REVIEW ARTICLE

CURRENT CONCEPTS

Chronic Lung Disease after Premature Birth

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In 1967, Northway et al. first described a new chronic respiratory disease, bronchopulmonary dysplasia, that developed in premature infants exposed to mechanical ventilation and oxygen supplementation.[1] Two decades later, the same authors found that clinically significant respiratory symptoms and functional abnormalities persisted into adolescence and early adulthood in a cohort of survivors of bronchopulmonary dysplasia,[2] suggesting that lung injuries early in life may have lifelong consequences. Bronchopulmonary dysplasia is now the most common chronic lung disease of infancy in the United States.

Today, newborns consistently survive at gestational ages of 23 to 26 weeks — 8 to 10 weeks younger than the infants in whom bronchopulmonary dysplasia was first described. New mechanisms of lung injury have emerged, and the clinical and pathological characteristics of pulmonary involvement have changed profoundly, although its natural history and outcome into adulthood are still largely unknown. It is only now that large populations of persons born prematurely are approaching adulthood, and they may be at increased risk for respiratory disease in adult life.

Characteristics of Bronchopulmonary Dysplasia

Any pulmonary disease resulting from a neonatal respiratory disorder is called chronic lung disease.[3] Bronchopulmonary dysplasia accounts for the vast majority of cases of chronic lung disease. Unfortunately, varying definitions of bronchopulmonary dysplasia have been used in the past, and this has contributed to the variability of the characteristics of populations reported in different studies. Bronchopulmonary dysplasia is now defined as the need for supplemental oxygen for at least 28 days after birth, and its severity is graded according to the respiratory support required near term (Table 1).[4] The diagnosis of bronchopulmonary dysplasia identifies most patients at increased risk for long-term respiratory sequelae. However, prolonged oxygen dependence in the neonatal period does not accurately predict the long-term respiratory outcome,[5] and accurate markers of chronic lung damage in premature infants are still lacking.[6] Indeed, infants with bronchopulmonary dysplasia may have a full clinical and functional recovery, and late respiratory symptoms and pulmonary-function abnormalities may appear even in patients who did not require prolonged oxygen supplementation as neonates.

Pathogenesis

Innumerable factors are potentially harmful to the immature lung. Depending on the timing, extent, and duration of the exposures, different patterns of pulmonary damage may occur (Fig. 1). What is now considered the "old" bronchopulmonary dysplasia was originally described in slightly preterm newborns with the respiratory distress syndrome who had been exposed to aggressive mechanical ventilation and high concentrations of inspired oxygen.[1] Diffuse airway damage, smooth-mus-

cle hypertrophy, neutrophilic inflammation, and parenchymal fibrosis reflected extensive disruption of relatively immature lung structures (Fig. 2).

The introduction of measures to prevent and treat the respiratory distress syndrome (e.g., antenatal corticosteroids and surfactant replacement) and a more conservative approach to respiratory care have brought about a substantial reduction in this old form of bronchopulmonary dysplasia. The overall prevalence of the condition, however, has not changed, because with the improved survival rate among infants born at earlier gestational ages, a new pattern of lung injury has emerged.[5] This "new" form of bronchopulmonary dysplasia is interpreted as a developmental disorder (Fig. 2). Despite being delivered several weeks before alveolarization begins, infants at risk for new bronchopulmonary dysplasia often have only mild respiratory distress syndrome at birth. But at this early developmental stage, even minimal exposure to injurious factors may affect the normal processes of pulmonary microvascular growth and alveolarization. Certain antenatal exposures (e.g., chorioamnionitis) may prime the lung's response, making it more susceptible to subsequent injury.[7] The normal structural complexity of the lung can be lost as a result: fewer, larger alveoli develop, and the overall surface available for gas exchange is reduced.[8] The airways are somewhat spared, and inflammation is usually less prominent than in the old form of the condition (Fig. 2). Genetic susceptibility[9] and hereditary influences on the expression of genes that are critical for surfactant synthesis, vascular development, and inflammatory regulation probably also have a role in the development of the new form.

Because these patients are surviving, it has not been possible to gather data on pathological findings in the lungs beyond infancy in survivors of bronchopulmonary dysplasia or prematurity. The characterization of the long-term pulmonary outcome after premature birth remains primarily clinical, with no insights from tissue examination to guide management.

Table 1. Causes of Chronic Lung Disease and Definition of Bronchopulmonary Dysplasia.*

Causes of chronic lung disease
Premature newborns
Bronchopulmonary dysplasia (old or new)
Prematurity
Status after respiratory distress syndrome
Term and near-term newborns
Bronchopulmonary dysplasia (old)
Pneumonia or sepsis
Aspiration syndromes
Persistent pulmonary hypertension of the newborn
Pulmonary hypoplasia
Diaphragmatic hernia
Congenital heart disease
Current definition of bronchopulmonary dysplasia
Diagnosis
Oxygen dependence for at least 28 postnatal days
Grading at 36 postmenstrual wk for infants born at <32 wk or at 56 days of life for infants born at ≥32 wk
Mild — FiO_2 0.21
Moderate — FiO_2 0.22–0.29
Severe — FiO_2 ≥0.30 or continuous positive airway pressure or mechanical ventilation required

* FiO_2 denotes fraction of inspired oxygen. The definition of bronchopulmonary dysplasia was adapted from Jobe and Bancalari.[4]

EPIDEMIOLOGY

Bronchopulmonary dysplasia almost always occurs in infants who are delivered at a gestational age of less than 30 weeks and who have a birth weight of less than 1500 g.[10] Approximately 60,000 infants under 1500 g (about 1.5% of all newborns) are born in the United States each year,[11] and bronchopulmonary dysplasia develops in about 20% of them.[12]

Treatment makes a considerable demand on health services, since bronchopulmonary dysplasia is still the most common chronic respiratory disease in infants and carries extremely high costs.[13] Moreover, it is a multisystem disorder that may be associated with a number of other conditions, including growth retardation, pulmonary hypertension, neurodevelopmental delay, hearing defects, and retinopathy of prematurity. Consequently, interdisciplinary follow-up is often required.[3]

CLINICAL AND FUNCTIONAL COURSE OF CHRONIC LUNG DISEASE WITH AGE

SYMPTOMS

Recurrent wheezing is markedly increased in infants born before 33 weeks of gestational age as compared with those born at term, and among the tiniest babies, the rate of readmission to the hospital for complications of respiratory tract in-

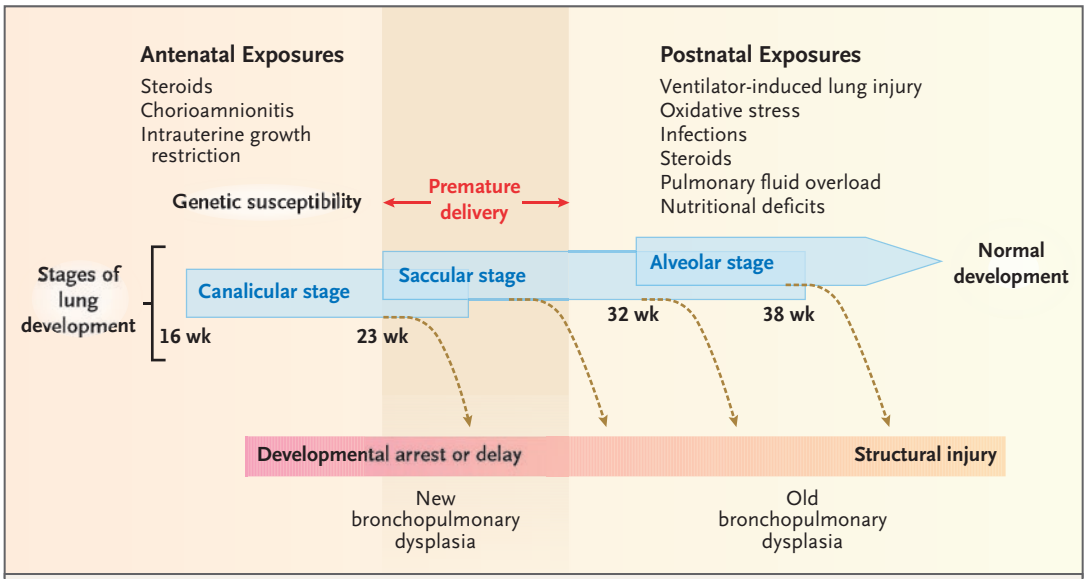


Figure 1. Stages of Lung Development, Potentially Damaging Factors, and Types of Lung Injury.

In premature newborns, the lungs are often exposed to several sources of injury, both before and after birth. Such exposures — as well as genetic susceptibility to problematic lung development — may cause direct airway and parenchymal damage and induce a deviation from the normal developmental path. Depending on the timing and extent of the exposures, lung injury may range from early developmental arrest (new bronchopulmonary dysplasia) to structural damage of a relatively immature lung (old bronchopulmonary dysplasia). Premature infants born at a gestational age of 23 to 30 weeks (region shaded light red) — during the canalicular and saccular stages of lung development — are at the greatest risk for bronchopulmonary dysplasia.

fection is high (up to 50% in the first year of life).[14] Survivors of bronchopulmonary dysplasia are clearly the most vulnerable,[14-16] and symptoms tend to be worse in children with more severe lung-function abnormalities.[17] Strict measures to prevent viral infection and avoid adverse environmental factors (e.g., passive smoking) are crucial in managing the care of these children.[3]

Several studies report increased rates of chronic coughing and wheezing among preschool[3,17] and school-age children who were born prematurely,[18-20] especially those in whom bronchopulmonary dysplasia developed or prolonged mechanical ventilation was required.[19,21] Cohort studies show a significantly greater prevalence of asthmalike symptoms and the use of inhaled asthma medication among persons 8 to 19 years old who were born prematurely — regardless of whether they had bronchopulmonary dysplasia — than among persons born at term.[22-26] A trend toward clinical improvement is usually seen over time, however; symptoms progressively subside, respiratory exacerbations become uncommon, and most persons lead apparently normal lives.[2,27] From school age onward, the relationship between clinical symptoms and lung function fades, and patients with marked airway obstruction detected by spirometry may be free of clinically significant respiratory disturbance.

PULMONARY FUNCTION

Most of the information on long-term lung function in survivors of bronchopulmonary dysplasia refers to patients who had the condition in the era before surfactant treatment was available or to selected populations of children who had severe pulmonary disease as neonates. Study results thus often reflect the outcome for children who had the old form of bronchopulmonary dysplasia, which may not coincide with the outcome for children with the new form, which usually develops in less mature patients at birth who receive markedly different care. Unfortunately, not enough information is currently available to allow a separate analysis of the pulmonary outcome for patients with new bronchopulmonary dysplasia.

Longitudinal studies show that survivors of bronchopulmonary dysplasia, though severely affected in the first months of life, have improved pulmonary compliance over time.[28,29] Nonethe-

less, analysis of forced expiratory flows shows substantial airflow limitation in numerous survivors during the first 3 years of life.[28,30] Airway function may even deteriorate during the first year of life in infants with bronchopulmonary dysplasia,[31] probably reflecting the coupled effects of an unresolved lung injury plus the developmental interferences related to prematurity itself, at a time when the infants are growing rapidly.[32] Similar airway-function abnormalities have also been reported in preterm infants without bronchopulmonary dysplasia,[33] underscoring the important influence of prematurity on developmental changes in the lung. The degree of airflow limitation in the first years of life also seems to predict later pulmonary function: in a small group of survivors of bronchopulmonary dysplasia who were followed from birth, forced expiratory flow at 2 years of age was closely related to forced expiratory volume in 1 second (FEV_1) at 8 years, suggesting tracking of lung function with time and negligible "catch-up" growth of the lung.[34] This finding points to an irreversible early airway-remodeling process.

Spirometric values reflecting airflow are consistently lower in survivors of bronchopulmonary dysplasia at any age than in controls born at term (Fig. 3), with substantial airway obstruction and alveolar hyperinflation.[15,37,40,41,43] In most studies, the mean FEV_1 values in patients with bronchopulmonary dysplasia are near or below the lower limit of the normal range. As shown in Figure 3, FEV_1 ranged from normal values to those indicating severely limited airflow in each single study of such patients, reflecting the heterogeneity in the functional expression of the disease. These data should be interpreted with caution, however, since they are not generally applicable to the whole population of survivors, and especially not to those with new bronchopulmonary dysplasia or mild neonatal pulmonary disease.

Patients who were born prematurely but did not have bronchopulmonary dysplasia usually fare better,[39] but they too may have airflow limitation at school age[38,41,43,45] and later.[24,25,46] Little is known about the development of lung function in such patients during childhood and adolescence because few longitudinal lung-function studies have been performed and no cohort studies have followed patients from birth through childhood and adulthood. Two small studies reported some improvement in airway obstruction[47] or lung hyperinflation[48] up to adolescence in survivors of bronchopulmonary dysplasia. On the other hand, Doyle et al. recently reported that survivors of bronchopulmonary dysplasia may have a substantial decline in pulmonary function over time, on the basis of data from a large cohort of patients with a birth weight of less than 1500 g who were followed from 8 to 18 years of age.[24]

Another functional abnormality clearly associated with preterm birth is airway hyperresponsiveness,[49] which may occur in 50 to 60% of adolescents with bronchopulmonary dysplasia.[2,25,48] The origin of airway hyperresponsiveness — genetic factors, lung injury, or abnormal airway development — in these children is unclear.[50] Reduced exercise performance has also been reported, with impaired ventilatory adaptation[42-44] and reduced gas transfer[35,36,43] during physical activity, despite tolerance of maximal exercise workloads and normal or only slightly reduced aerobic capacity, according to most studies.[15,44]

The conclusions drawn from these physiological studies were based on measurements of forced expiratory volume and airflow, which are known to be relatively insensitive to peripheral airway disease. Moreover, there may be a selection bias in lung-function studies if some survivors of bronchopulmonary dysplasia with associated neurodevelopmental delay had to be excluded because they were unable to perform lung-function or exercise tests. We may thus have an incomplete picture of the true prevalence of respiratory disease in such cohorts.

OLD VERSUS NEW BRONCHOPULMONARY DYSPLASIA

The long-term pulmonary outcome after premature birth is difficult to gauge because of numerous confounding factors, including heterogeneous study populations and controls as well as the use of ambiguous terminology.[49] New bronchopulmonary dysplasia is associated with a milder neonatal respiratory course[27]; indeed, the incidence of severe bronchopulmonary dysplasia is declining.[51] Overall, mild forms of chronic lung disease are much more frequent today than in the past. Whether these changes point toward a better ultimate respiratory outcome is still not known.[27]

Patients with mild chronic lung disease usually have better spirometric results in the long

term than those with a severe neonatal course,[25] so a better respiratory prognosis overall might be expected. However, there is currently no clear evidence of the long-term beneficial effects of improved neonatal care. Among young children who were born preterm after the introduction of antenatal corticosteroids and surfactant replacement, the prevalence of respiratory symptoms and the need for inhaled drugs remain high.[16] Although it is difficult to compare the data, there is no evidence that children with bronchopulmonary dysplasia born since the introduction of surfactant-replacement therapy have better spirometric results at school age than those born in the presurfactant era (Fig. 3). Two recent studies[22,52] evaluating successive cohorts of infants who weighed less than 1000 g at birth or who were born before a gestational age of 29 weeks also showed that the advent of surfactant therapy and generally improved neonatal care did not reduce airflow limitation at school age. The benefits associated with better care may have been partially masked by the progressive improvement in the survival of the most immature infants.[22,52]

Indeed, prematurity itself has a very important independent influence on the long-term respiratory prognosis, and today, most infants at increased risk for bronchopulmonary dysplasia are delivered at a gestational age that is close to the threshold for viability (23 to 26 weeks). Thus, a prognostic characterization of new bronchopulmonary dysplasia remains elusive — not enough time has elapsed to allow an adequate evaluation of how the increasing survival rate among premature babies will influence their ultimate respiratory outcome.

ASTHMALIKE SIGNS AND SYMPTOMS

Symptoms resembling those of asthma and spirometric evidence of airflow limitation in children who had bronchopulmonary dysplasia as infants are often imprecisely labeled as asthma,[26,49] and such children are frequently treated with inhaled corticosteroids, even though there is no evidence to support this practice.[3,10,53-55] Children with asthma and those who have survived bronchopulmonary dysplasia share some clinical characteristics, but available evidence suggests that the two obstructive lung diseases do not have the same underlying airway inflammation.[54]

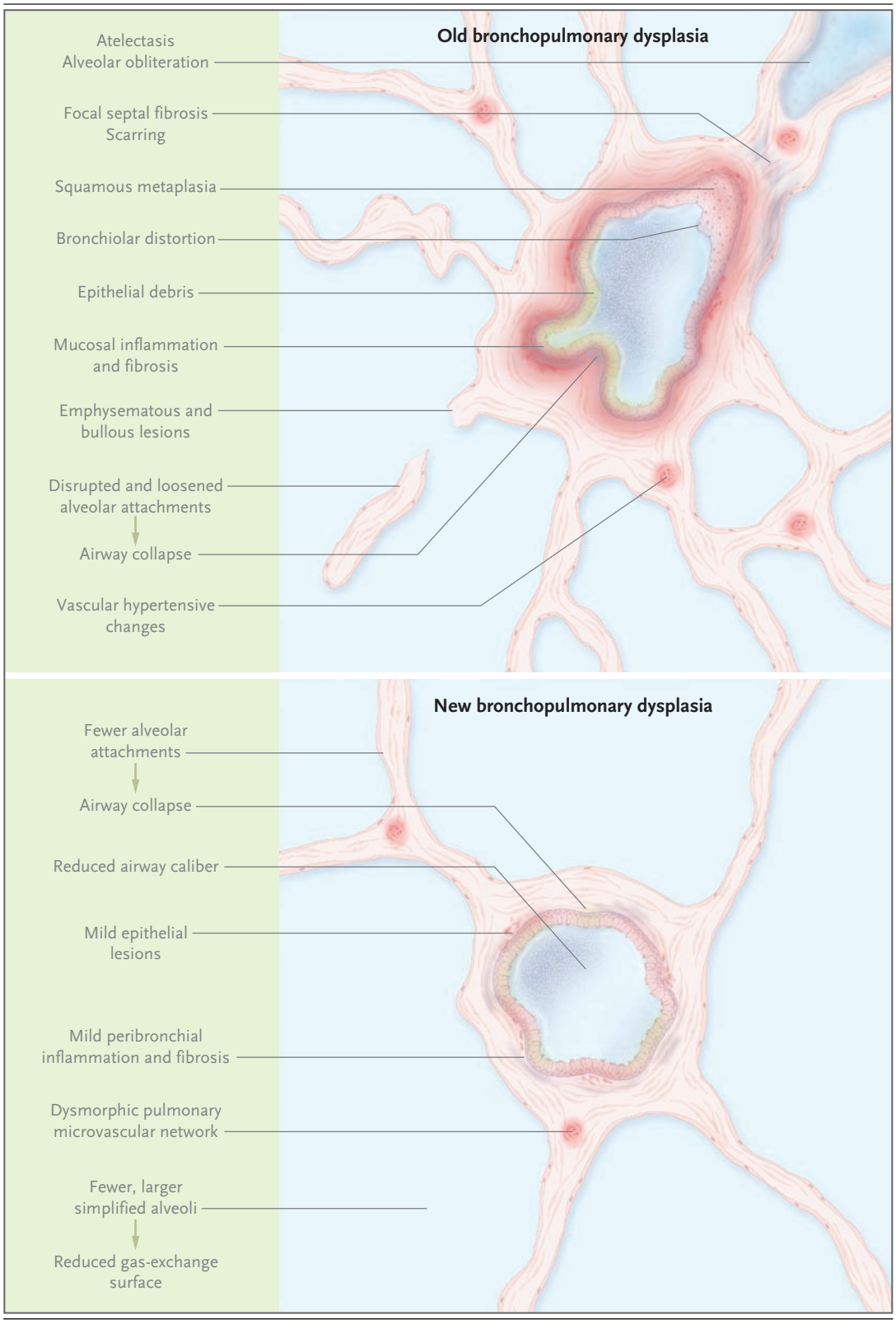
Figure 2 (facing page). Airway and Parenchymal Damage in Old and New Bronchopulmonary Dysplasia.

"Old" and "new" bronchopulmonary dysplasia are two different morphologic outcomes of variable combinations of factors capable of injuring lungs of differing maturity. In old bronchopulmonary dysplasia, intense inflammation and disruption of normal pulmonary structures lead to a nonhomogeneous airway and parenchymal disease. In contrast, the main feature of new bronchopulmonary dysplasia is diffusely reduced alveolar development, which is associated with a clinically significant loss of surface area for gas exchange, with airway injury, inflammation, and fibrosis that are usually milder than in old bronchopulmonary dysplasia.

Although eosinophil-driven inflammation is central in childhood asthma, exhaled nitric oxide (high levels of which are a biomarker of eosinophilic inflammation and responsiveness to corticosteroids) is reportedly normal in children with bronchopulmonary dysplasia.[45] Another difference is that airflow limitation is only partially reversed by β_2-agonists in children who had bronchopulmonary dysplasia in infancy, suggesting a stabilized remodeling process.[25,41,45] In addition, high-resolution computed tomographic studies have documented morphologic differences in the lungs between children with asthma and those with bronchopulmonary dysplasia. Although thickening of airway walls and areas of low attenuation may be seen in both diseases, scattered parenchymal fibrosis (linear opacities facing triangular subpleural opacities) and architectural distortion are common findings in survivors of bronchopulmonary dysplasia but are unusual in children with asthma.[56] Finally, preterm babies do not have an increased prevalence of atopy,[2,26] a major risk factor for childhood asthma. The term "asthma" should be used with caution because asthma and chronic lung disease are two separate clinical entities — some symptoms overlap, but the causal mechanisms, risk factors, responses to treatment, and natural history are different.[26,49,57]

TREATMENT

Good clinical trials of approaches to prevention and treatment have been conducted for evolving bronchopulmonary dysplasia[3,5,53] but not for persistent disease in childhood and adulthood.[3,10] Corticosteroid therapy is controversial. Because of



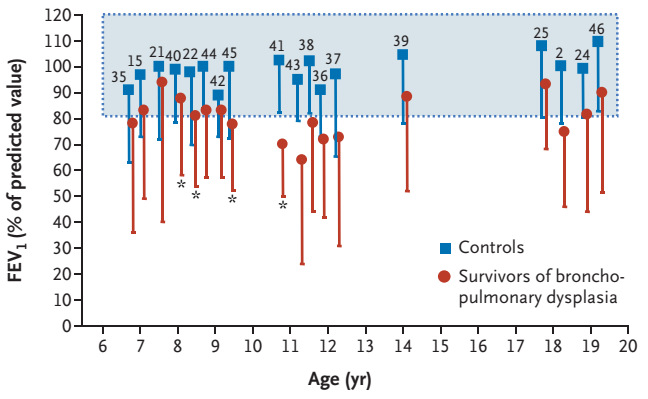


Figure 3. FEV_1 Values in Children, Adolescents, and Young Adults Who Were Born Prematurely and Had Bronchopulmonary Dysplasia, as Compared with Controls Born at Term.

Data (presented as means −2 SD) are from 18 studies, reported since 1990, in which survivors of bronchopulmonary dysplasia who were 6 to 19 years of age were compared with a reference population born at term. In all but two studies, the mean forced expiratory volume in 1 second (FEV_1) was significantly lower in the patients with bronchopulmonary dysplasia than in the healthy controls. Eighty percent of the predicted FEV_1 value is the accepted lower limit of the normal range. An asterisk indicates that the study was performed after the introduction of surfactant therapy. The studies were conducted in the United States,[2,15,35-37] Australia,[22,24,38,39] Finland,[21,40,41] Canada,[42,43] Italy,[44,45] Norway,[25] and the Netherlands.[46] The numbers within the graph refer to the reference numbers of the studies.

the clinically significant role of inflammation in the pathogenesis of bronchopulmonary dysplasia, systemic corticosteroids have long been used, and such treatment rapidly improves lung mechanics.[3,5] Currently, however, the routine use of corticosteroids in premature newborns is discouraged because of serious short-term adverse effects and the risk of neurodevelopmental impairment.[58] After discharge from the neonatal unit, infants with bronchopulmonary dysplasia may be given short courses of systemic corticosteroids for acute wheezing.[3] The use of inhaled corticosteroids for prophylaxis in children with established bronchopulmonary dysplasia has neither reduced the incidence of symptoms nor improved the outcome.[53-55,59]

Inhaled bronchodilators, including β_2-agonists and anticholinergic agents, can improve short-term lung function, but whether they can prevent exacerbations and improve the quality of life remains to be seen.[3,27,53] Without reliable evidence, it makes sense to use inhaled bronchodilators only in patients with clinical or functional signs of reversible airway obstruction and to treat exacerbations. When inhaled drugs are used, the method of administration is important. Metered-dose inhalers, with a spacer and mask, seem to have several advantages over nebulizers.[3,53]

The use of diuretics in infants with bronchopulmonary dysplasia can be associated with an improvement in lung mechanics. The role of continuous diuretic therapy is unclear,[5,27] but it is usually considered only for infants who are receiving high amounts of supplemental oxygen or who have associated cardiac failure.

Palivizumab (a humanized monoclonal antibody) can be used as prophylaxis against infection with respiratory syncytial virus. Such treatment should be considered for children less than 2 years old who require medical therapy for chronic lung disease within 6 months before the start of the season for the virus.[60]

Many pharmacotherapy issues remain to be explored in children with bronchopulmonary dysplasia.[10] For instance, it is not known whether treatment should be initiated when there is reduced lung function without the presence of symptoms. Furthermore, no studies have evaluated the efficacy of long-term use of antiinflammatory agents to prevent airway remodeling in patients with bronchopulmonary dysplasia. The use of leukotriene-receptor antagonists and long-acting β_2-agonists in these patients has not been explored.

NATURAL HISTORY OF AIRFLOW OBSTRUCTION

Lung function, as reflected by FEV_1, normally increases to a maximal value in early adulthood, remains stable for some years, and then declines (by about 30 ml per year) until senescence, never reaching values associated with disability.[61] The situation is more complex in susceptible subgroups of cigarette smokers, in whom the rate of decline may be rapid (about 60 ml per year) and in whom disabling obstructive airway disease may develop (Fig. 4). This model applies to persons with optimal lung development but not to those, such as survivors of bronchopulmonary dysplasia, in whom lung function is suboptimal because of damage in the perinatal period.[24,34] In some young-adult survivors of bronchopulmo-

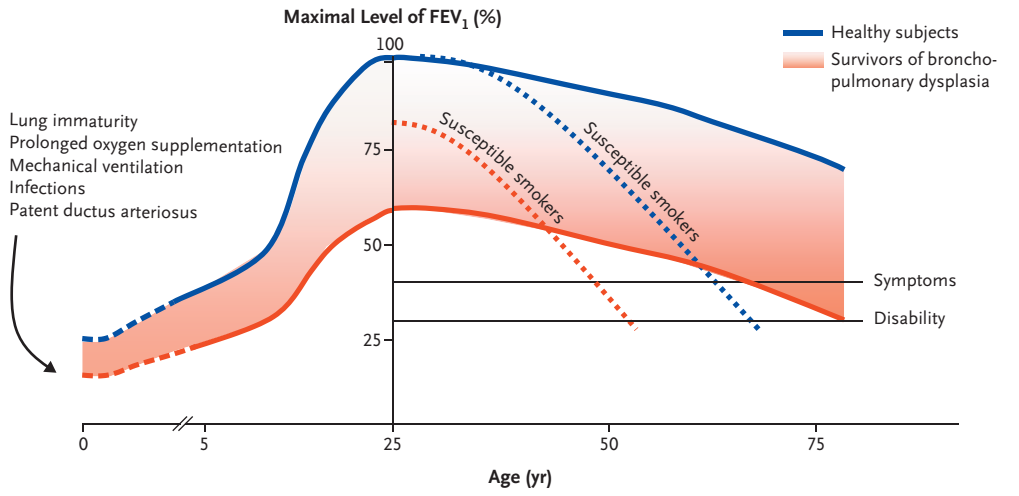


Figure 4. Theoretical Model of Changes in FEV_1 in Survivors of Bronchopulmonary Dysplasia and Healthy Subjects According to Age.

Theoretical curves are shown for the forced expiratory volume in 1 second (FEV_1) in healthy subjects and survivors of bronchopulmonary dysplasia. Survivors of bronchopulmonary dysplasia may have variable airflow limitation from the first years of life, with little evidence of "catch-up" growth in lung function. In some of these patients, FEV_1 does not reach the normal maximal value in early adulthood, and the phase of declining FEV_1 values starts from a substantially reduced maximal value. Whether the rate of decline with advancing age will parallel that among healthy persons or will be accelerated is not known. The dashed lines represent the potential effect of smoking on the rate of decline of FEV_1 in susceptible subjects. Values for FEV_1 in the first 3 years of life are extrapolated from measurements of maximal flow at functional residual capacity. Adapted from Fletcher and Peto.[61]

nary dysplasia, the maximal FEV_1 value is less than 80% of the predicted value (Fig. 3).[24,46] It is not known whether the decline in respiratory function in adults who had bronchopulmonary dysplasia as children will be normal or whether it will be early or accelerated. Smoking is a well-known risk factor for a steeper age-related decline in lung function[61] and the development of chronic obstructive pulmonary disease (COPD) in later life. Almost 30% of people born prematurely smoke as young adults,[24,25] and the reduction in respiratory function is several times greater for them than for smokers who were born at term.[62] Efforts to prevent smoking among people who were born prematurely should be actively promoted.

Some investigators have expressed concern that survivors of preterm birth and bronchopulmonary dysplasia may be susceptible to COPD in later life.[2,5,24,25,50] There may be an overlap in the clinical and physiological characteristics of the two conditions, but longer follow-up and data on lung pathological findings in long-term survivors of bronchopulmonary dysplasia will be needed before it can be included in the well-established diagnosis of COPD.

CONCLUSIONS AND FUTURE DIRECTIONS

Chronic lung disease can no longer be considered only a pediatric disease. For some infants born prematurely, especially those with bronchopulmonary dysplasia, substantial obstructive lung disease persists into adolescence and young adulthood. This pulmonary derangement remains latent in most people, but a reduced respiratory reserve could increase the risk of a COPD-like phenotype later in life. Advances in neonatal care have increased survival after preterm birth. Because many of these survivors are now approaching adulthood, family doctors and chest physicians will be seeing more cases of this novel chronic pulmonary disease, which begins in neonatal life.

The pathogenesis of bronchopulmonary dys-

plasia is still elusive, and its treatment is empirical. Tools should be developed for phenotype-specific diagnosis and management of chronic lung disease. Long-term surveillance studies will be needed if we are to better understand the natural history of chronic lung disease after premature birth.

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