uncertain; however, previous attempts to identify a subgroup with highly “probable tuberculosis” on clinical grounds have been abandoned, and clinical relevance is indicated by the fact that these children received tuberculosis treatment (4).

Ultra was positive in a few of these children with “unconfirmed tuberculosis,” which introduces the dilemma of how best to assess the diagnostic performance of a test if the accepted reference standard has poor sensitivity. Given the excellent specificity of Ultra, it would be highly informative to consider Ultra’s diagnostic

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