measurements, as well as acceptable measurements in more than 1,000 children aged 5–12 years. A comparison of children living in a range of locations in India with those of Indian heritage who were living in London in the United Kingdom revealed significantly higher FEV₁ and FVC (per z-scores relative to reference values derived from Indian populations) in the London residents. However, when the India-resident children were subgrouped into urban, semiurban, and rural areas of residence, it was discovered that the urban-residing children from India had spirometric measures that were indistinguishable from those measured in the London contingent. In contrast, the rural-residing Indian children had FEV₁ and FVC measures that were 0.9 z-scores lower, and the semiurban Indian group had measures 0.5 z-scores lower, than the India urban and London groups. Assuming that the genetically determined physical characteristics relating predicted lung volumes to height, age, and sex are relatively constant for the general population of India, these results suggest strongly that differences in living conditions among these subpopulations have a significant effect on lung development or lung function. This is useful information, as it identifies a population that could hold clues to mechanisms by which environmental conditions may affect lung development in utero or in early life and that may benefit from interventions to improve lung health.

The authors also report that the z-FEV₁/FVC was not significantly different among the subpopulations, suggesting a restrictive (reduced lung size), rather than obstructive, pattern in the nonurban residents. This needs to be confirmed with a measure of total lung capacity (TLC), which would not be possible for population screening but could be attempted in a representative sample of participants. In persons with normal respiratory systems, the primary determinant of FEV₁ is FVC, the primary determinant of FVC is TLC, and the primary determinant of TLC is thoracic volume, which relates to height and chest dimensions. Thus, the surrogate measures (height, age, sex, ethnic heritage) that are used to compute reference ranges for spirometry mostly function as an estimate of TLC. If the actual TLC is significantly different from the expected TLC, this will affect the z-FEV₁ and z-FVC but will not affect the z-FEV₁/FVC unless the TLC is altered by a process that also affects airway integrity or lung elastic recoil. The alternative scenario that may cause a proportional decrease of FEV₁ and FVC is premature airway closure during forced expiration (2), although this is unlikely in the absence of chronic respiratory symptoms.

The authors employed a multivariate model that included family affluence score, exposure to household tobacco smoke,

exposure to indoor biomass smoke, z-body weight, and z-body mass index, but these variables were nearly qualitatively associated with place of residence, so none emerged as strong correlates with the spirometric measures. Specific data regarding maternal tobacco use during pregnancy, premature births, birth weight, and detailed socioeconomic indicators were not available, and thus these factors, which have been associated with postnatal lung function (3–5), could not be assessed. Ultimately, a prospective interventional study or a careful case control study, analogous to the prenatal vitamin A trial in an undernourished Nepali population (6), will be needed to determine the potentially correctable factors that could improve lung development in this rural India population. ■

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Pulmonary Hypertension in Premature Infants Sharpening the Tools of Detection

Bronchopulmonary dysplasia (BPD), the most common chronic lung disease of infancy, is characterized by alveolar simplification and developmental arrest of the lungs. BPD is

a major complication of prematurity that affects one-third of extremely low-birth-weight infants, or 10,000 babies annually in the United States, and results in substantial long-term pulmonary and neurodevelopmental morbidity (1, 2). Improved survival of extremely premature babies has led to increased recognition of pulmonary hypertension (PH) and right ventricular failure in 12–25% of infants with BPD (3–8).

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Risk factors for BPD-associated PH include low birth weight, intrauterine growth restriction, oligohydramnios, and duration of mechanical ventilation with oxygen (5, 8). Once infants develop PH, little is known about how to best treat them. Poor outcomes are common, including up to 50% mortality by 2 years of life, increased risk for tracheostomy, and a 4.6-fold risk for death versus matched BPD infants without PH (4, 6, 8, 9). For those who do survive, the long-term consequences remain to be seen, as the oldest survivors are just reaching young adulthood. Adolescent survivors of BPD have been described to have persistent airway obstruction and reductions in airflow (10), but there are scant long-term data on infants discharged with PH in addition to BPD. It seems likely that the developmental arrest of the lungs and the pulmonary vasculature that accompanies BPD and PH will be accompanied by further cardiopulmonary morbidity as infants grow into childhood and adolescence.

The underlying pathophysiology of BPD-associated PH is complex and poorly understood. After birth, pulmonary arterial pressure decreases more slowly in preterm relative to term infants, especially in the presence of respiratory failure (11). Alterations of NO-cyclic guanosine monophosphate signaling disrupt lung and pulmonary vascular development in animal models of prematurity and lung injury (12–14), but these findings have not been successfully translated into therapeutic advances. Vascular agents such as iNO and sildenafil may acutely improve pulmonary artery pressure, but their long-term efficacy remains uncertain and poorly studied (15–17). A major barrier in conducting larger scale studies of promising therapies has been the identification of appropriate patients for inclusion. Moreover, until recently, there has been little evidence to guide the practitioner in when and how to perform PH screening in preterm babies. Part of the reason for this knowledge gap is that echocardiography is technically challenging in the face of patient agitation or concurrent illness and may not correlate well with PH severity, as measured by cardiac catheterization (18). In contrast, cardiac catheterization carries increased risk for procedure-related complications in vulnerable small infants. Serum biomarkers such as B-type natriuretic peptide or asymmetric dimethylarginine have not yet been well validated as predictors of disease severity in infants with BPD-associated PH (19–21).

In this issue of the *Journal*, the report by Mourani and colleagues (pp. 87–95) is the first to prospectively examine rates of both early (at 7 days) and late (at 36-week corrected gestational age) PH in a large population of premature infants (22). This study provides a comprehensive look at how the choice of echo parameters affects the incidence of PH. Using the “strictest” criteria of pulmonary artery pressure, as estimated by the tricuspid valve regurgitant jet, the authors found rates of early PH comparable to those found in other single-center prospective studies (7, 23). However, rates were considerably higher when the diagnostic criteria were expanded to include any of the following: right ventricle systolic pressure higher than 40 mm Hg, right ventricle systolic pressure/systemic systolic blood pressure ratio higher than 0.5, any cardiac shunt with bidirectional or right-to-left shunting, or any degree of ventricular wall septal flattening. In particular, findings of septal wall flattening and RV dilation

occurred in up to 40% of preterm babies at 7 days of age and were most predictive of BPD and late PH. These used to be considered subtle findings of unclear significance, but they should now be viewed as important markers of PH in preterm babies.

Similar to previous reports, Mourani and colleagues found that early PH did not universally predict BPD and later PH (7). Thus, later screening remains necessary to identify those infants needing long-term follow-up after discharge. Mourani and colleagues also noted an association between lower birth-weight Z-scores and risk for PH, reinforcing other reports suggesting that infants with intrauterine growth restriction are a high-risk population of infants for future screening protocols (8). Perhaps the most surprising finding was that 10% of infants with no or mild BPD had detectable pulmonary hypertension at 36-week corrected gestational age. This novel observation suggests that a primary vascular injury may occur in some infants, independent of the lung disease. Whether this PH is clinically significant and portends the same degree of long-term morbidity and mortality as in infants with more severe associated lung disease will require further study.

Adding these prospective data to other recent reports, we recommend using Mourani and colleagues’ screening algorithm to assess for the presence of PH in all premature infants with moderate and severe BPD at 36-week corrected gestational age. The use of earlier testing, and of screening premature infants in the no and mild BPD categories, should be prioritized as an area of future investigation. Future studies should also build on Mourani and colleagues’ findings by using these screening tools to select high-risk populations for prevention and therapeutic intervention trials. We hope that Mourani and colleagues’ study will help unite neonatology, pulmonary, and critical care physicians in identifying the best strategies to prevent and reverse this devastating disease. ■

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Therapy for *Mycobacterium avium* Complex Lung Disease It Ain't Perfect, but It's Progress

The evidence suggests that nontuberculous mycobacterial (NTM) lung disease burden in the United States is increasing (1, 2). This has focused attention on the limited therapeutic options. Treatment recommendations in the most recent American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA) guideline arise primarily from single-center studies, small case series, and expert opinion (3). For *Mycobacterium avium* complex (MAC) lung disease, the guidelines recommend a multidrug macrolide-based regimen including at least 12 months of treatment after sputum conversion to culture negative. It is suggested that three times weekly (TIW) therapy is appropriate for patients with disease characterized by nodules and bronchiectasis (NB disease) (3).

In this issue of the *Journal*, Jeong and colleagues (pp. 96–103) report the efficacy of macrolide-based MAC therapy for treatment-naïve NB MAC lung disease (4). In this observational study of mixed retrospective and

prospective design, 99 patients received daily MAC therapy over a 5-year period, and 118 patients received it over a subsequent 2-year period. The pharmacotherapeutic regimen consisted of clarithromycin or azithromycin, rifampin and ethambutol with the addition of intravenous streptomycin for the majority of patients on daily therapy. There were no differences in symptom or radiographic improvement, sputum culture conversion rate, time to sputum culture conversion, or microbiologic recurrence between the daily and TIW treatment groups. Antibiotic treatment duration was longer in the daily therapy group with more frequent modification of the initial antimicrobials. Due to lack of long-term follow-up, relapse and reinfection rates were not addressed.

The favorable response to both daily and intermittent therapy is consistent with another recent study evaluating TIW therapy for NB MAC lung disease (5). These studies support the ATS/IDSA