The Clinical Evaluation of Severe Bronchopulmonary Dysplasia

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Practice Gaps

Infants with severe bronchopulmonary dysplasia have heterogenous clinical presentations, with varying degrees of airway, lung parenchyma, and pulmonary vascular disease, as well as multisystem comorbidities. These infants benefit from a comprehensive, multidisciplinary evaluation and individualized treatment with a chronic care model that prioritizes long-term respiratory and neurodevelopmental goals.

Abstract

Bronchopulmonary dysplasia is a common disease of prematurity that presents along a wide spectrum of disease severity. Infants with high severity require prolonged hospitalizations and benefit from multidisciplinary care. We describe our approach to the evaluation of infants with severe bronchopulmonary dysplasia. Important considerations include the phenotypic heterogeneity in clinical presentation that necessitates individualized care, the common presence of comorbidities and importance of a comprehensive multisystem evaluation, and the value of applying a chronic care model that prioritizes long-term respiratory and neurodevelopmental goals. Key features of the history, physical examination, and diagnostic studies are discussed with these considerations in mind.

Objectives After completing this article, readers should be able to:

1. Perform a comprehensive evaluation of infants with severe bronchopulmonary dysplasia.
2. Identify comorbid conditions that can influence the evolution of lung disease in severe bronchopulmonary dysplasia.
3. Assess if an infant with severe bronchopulmonary dysplasia is receiving adequate invasive or noninvasive respiratory support.

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ABBREVIATIONS

BPD	bronchopulmonary dysplasia
CPAP	continuous positive airway pressure
CT	computed tomography
CXR	chest radiography
GA	gestational age
MRI	magnetic resonance imaging
PEEP	positive end-expiratory pressures
PEEPi	intrinsic positive end-expiratory pressures
PFT	pulmonary function testing
PH	pulmonary hypertension
PMA	postmenstrual age
sBPD	severe bronchopulmonary dysplasia
UTE	ultrashort echo-time

INTRODUCTION

The objective of this review is to provide a framework to guide the clinical evaluation of infants with established severe bronchopulmonary dysplasia (sBPD) during the postnatal hospitalization. Several key considerations will be highlighted throughout the review. First, infants with sBPD are a heterogeneous group of patients. Impaired pulmonary gas exchange in sBPD can have various causes, and individual patients can have distinct clinical phenotypes. Second, although infants are cared for in an acute care setting, sBPD is a chronic disease with long-term health implications. A chronic care model that considers long-term goals is most appropriate. Third, while the term "bronchopulmonary" centers this disease on the lungs, sBPD is a multisystem disease and common comorbidities of preterm birth directly and indirectly affecting lung health are often seen. Unfortunately, there is a paucity of data in the published literature to guide an evidence-based approach to the evaluation of infants with sBPD. What we describe primarily reflects the clinical experience of the Newborn and Infant Chronic Lung Disease Program at Children's Hospital of Philadelphia (CHOP), an interdisciplinary program dedicated to the care of infants with sBPD.

The Wide Severity Spectrum of BPD

A key shortcoming of early definitions of BPD was the dichotomous classification of this disease as either absent or present, failing to acknowledge the wide spectrum of disease severity. (1)(2) To address this, a National Institutes of Health (NIH) workshop defined BPD as "severe" in infants born before 32 weeks' gestational age (GA) who require supplemental oxygen for 28 or more cumulative days, and either more than 30% supplemental oxygen and/or positive pressure support at 36 weeks' postmenstrual age (PMA). (3) The predictive validity of the classification was supported by Ehrenkranz and colleagues, who showed that infants with sBPD had higher rates of pulmonary and neurodevelopmental morbidities at 18 to 22 months' corrected age than those with no, mild, or moderate BPD. (4) Although preferable to dichotomous definitions, the NIH classification of "severe BPD" still includes a wide segment of the severity spectrum and fails to differentiate between infants with meaningful differences in respiratory disease severity. For example, a preterm infant receiving 30% oxygen via nasal cannula and an infant struggling to maintain adequate gas exchange despite 100% oxygen on mechanical ventilation are both classified as severe. Writing on behalf of the BPD Collaborative, Abman and colleagues highlighted this shortcoming, and proposed subdividing sBPD into type I and II, with the latter identifying ongoing ventilator dependence at 36 weeks' PMA. (5) Recently, Jensen and colleagues defined BPD through a data-driven approach to identify the classification scheme with the strongest predictive validity for death or serious respiratory morbidity at 18 to 26 months' corrected age. (6) On the basis of these results, infants receiving high-flow nasal cannula (>2 L/minute) or noninvasive positive pressure at 36 weeks' PMA have grade 2 BPD, whereas infants receiving invasive mechanical ventilation at 36 weeks' PMA have grade 3 BPD, irrespective of the degree of oxygen supplementation. The guidance in this review uses the term sBPD to describe infants with grade 2 and 3 BPD. (6) As shown in Fig 1, it is predominantly these infants who remain hospitalized beyond 50 weeks' PMA and require the kind of comprehensive evaluation we describe.

Phenotypes of sBPD

A key element of our evaluation is identifying disease phenotypes. The term "phenotype" is used in clinical medicine to describe observable characteristics that vary among individuals with the same disease. The goal is to classify patients into subcategories that have different prognoses or treatment responses, facilitating individualized care. Phenotypes are particularly relevant to BPD because this disease is defined by the presence of therapies (respiratory support and/or supplemental oxygen) used to treat a wide range of pathophysiologic processes. The term phenotype has been applied to describe and classify BPD on the basis of several observable characteristics, including disease severity grade, (5)(7) infant pulmonary function testing patterns (restrictive, obstruction, mixed), (8) and the anatomic location of pathology. (9)(10)(11) Each is valid and considered in our clinical evaluation. We primarily classify infants on the basis of present or absent pathology in the lung parenchyma, airway, and pulmonary vasculature (Fig 2). (9) Parenchymal disease can be homogeneous or heterogeneous. Homogeneous disease has diffuse uniform haziness on chest radiography and pathology consistent with fewer, larger alveoli, whereas heterogeneous disease also has alternating areas of hyperinflation, atelectasis, and fibrosis. (7) Pathology in the developing airways is typically a consequence of longstanding distending pressures and weak stromal support from generalized alveolar simplification. (12) Disease typically involves a narrowing or collapse of the airway anywhere from the subglottic trachea to the distal bronchioles and can be fixed (eg, subglottic stenosis), dynamic (eg, tracheobronchomalacia), or reactive (eg, bronchoconstriction) in nature. Tracheobronchomalacia is particularly common in patients with sBPD. Although tracheobronchomalacia improves

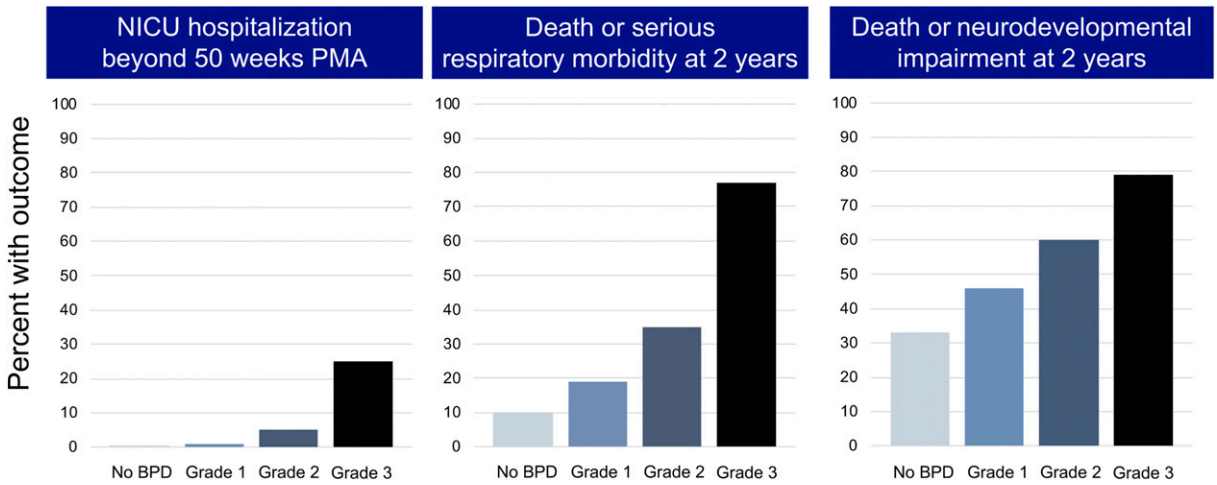

Figure 1. Higher BPD severity grades are associated with worse health outcomes. Data from Jensen et al. (6) Infants were born at less than 32 weeks' gestational age between 2011 and 2015 at centers participating in the National Institutes of Child Health and Human Development Neonatal Research Network (United States). Outcomes were assessed at 18 to 26 months' corrected age. BPD=bronchopulmonary dysplasia; PMA=postmenstrual age.

with time and growth, its presence is associated with longer hospitalizations and higher tracheostomy rates. (11)(13) Pulmonary vascular disease is attributed to maldevelopment of the pulmonary vasculature, with abnormal angiogenic factors arising in the setting of alveolar hypoxia and inflammation. The end result is a pulmonary vascular bed with abnormal structural remodeling and vascular tone, and a lower available cross-sectional area for gas exchange. Features of multiple phenotypes are often present in an infant with sBPD. In a recently published study from our program,

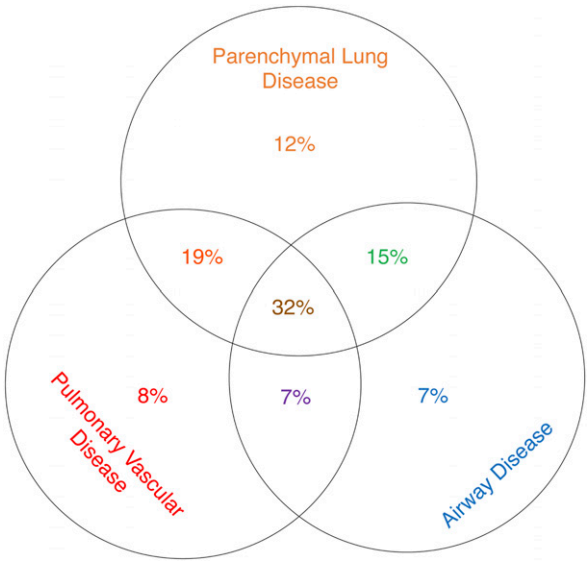

Figure 2. Phenotypes of severe bronchopulmonary dysplasia (BPD) by anatomic location of pathology. Infants with severe BPD can have pathology of the airway, lung parenchyma, and/or pulmonary vasculature. Overlapping phenotypic features are common, as noted by the proportion of subjects with isolated disease versus multiple, overlapping features as per Wu et al. (11)

73% of these patients had multiple phenotypic features, and the concomitant presence of all 3 was the most common (32%) of all possible combinations (Fig 2). (11)

A Chronic Lung Disease with Long-term Health Consequences

Most infants with sBPD have ongoing respiratory morbidity and neurodevelopmental impairments beyond infancy (Fig 1). (6) A multidisciplinary chronic care model that prioritizes stability, growth, and age-appropriate developmental interventions has been adopted by several centers, with a goal of prioritizing long-term respiratory and neurodevelopmental outcomes. (5) Critical to this strategy is providing adequate respiratory support. We use this term to refer to both "invasive" respiratory support (ie, mechanical ventilation through an endotracheal or tracheostomy tube) and "noninvasive" respiratory support that provides continuous distending airway pressure (continuous positive airway pressure [CPAP]) through the nose or mouth. Objective criteria to define adequate respiratory support in patients with sBPD are often lacking, necessitating subjective assessments. In addition, given the degree of disease heterogeneity, a single approach cannot be used for all patients. We consider respiratory support to be adequate when it not only supports acceptable gas exchange, but also promotes the stability needed for growth and development. As these can only be observed over time, assessing the adequacy of respiratory support may require days or weeks. In contrast to respiratory distress syndrome, rapid improvements in lung disease are not expected in established sBPD. Reductions in respiratory support (ie, "weaning") that maintain adequate support are often achieved slowly, and the rapid

weaning typically seen in the management of respiratory distress syndrome can be harmful. When an infant is expected to require respiratory support for at least several months beyond 40 weeks PMA, we consider tracheostomy placement for long-term ventilatory support to be a valuable therapeutic intervention to promote long-term respiratory and neurodevelopmental outcomes.

Beyond the Lungs: Evaluation of sBPD as a Multisystem Disease

Infants with sBPD typically have comorbidities of preterm birth that extend beyond the airway, lung parenchyma, and pulmonary vasculature, and influence long-term respiratory and neurodevelopmental outcomes. A comprehensive evaluation of infants with sBPD includes a thorough multisystem assessment of both past and present comorbid conditions that is best achieved through the integrated perspectives of multidisciplinary providers. (5)(14) Although a complete description of all comorbidities possible in infants with sBPD is beyond the scope of this review, we highlight common findings in the sections that follow.

COMMON FEATURES OF THE EVALUATION

A thorough history and physical examination, followed by targeted diagnostic studies, form the basis for the clinical evaluation of infants with sBPD. Together, they can help identify phenotypic features and comorbidities, and assess the adequacy of past and current respiratory support. These findings then serve to guide our short- and long-term management, including degree and mode of respiratory support, choice of potentially useful medications, and potential interventions, such as tracheostomy placement.

Pregnancy and Perinatal History

The etiology of BPD is multifactorial, with antenatal, perinatal, and postnatal risk factors. Known risk factors include male sex, chorioamnionitis, and preeclampsia. (9) A history of prolonged rupture of membranes and/or oligohydramnios suggests an increased risk for pulmonary hypoplasia. Birth GA is the most important risk factor, because the incidence of BPD increases with each progressive week of prematurity. (15) Intrauterine growth restriction is an independent risk factor for BPD and is strongly associated with the subsequent development of pulmonary vascular disease. (16)(17) Growth restriction may also increase the vulnerability of lung injury after preterm birth by exacerbating the degree of developmental immaturity relative to that expected for a given GA. Similarly, exposure to intrauterine stress and inflammation may initiate a process of maldevelopment before postnatal injury begins. (18)(19) Infants who develop sBPD but lack known risk factors may warrant further evaluation for atypical physiologic processes to explain their lung disease.

Respiratory Support History

Developing a chronologic timeline that details initial and subsequent modes (invasive vs noninvasive) and degrees (mean airway pressure and supplemental oxygen levels) of respiratory support can help predict respiratory disease course and phenotype. The infants with the most severe lung disease often have a history of high oxygen and ventilator requirements since birth. The presence of air leak syndromes, including pulmonary interstitial emphysema with early cystic changes noted on chest radiography, is consistent with the development of a heterogenous parenchymal pathology. In our experience, many of these infants are dependent on invasive respiratory support beyond term PMA and may be ventilator dependent for months or years. Other infants with sBPD have initial respiratory distress, followed by rapid improvement and extubation to noninvasive support with subsequent stability. Alternatively, they have an unremarkable early course without the need for invasive support or high supplemental oxygen. However, this is sometimes followed by difficulty in further respiratory weaning and an insidiously worsening status. A pulmonary vascular disease–predominant phenotype may follow this pattern, with clinical stagnation and subsequent worsening noted as the lungs "outgrow" a maldeveloped pulmonary vasculature. It is not uncommon to elicit a history in which an infant is weaned to low-flow nasal cannula or entirely off respiratory support and subsequently develops signs of respiratory distress. These infants may fail to sustain adequate growth, have subtle increases in their baseline work of breathing, and develop new-onset or worsening episodic desaturations. This might be interpreted as a new insult exacerbating lung disease, such as reflux or infection, when in fact the infant was not ready to be weaned and is showing delayed signs of inadequate respiratory support.

Airway History

Most infants with sBPD have undergone endotracheal intubation on 1 or more occasions. A history of a difficult or traumatic intubation increases concerns for subglottic stenosis. An infant with a history of multiple failed extubations despite relatively low ventilator settings should raise concerns for an airway-predominant phenotype. Acute episodes of hypoxemia ("BPD spells") with or without bradycardia are common in infants with airway and vascular phenotypes. In airway phenotypes, spells may occur following changes in resistance to airflow from the collapse of central airway

segments or bronchoconstriction. These events often resolve with the delivery of higher positive pressures. Infants with pulmonary vascular disease may have spells in response to pain or agitation. Some of these events are associated with efforts at passing stools, with changes in intra-abdominal pressures dynamically compromising gas exchange. A careful description of the event and inciting factors by bedside providers can help determine the underlying cause. For infants receiving invasive respiratory support, the size of the endotracheal tube and presence or absence of an air leak around the endotracheal tube should be evaluated. This can inform the likelihood of improving gas exchange with a larger endotracheal tube or suggest the presence of upper airway stenosis or edema. For infants receiving noninvasive respiratory support, knowledge of which interfaces have been used and their impact on infant comfort and skin and nasal septum integrity are useful components of the history.

Cardiac, Vascular, and Lymphatic History

Pulmonary hypertension (PH) is common in patients with sBPD, with cohort studies reporting an incidence of 29% to 58%. (20)(21) PH can develop early or late in the postnatal course. In 1 prospective study, echocardiographic evidence of PH was present by 7 days of age in 42% of very-low-birthweight infants and identified as a risk factor for sBPD and persistent PH beyond 36 weeks' PMA. (20) The late development of PH following unsuccessful attempts to wean respiratory support may be a consequence of alveolar hypoxia leading to pulmonary vasoconstriction. Providing adequate respiratory support is a fundamental component of managing PH in these patients, and in some cases invasive ventilation is necessary.

Although evaluating PH is essential, other disorders of the cardiovascular system also contribute to morbidity. Systemic hypertension is identified in up to 50% of infants with BPD during the first year of age. (14) The etiology is likely multifactorial and discrete causes such as renal artery stenosis are not commonly identified. It is often responsive to medical therapy and resolves over time. (14)(22) Abnormalities in left heart performance can also be considered. (23) The causes of left ventricular hypertrophy are poorly understood, but it is associated with chronic hypoxemia, neurohormonal factors, and systemic hypertension. (14) Recently, Mourani and colleagues described 2 infants with sBPD whose clinical status improved markedly following afterload reduction for left ventricular diastolic dysfunction. (24) Extracardiac shunts, such as a patent ductus arteriosus or aortopulmonary collaterals, may impair lung mechanics because of excessive pulmonary blood flow. (22)

Acquired pulmonary vein stenosis is a manifestation of pulmonary vascular disease diagnosed in 5% of infants with sBPD at a median age of 6 months. It could be considered in infants who present with insidious and progressive respiratory distress and hypoxemia. The etiology of the disease remains unclear and mortality rates are high. (17)

Lymphatic dysfunction is on the differential diagnosis for an infant with a history of chylothorax, chylous ascites, and/or generalized anasarca without other identifiable causes. Altered lymphatic flow has not been widely described in sBPD but is a recognized phenomenon. (25) The proposed etiology includes maldevelopment of lymphatic structures and chronically elevated intrathoracic pressures impairing lymphatic flow. In collaboration with the Center for Lymphatic Imaging and Interventions at CHOP, we have used magnetic resonance lymphangiography to diagnose lymphatic disorders in several infants with sBPD. Severe lymphatic dysfunction is challenging to treat and is associated with high mortality. Potential therapeutic interventions are available, and some infants will spontaneously recover over the course of several months. (26)(27)

Growth, Nutrition, and Gastrointestinal History

Growth plays a critical role in the development of and recovery from sBPD, while also serving as a marker of adequate respiratory support. When possible, growth charts should be obtained from referral hospitals and carefully maintained. Assessments include an evaluation of weight, length, and the weight-to-length ratio over time. A history of both intra- and extrauterine growth failure is common. (28) Infants with sBPD often have high caloric requirements, but their nutritional needs are variable and change over time. (5) For example, changes in respiratory support can influence work of breathing and energy expenditure, with a subsequent impact on growth.

Current nutritional status and goals are accurately characterized best through multidisciplinary care with registered dietitians familiar with this population. Nutritional deficits can be complex and may result from insufficient intake or absorption to meet demands, and/or excessive gastrointestinal or renal losses. Interval gains in weight without linear growth can reflect worsening edema or increasing adiposity. We review both linear and weight growth velocity weekly. Changes in growth trajectory may identify inadequate respiratory support in the absence of overt signs of respiratory distress, particularly when weaning.

The medical history may also reveal comorbid conditions influencing growth, such as necrotizing enterocolitis. The impact of gastroesophageal reflux with microaspiration on the trajectory of lung disease in sBPD remains unclear and future research is needed.

Medication History

Infants with sBPD are exposed to many medications. (29) Despite unclear research evidence of efficacy, diuretics,

glucocorticoids, bronchodilators, and pulmonary vasodilators are all frequently prescribed. A history of absent therapeutic response to a specific medication or class may help avoid repeating ineffective therapies. In addition, the medication exposure history may add context to help interpret a clinical presentation. For example, a history of multiple courses of dexamethasone alerts providers to a possible contributor of linear growth failure and is a risk factor for iatrogenic adrenal insufficiency. The accretion of minerals needed to support bone health may be adversely affected by exposure to gastric acid inhibitors, corticosteroids, and diuretics. (30)

Targeted medication use is one example of how disease phenotyping can play a valuable role in the evaluation of patients with sBPD. In infants at high risk of developing BPD, Lewis and colleagues found that specific genetic polymorphisms are associated with the response to systemic corticosteroids. (31) In another example, Shepherd and colleagues demonstrated that infants with sBPD with an obstructive phenotype detected on infant pulmonary function testing were more likely to respond to albuterol than infants with a restrictive phenotype. (8)

Neurodevelopmental History

A history of brain injury, including intracranial hemorrhage, may be present and relevant to ongoing developmental assessments. Head circumference trajectories should be monitored, because at-risk infants may develop hydrocephalus beyond term PMA. Given the high rates of neurodevelopmental impairment in infants with sBPD, with or without prior brain injury, evaluation by occupational, physical, and speech language pathologists are fundamental to our approach. Repeated assessments over time from these therapists can identify signs of inadequate respiratory support that would be otherwise overlooked. For example, an infant may lose the ability to participate in developmental therapies if weaned excessively. Objective assessments such as the Hammersmith Infant Neurological Examination and Test of Infant Motor Performance can be completed at the bedside. (32)(33)

Physical Examination

Routine elements of the physical examination common to newborns and infants are part of the evaluation of infants with sBPD. Here, we highlight elements of particular relevance to infants with sBPD. The physical examination should be conducted while the infant is asleep, awake at rest, and during activities, such as handling for diaper changes, position changes, or developmental therapies. Increased work of breathing including tachypnea, head bobbing, retractions, or nasal flaring may be observed only with activity, but nonetheless be a sign of inadequate respiratory support. Overall alertness and behavioral state should be noted. Infants may lack quiet awake periods, when they sleep excessively and/or appear agitated and uncomfortable when awake. This may be a sign of inadequate respiratory support that is easily confused with discomfort or pain.

For infants on relevant modes of mechanical ventilation, the ability to spontaneously trigger a ventilator-supported breath is an element of our examination. We refer to an inability to activate the ventilator as a "wasted effort"—this is discussed further in the context of interpreting ventilator waveforms. Noting the extent, location, and character of edema is useful. Generalized edema may indicate impaired nutritional status related to hypoalbuminemia, lymphatic dysfunction, or cardiac failure. Eustachian tube dysfunction from CPAP increases the risk of serous otitis media. Bedside evaluations can be challenged by impacted cerumen and stenotic canals. In this case, auditory examinations can be performed, with the patient under anesthesia, in coordination with other surgical interventions. Interfaces used for noninvasive support can compromise facial skin integrity, and examinations should routinely assess for breakdown. The cardiac examination should include an evaluation for evidence of PH, including the intensity of the second heart sound and the presence of a parasternal right ventricular heave. Right heart failure from PH can lead to hepatomegaly and ascites. Inguinal hernias are common and can be large and prone to intermittent incarceration; obstruction may complicate nutritional intake.

The neurologic examination can include an assessment of general activity, tone, and strength, including asymmetry. Subtle abnormalities such as ankle clonus are not uncommon. Although most providers are not formally trained in comprehensive developmental assessments, an ability to appreciate the presence or absence of typical milestones is useful.

Pulmonary Function Tests and Ventilator Waveforms

Pulmonary function tests (PFTs) and ventilator waveforms can provide objective data to describe pulmonary mechanics and help guide ventilator strategies or evaluate a patient's response to a therapy. (34) Specific guidelines for optimal lung function testing to monitor BPD were developed by the American Thoracic Society in 2013. (35) This report acknowledges that population-based reference data are lacking and that it is unclear whether routine monitoring improves outcomes in BPD. In addition, access to this specialized equipment and the personnel trained to accurately conduct testing is not available in many neonatal units. Our program has not adopted infant PFTs as part of our routine evaluation. However, some colleagues within

the BPD Collaborative have successfully done so. In 1 published example, Shepherd and colleagues conducted PFTs on infants with sBPD to identify obstructive, restrictive, or mixed phenotypes. (8) Although all 3 phenotypes were observed, a predominantly obstructive phenotype was most common. Infants with this phenotype had more days on the ventilator and a tendency toward more frequent tracheostomy placement.

Although less rigorous than PFTs, useful data describing pulmonary mechanics can be obtained from ventilator waveforms readily available on most modern ventilators. Ventilator waveforms give providers the ability to make dynamic assessments of changing pulmonary mechanics. The slope of the pressure-volume loop gives the clinician an estimate of lung compliance that can be assessed repeatedly as changes in ventilator support parameters or medications are applied, or as a patient's lung disease evolves. Flow-time waveforms and flow-volume loops can be evaluated to help determine the presence of an obstructive component and determine if interventions lead to improvements. A comprehensive review of pulmonary waveforms is beyond the scope of the current review, but available in a recent publication by Mammel and Donn. (36)

A specific application of ventilator waveforms is in the evaluation of set positive end-expiratory pressures (PEEP) and intrinsic PEEP (PEEPi). In patients with an obstructive component and severe resistance to airflow, the time for full expiration may be insufficient. This leads to an accumulation of air in the lungs over multiple respiratory cycles, a process referred to as *dynamic hyperinflation*. This contributes to the development of PEEPi, which describes an increase in alveolar pressure at end expiration caused by accumulated air, rather than the PEEP selected as a ventilatory parameter. An evaluation of ventilator waveforms can alert providers to the risk of PEEPi. In examining the flow-time waveform, when the tracing of the expiratory arm does not return to the baseline of zero flow before the initiation of the next inspiration, the infant is at risk for air trapping; this will lead to dynamic hyperinflation and PEEPi. Patient-ventilator asynchrony is also suggestive of PEEPi. With PEEPi, the negative inspiratory pressure generated by the patient must be sufficient to first overcome the PEEPi, and then generate sufficient flow to trigger a ventilator-supported breath. When the infant is unable to generate sufficient force to overcome the intrinsic pressure, the inability to trigger the ventilator results in a "wasted effort."

IMAGING

Chest Radiography

Chest radiography (CXR) has been used for decades to evaluate lung disease. Useful findings include the degree of lung expansion, presence of infiltrates, atelectasis, cystic changes, air leaks, pleural effusion, diaphragm asymmetry, and malpositioned endotracheal tubes. However, it is limited in its ability to assess the degree of lung injury, and the distortion of parenchymal architecture in sBPD can make it difficult to appreciate abnormal findings. Figure 3 provides an example of how CXR can fail to identify pathology that is recognized with more sophisticated imaging techniques.

Computed Tomography

Chest computed tomography (CT) provides a 3-dimensional visualization of the lung parenchyma and airways and, when combined with angiography, also describes the heart and pulmonary vasculature. Chest CT can help characterize disease phenotype as well as overall distortion of lung architecture and illustrate the degree of parenchymal heterogeneity. (37) It can be used to identify or better characterize occult infection abscesses, lobar emphysema,

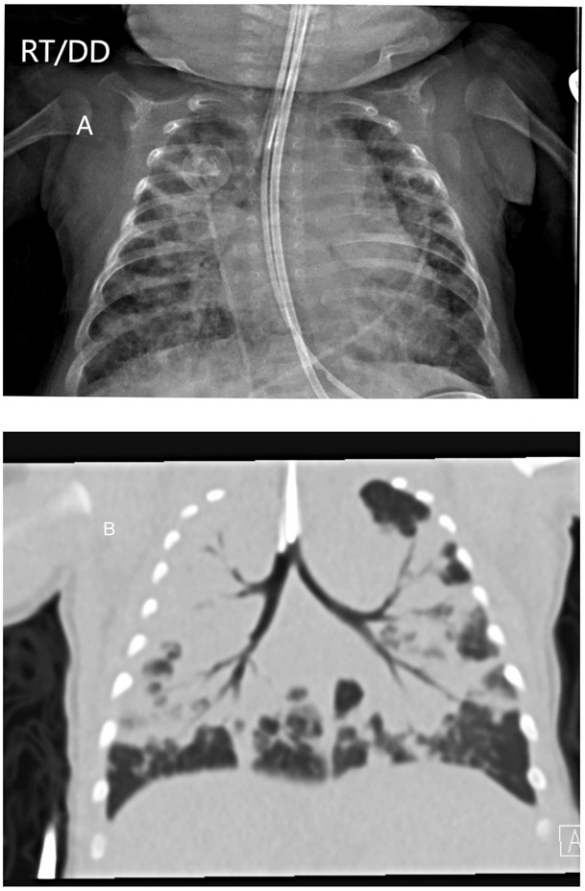

Figure 3. Chest computed tomography can identify abnormalities not appreciated on chest radiography in infants with severe bronchopulmonary dysplasia. A. The chest radiograph shows findings of patchy atelectasis consistent with chronic lung disease. B. Chest computed tomography reveals diffuse infiltrates with posterior prominence. In response, bronchoalveolar lavage was performed and identified a *Staphylococcus aureus* lower respiratory tract infection.

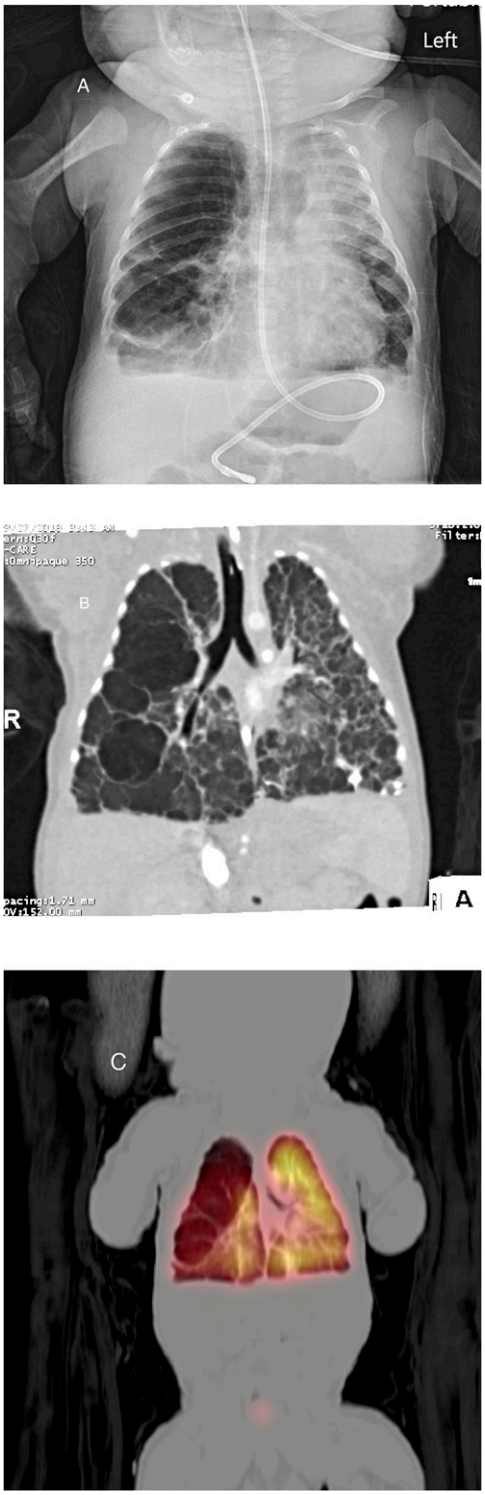

Figure 4. Use of single photon emission computed tomography to evaluate acquired lobar emphysema in an infant with severe bronchopulmonary dysplasia (BPD). A. The chest radiograph shows a hyperinflated right upper lobe with herniation into the left hemithorax. B. Chest computed tomography with single photon emission computed tomography (C) was notable for an emphysematous right upper lobe that lacked ventilation and perfusion. Based on these findings, a right upper lobectomy was performed, with subsequent improvement in lung mechanics.

infiltrates, and atelectasis. Considering the long-term risks of exposing infants to ionizing radiation, low-dose radiation protocols developed specifically for neonatal/pediatric chest CT should be used. (38) Hybrid imaging such as single photon emission CT can help evaluate the ventilation and perfusion of individual lobes. (39) We have found this imaging technique to be particularly useful in cases in which lobectomy is being considered to manage acquired lobar emphysema (Fig 4).

Magnetic Resonance Imaging

Historically, conventional magnetic resonance imaging (MRI) has not been used for lung imaging because of the long acquisition times and susceptibility to motion artifact which necessitates sedation. Ultrashort echo-time (UTE) MRI produces high-quality pulmonary and airway imaging while avoiding exposure to ionizing radiation, and the image quality of the lung parenchyma is comparable to that of chest CT. Hysinger and colleagues reported that UTE MRI can provide an objective and quantitative assessment of tracheomalacia comparable to bronchoscopy. Critser and colleagues have shown that UTE MRI–based indices are more predictive than echocardiography for outcomes such as respiratory support duration and the need for pulmonary vasodilators in patients with PH. (40)(41) UTE MRI sequences are available from major MRI manufacturers and thus are not limited to research settings. Hyperpolarized-gas MRI is another novel technique that holds great promise for the evaluation of patients with sBPD. This technique requires specialized equipment to prepare hyperpolarized xenon gas but has the potential to provide unmatched functional and microstructural data including ventilation, diffusion, and gas exchange.

Bronchoscopy

As discussed, many infants with sBPD have airway pathology. Flexible nasopharyngolaryngoscopy can be used to evaluate the vocal folds and supraglottis and provide a limited evaluation of the subglottis in infants receiving noninvasive respiratory support without anesthesia. The small caliber of the fiberoptic scopes limits the ability to perform interventional procedures, though suctioning for airway clearance and sampling for microbiologic studies is possible. In contrast, rigid microlaryngoscopy and bronchoscopy require anesthesia and are usually performed in the operating room, but allow for a wide range of diagnostic and interventional procedures. Although rigid bronchoscopy offers limited ability to assess the airways distal to the mainstem bronchi, flexible bronchoscopy can evaluate the more distal bronchial tree. This can be done in the operating room or at the bedside of intubated infants. In general, we have found

TABLE. **Genetic Diagnoses Considered in Infants with Severe Bronchopulmonary Dysplasia**

CATEGORY OF DISEASE	DIAGNOSIS	GENE(S) IDENTIFIED
Developmental and/or interstitial lung disease	Alveolar capillary dysplasia with malalignment of the pulmonary veins	*FOXF1*
	Interstitial lung disease	*COPA, NKX2.1*
	Idiopathic pulmonary fibrosis/familial pulmonary fibrosis	*DKC1, TERC, TERT*
	Emphysematous lung disease	*FLNA*
Impaired mucociliary clearance	Cystic fibrosis	*CFTR*
	Primary ciliary dyskinesia	*ARMC4, C21ORF59, CCDC103, CCDC114, CCDC151, CCDC39, CCDC40, CCDC65, CCNO, DNAAF1, DNAAF2, DNAAF3, DNAAF5, DNAH1, DNAH11, DNAH5, DNAH6, DNAH8, DNAI1, DNAI2, DNAL1, DRC1, DYX1C1, GAS8, HYDIN, INVS, LRRC6, MCIDAS, NME8, OFD1, RPGR, RSPH1, RSPH3, RSPH4A, RSPH9, SPAG1, ZMYND10*
Surfactant deficiency or dysfunction	Surfactant protein deficiency	*SFTPB, SFTPC*
	ABCA3 transporter deficiency	*ABCA3*
Pulmonary vascular disorder	Pulmonary hypertension	*ACVRL1, BMPR1B, BMPR2, CAV1, EIF2AK4, ENG, GDF2, JAG1, NOTCH2, KCNA5, KCNK3, RASA1, SMAD4, SMAD9, TBX4*
Other disorders of unknown etiology	Pulmonary interstitial glycogenosis	No
	Neuroendocrine cell hyperplasia of infancy	No
	Pulmonary alveolar proteinosis	*CSF2RA, CSF2RB, GATA2, SLC7A7, MARS*

flexible bronchoscopy to be a safe and informative diagnostic tool. It can identify the presence or absence of tracheobronchomalacia, as well as the level of PEEP that prevents airway collapse. (42) If a lower respiratory tract infection is a concern, bronchoalveolar lavage can be performed to obtain mircrobiologic cultures and cell counts. It may identify other airway anomalies, for example, the presence of an H-type fistula that could explain an atypical disease course.

Echocardiography and Cardiac Catheterization

The comprehensive evaluation of PH is beyond the scope of this review. We refer the reader to published recommendations to guide the evaluative approach to screening for PH in sBPD. (14)(43) We perform screening echocardiography at 36 weeks' PMA and then monthly to screen for PH, as recommended in guidelines published by the BPD Collaborative. (5) There are known limitations in the sensitivity and specificity of echocardiography to identify PH, and cardiac catheterization is recommended when there are uncertain findings, concerns for inadequate response to pulmonary vasodilators, or more precise measures of pulmonary pressures and vasoreactivity are needed. (43)

Lung Biopsy

Lung biopsy is reserved for cases when we suspect a diagnosis other than sBPD. Often, this arises when the lung disease is out of proportion to known risk factors, or when an infant follows an atypical clinical course. Because lung biopsy is invasive and many of the disorders it diagnoses lack specific treatments, we typically first pursue genetic testing. Some of the diseases that can be diagnosed or ruled out on lung biopsy include late presentation of alveolar-capillary dysplasia, pulmonary interstitial glycogenolysis, and other interstitial lung disorders. The procedural risks in this age group are unclear but include pneumothorax and development of a bronchopleural fistula; in older children, complications have been reported in up to 24% of cases. (44)

Genetic Studies

Susceptibility to BPD is suspected to be influenced by genetic polymorphisms. This is supported by twin studies suggesting a heritable component of BPD, though genome-wide studies have not definitively identified specific genes. (45)(46)(47)(48)(49) For patients who have a particularly severe or atypical phenotype, we have developed a genetic sequencing panel to identify cases with another etiology for

the lung disease. The method used in this panel is a targeted capture of the panel genes followed by next-generation sequencing. Diagnoses captured include childhood interstitial lung diseases, primary ciliary dyskinesia, and genetic causes of PH; a complete list is available in the Table. Although in many cases identification of a mutation in one of these genes will not acutely change care, it may provide the family with prognostic information, inform a reassessment of the goals of care, or allow for genetic counseling relevant to future pregnancies. An alternative to the gene panel described is whole exome sequencing. Either option takes several weeks or longer for results and the costs, risks, and benefits need to be considered.

SUMMARY AND CONCLUSIONS

Severe BPD is a heterogenous developmental disease of prematurity with variable phenotypic presentations—no 2 patients are the same. A comprehensive evaluation is best achieved with a multidisciplinary approach that recognizes sBPD as a multisystem disease. Each patient with sBPD warrants a thorough and comprehensive evaluation to guide individualized management with a chronic care perspective that prioritizes long-term respiratory and neurodevelopmental outcomes.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the clinical features of bronchopulmonary dysplasia/chronic lung disease.
- Recognize the laboratory, radiographic, and other imaging features of bronchopulmonary dysplasia/chronic lung disease.
- Know the management of bronchopulmonary dysplasia/chronic lung disease.

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1. Severe bronchopulmonary dysplasia (sBPD) is defined as supplemental oxygen requirement greater than 30% for 28 or more cumulative days and/or positive pressure support at 36 weeks' postmenstrual age (PMA) in infants born before 32 weeks' gestational age (GA). Subsequently, Abman and colleagues proposed to classify sBPD into 2 distinct types (I and II) to distinguish infants with ongoing ventilator dependence at 36 weeks PMA (type II) from less affected infants. This classification was recently further refined by Jensen and colleagues to improve its predictive validity for death or serious respiratory morbidity. Which of the following infants meets the criteria for type 2 sBPD according to the Jensen et al classification (6)?
    A. A 36 weeks' PMA infant receiving high-flow nasal cannula at 1 L/minute and 100% fraction of inspired oxygen (FiO_2).
    B. A 50 weeks' PMA infant on low-flow nasal cannula at 100 mL/minute and 100% FiO_2.
    C. A 36 weeks' PMA infant requiring noninvasive positive pressure and 21% FiO_2.
    D. A 42 weeks' PMA infant requiring invasive mechanical ventilation and 21% FiO_2.
    E. A 38-weeks' PMA infant requiring invasive mechanical ventilation and 50% FiO_2.
2. sBPD is a heterogeneous disorder encompassing multiple phenotypes. Disease classification is based on the presence or absence of pathology of the lung parenchyma, airway and pulmonary vasculature. Which of the following is the most commonly occurring phenotype in infants with sBPD?
    A. Isolated parenchymal lung disease.
    B. Isolated pulmonary vascular disease.
    C. Parenchymal lung disease and pulmonary vascular disease.
    D. A combination or parenchymal, pulmonary vascular, and airway diseases.
    E. Isolated airway disease.
3. sBPD is a multisystem disorder requiring a multidisciplinary approach for diagnosis of comorbidities and treatment. The cardiovascular system is often affected in infants with sBPD. Which of the following statements regarding the cardiovascular comorbidities associated with sBPD is correct?
    A. Pulmonary hypertension (PH) is common, occurring in up to 70% of very-low-birthweight (VLBW) infants with sBPD.
    B. Systemic hypertension occurs in up to 50% of infants with BPD during the first year of age.
    C. Acquired pulmonary vein stenosis occurs in about 5% of infants with sBPD at a median age of 12 months.
    D. Systemic hypertension does not respond well to medical therapy and often lasts into adulthood.
    E. Echocardiographic evidence of PH is present in 10% of VLBW infants and is a risk factor for sBPD and persistent PH beyond 36 weeks' PMA.
4. Intrinsic positive end-expiratory pressures (PEEPi) can develop in mechanically ventilated infants with sBPD. PEEPi represents the increase in alveolar pressure at end expiration caused by accumulated air over several respiratory cycles (dynamic hyperinflation), rather than the selected ventilator PEEP. Which of the following statements does NOT suggest the presence of PEEPi?
    A. The expiratory arm does not return to the baseline of zero flow before the initiation of the next breath of the flow-time waveform.
    B. The presence of patient-ventilator asynchrony.
    C. Inability to trigger the ventilator.
    D. A disease pathology characterized by an obstructive component with severe resistance to air-flow.
    E. The expiratory volume consistently returns to zero on the pressure-volume loop.
5. Imaging techniques are important to monitor disease progression and guide treatment decisions in infants with sBPD. Chest radiography (CXR) are helpful in assessing the degree of lung expansion as well as the presence of infiltrates, atelectasis, cystic changes, air leaks, pleural effusion, and diaphragm asymmetry. However, the distortion of the parenchymal architecture seen in sBPD can make it challenging to appreciate abnormal findings. As such, advanced imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) may be helpful in some patients. Which of the following statements regarding advanced imaging for sBPD is INCORRECT?
    A. Low-dose radiation protocols for chest CT are available for neonatal and pediatric patients.
    B. Ultrashort echo-time (UTE) MRI has the advantage of being less susceptible to motion artifacts than conventional MRI produces images of comparable quality than those obtained with a chest CT.
    C. The use of UTE MRI is limited to research protocols.
    D. UTE MRI can provide an objective and quantitative assessment of tracheomalacia that is comparable to that obtained with a bronchoscopy.
    E. UTE MRI–based indices are more predictive than echocardiography for outcomes such as respiratory support duration and need for pulmonary vasodilators in patients with PH.

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