

Long-Term Pulmonary Outcome in the Preterm Infant

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Key Words

Prematurity · Bronchopulmonary dysplasia · Lung function · Airway obstruction

Abstract

Chronic respiratory morbidity is common following premature birth, particularly if complicated by the development of bronchopulmonary dysplasia (BPD). Affected infants can remain oxygen dependent for many months and frequently require hospital readmission in the first 2 years after birth. Troublesome, recurrent respiratory symptoms requiring treatment are common in prematurely born children, especially those who had BPD. The most severely affected may remain symptomatic and have evidence of airway obstruction even as adults. The studies examining adolescents and adults usually report patients who had 'classical' BPD, that is they often had had severe respiratory failure in the neonatal period with chronic pulmonary fibrosis and airway smooth muscle hypertrophy. Nowadays, infants are described as having 'new' BPD, developing chronic oxygen dependence despite initially minimal or even no respiratory distress. Affected patients, however, have reduced alveolarisation and experience deterioration in lung function over the 1st year after birth. It is essential to determine if they have 'catch up' and identify which strategies impair and most importantly promote lung growth in this very-high-risk population.

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Introduction

Chronic respiratory morbidity is a common adverse outcome of premature birth, particularly in infants who develop bronchopulmonary dysplasia (BPD). Unfortunately, BPD occurs frequently in infants born very prematurely, affecting in one series more than 40% of infants born prior to 29 weeks of gestation [1] and in another 77% of 4,866 infants born prior to 32 weeks of gestation with a birth weight of less than 1 kg [2]. Various criteria have been used to diagnose BPD, but at a National Institute of Child Health and Human Development sponsored workshop [3] a consensus was reached that BPD should be diagnosed if an infant remained oxygen dependent for at least 28 days. In addition, infants are reassessed at a later date according to their maturity at birth to determine whether they had mild, moderate or severe BPD [3]. Infants so diagnosed have been demonstrated to be at high risk of adverse pulmonary and neurodevelopmental outcomes in infancy [2].

This review describes the long-term pulmonary outcome of preterm infants, particularly those who developed BPD. The reports of older children and adults include patients who had 'classical' BPD, who often had had severe respiratory failure in the neonatal period with pulmonary fibrosis and airway smooth muscle hypertrophy. Nowadays, infants may become chronically oxygen dependent despite minimal or even no respiratory distress immediately after birth and are described as suffering

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from 'new' BPD [4]. Such infants have less inflammation and fibrosis but at postmortem have dilatation of the distal gas exchange units and reduced alveolarisation [5], perhaps resulting from interference/interruption of the normal signalling for terminal maturation of alveolarisation of the lungs [4]. Impaired angiogenesis during BPD may lead to decreased alveolarisation [6]. Whether affected children experience catch-up growth is not known; if they do not, then their long-term outcome could potentially be worse than that of those who had classical BPD.

Pulmonary Outcomes

Chronic Oxygen Dependence

Preterm infants with BPD may require supplementary oxygen for many months or even years [7], although few remain oxygen dependent beyond 2 years of age [8]. Provision of supplementary oxygen at home allows earlier discharge from hospital but can adversely affect a family's quality of life [9]. Infants requiring supplementary oxygen at home have the most severe lung disease, as evidenced by their need for hospital readmission in the first 2 years after birth being twice that of those with BPD who are not home oxygen dependent [7]. In addition, even when they are no longer home oxygen dependent, they still have more outpatient attendances and are more likely to wheeze and require an inhaler between 2 and 5 years of age [8].

Rehospitalisation

In the first 2 years after birth, readmission to hospital is common, particularly in infants with BPD. In one series, 73% of infants with BPD required at least one readmission and 27% had three or more readmissions [10]. The majority of admissions are for respiratory disorders and rehospitalisation is particularly increased in infants, regardless of BPD status, who have a respiratory syncytial virus lower respiratory tract infection [11]. Hospitalisation rates decline after the 2nd year being infrequent in 14-year-old children who had been born preterm, regardless of their BPD status [12].

Respiratory Symptoms

Recurrent respiratory symptoms requiring treatment are common in prematurely born children, particularly in those who had BPD. Examination of 492 infants born prior to 29 weeks of gestational age from the United Kingdom Oscillation Study revealed that 27% were coughing and 20% wheezing at both 6 and 12 months and 6% were

coughing and 3% wheezing more than once a week [13]. Fourteen percent had taken bronchodilators and 8% inhaled steroids [13]. BPD was a significant risk factor for wheeze (odds ratio 2.7) and medication requirement (odds ratio 2.4); male gender was a significant risk factor for all adverse pulmonary outcomes. Recurrent wheezing illness is also common in the first 2 years after birth in infants who had respiratory distress syndrome without subsequent BPD, being at least twice more likely than in controls [14]. At preschool age respiratory symptoms remain common; in one BPD cohort, 28% coughed more than once a week and 7% wheezed more than once a week [8]. In another study, approximately one third of prematurely born preschool children, regardless of BPD status, coughed in the last 12 months and more than 10% wheezed [15]; the BPD children, however, had worse lung function as assessed by the forced oscillation and interruption techniques. At school age, prematurely born children, particularly if they had BPD, are more likely to be symptomatic than their classroom colleagues born at term. In a cohort of 7- to 8-year-olds, whereas 30% of BPD children and 24% of prematurely born children without BPD were wheezing only 7% of term controls were so affected [16]. The most severely affected remain symptomatic in adulthood; in one series, 23% of young adults who had BPD had respiratory symptoms, wheeze and need for long-term medication [17]. Similarly, in a nationwide follow-up study in the Netherlands, the prevalence of doctor-diagnosed asthma was significantly higher in 19-year-olds born prior to 32 weeks of gestation than age-matched controls [18]. There was, however, an effect of gender. Whereas women who had had BPD had more asthma (24 vs. 5%; $p = 0.001$) and shortness of breath during exercise (43 vs. 16%; $p = 0.008$) than the controls, the prevalence of reported symptoms by men who had had BPD was similar to the controls [18]. Different patterns of thoracic growth in term-born children leads at the end of puberty to approximately 25% improved lung function in males than females. The authors therefore speculated that a similar process may take place in the prematurely born population and explain the differences they found in symptoms according to gender [18].

Lung Function Abnormalities

Studies of prematurely born infants with BPD at 36 weeks' postmenstrual age and at term showed they have lower lung volumes [19, 20]; they also have reduced gas-mixing efficiency at term [20]. These findings are suggestive of impairment of lung development. Prematurely born infants, particularly those who were wheezing at

follow-up, have airway obstruction (a raised airway resistance and gas trapping) in the first 2 years after birth [21]. These findings have been confirmed in a recent study which additionally highlighted that the number of days of wheeze significantly correlated with the degree of gas trapping in very prematurely born infants [22]. As the children improve clinically with increasing age, their lung function improves, but even at school age, particularly in those with ongoing recurrent respiratory symptoms, evidence of poor airway growth persists. Indeed, at 8–9 years of age, children born before 28 weeks of gestation and extremely low birth weight (<1,000 g) compared to controls had substantially diminished respiratory function reflecting airflow abnormalities [23]. These abnormalities are particularly marked in children who had had BPD; in one series, 83% of those who had BPD and 23% of those born prematurely without BPD had evidence of bronchial obstruction at 8–14 years of age; 79% of those with bronchial obstruction were symptomatic [24]. In addition, school age children with BPD have reduced absolute and size-corrected flow rates compared with controls matched for age and size [25]. A strong correlation was demonstrated between the maximum flow at functional residual capacity at 2 years of age and forced expiratory volume in 1 s at school age, suggesting persistent airflow limitation in some patients with BPD [25]. Gas transfer is also abnormal in young children who had BPD, with reduced gas transfer (DLCO) and alveolar volume (VA) at rest and a lack of increase in DLCO/VA dur-

ing exercise suggesting reduced alveolar surface area [26]. In adolescents evidence of airway obstruction and hyper-reactivity and an increased responsiveness to histamine have been documented [27, 28]; in addition, apparently asymptomatic BPD patients desaturate on exercise [29]. The worst affected have evidence of airway obstruction in adulthood [17], 52% of a cohort who had severe BPD had reactive airway disease and 24% had fixed airway obstruction.

Although few of the present population of very preterm infants require very high levels of respiratory support, they are exposed to other insults which could have long-term effects on their lung function. Chorioamnionitis is a common precipitant of preterm labour and alveolarisation is suppressed following exposure to intra-amniotic endotoxin [30]. Administration of betamethasone in animal models results in a similar effect [30], and prematurely born infants are routinely exposed to antenatal corticosteroids. Unfortunately, early abnormal lung function appears to increase the risk of symptomatic respiratory syncytial virus lower respiratory tract infection [31], and this is associated with chronic respiratory morbidity in prematurely born children, with [10] or without BPD [11]. The lung function of prematurely born infants declines over the 1st year after birth [32, 33]. It is essential to determine if they have ‘catch up’ and identify which strategies impair and most importantly promote lung growth in this very-high-risk population.

References

- Johnson AH, Peacock JL, Greenough A, Marlow N, Limb ES, Marston L, Calvert SA; for the United Kingdom Oscillation Study Group: High frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. *N Engl J Med* 2002;347: 633–642.
- Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, Wrage LA, Poole K; for the National Institutes of Child Health and Human Development Neonatal Research Network: Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics* 2005;116:1353–1360.
- Jobe AH, Bancalari E: Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001; 163:1723–1729.
- Jobe AH: The new bronchopulmonary dysplasia: an arrest of lung development. *Pediatr Res* 1999;46:641–643.
- Husain AN, Siddiqui NH, Stocker JT: Pathology of arrested acinar development in postsurfactant bronchopulmonary dysplasia. *Hum Pathol* 1998;29:710–717.
- Thebaud B: Angiogenesis in lung development, injury and repair: implications for chronic lung disease of prematurity. *Neonatology* 2007;91:291–297.
- Greenough A, Alexander J, Burgess S, Chetcuti PAJ, Cox S, Lenney W, Turnbull F, Shaw NJ, Woods A, Boorman J, Coles S, Turner J: Home oxygen status on rehospitalisation and primary care requirements of chronic lung disease infants. *Arch Dis Child* 2002;86: 40–43.
- Greenough A, Alexander J, Burgess S, Bytham J, Chetcuti PAJ, Hagan J, Lenney W, Melville S, Shaw NJ, Boorman J, Coles S, Pang F, Turner J: Preschool health care utilisation related to home oxygen status. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F337–F341.
- McLean A, Townsend A, Clark J, Sawyer MG, Baghurst P, Haslam R, Whaites L: Quality of life of mothers and families caring for preterm infants requiring home oxygen therapy: a brief report. *J Paediatr Child Health* 2000;36:440–444.
- Greenough A, Alexander J, Burgess S, Chetcuti PAJ, Cox S, Lenney W, Turnbull F, Shaw NJ, Woods A, Boorman J, Coles S, Turner J: Health care utilisation of chronic lung disease infants related to hospitalisation for respiratory syncytial virus infection. *Arch Dis Child* 2001;85:463–468.
- Broughton S, Roberts A, Fox G, Pollina E, Zuckerman M, Chaudhry S, Greenough A: Prospective study of health care utilisation and respiratory morbidity due to RSV infection in prematurely born infants. *Thorax* 2005;60:1039–1044.

- 12 Doyle LW, Cheun MMH, Ford GW, Olinsky A, Davis NM, Callanan C: Birth weight <1,501 g and respiratory health at age 14. *Arch Dis Child* 2001;84:40–44.
- 13 Greenough A, Limb E, Marston L, Marlow N, Calvert S, Peacock J: Risk factors for respiratory morbidity in infancy following very premature birth. *Arch Dis Child* 2005;90: F320–F323.
- 14 Koivisto M, Marttila R, Saarela T, Pokela ML, Valkama AM, Hallman M: Wheezing illness and rehospitalisation in the first two years of life after neonatal respiratory distress syndrome. *J Pediatr* 2005;147:486–492.
- 15 Vrijlandt EJ, Boezen KM, Gerritsen J, Stremelaar EF, Duiverman EJ: Respiratory health in prematurely born school children with and without bronchopulmonary dysplasia. *J Pediatr* 2007;150:256–261.
- 16 Gross SJ, Iannuzzi DM, Kveselis DA, Anbar RD: Effect of preterm birth on pulmonary function at school age: a prospective controlled study. *J Pediatr* 1998;133:188–192.
- 17 Northway WH Jr, Moss RB, Carlisle KB, Parker BR, Popp RL, Pitlick PT, Eichler I, Lamm RL, Brown BW Jr: Late pulmonary sequelae of bronchopulmonary dysplasia. *N Engl J Med* 1990;323:1793–1799.
- 18 Vrijlandt EJ, Gerritsen J, Marike Boezen H, Duiverman EJ; the Dutch POPS-19 Collaborative Study Group: Gender differences in respiratory symptoms in 19-year-old adults born preterm. *Respir Res* 2005;6:117.
- 19 Greenough A, Dimitriou G, Bhat RY, Broughton S, Hannam S, Rafferty GF, Leipala JA: Lung volumes in infants who had mild to moderate bronchopulmonary dysplasia. *Eur J Pediatr* 2005;164:583–586.
- 20 Hjalmarson O, Sandberg KL: Lung function at term reflects severity of bronchopulmonary dysplasia. *J Pediatr* 2005;146:86–90.
- 21 Yuksel B, Greenough A: Relationship of symptoms to lung function abnormalities in preterm infants at follow-up. *Pediatr Pulmonol* 1991;11:202–206.
- 22 Broughton S, Thomas MR, Marston L, Calvert SA, Marlow N, Peacock JL, Rafferty GF, Greenough A: Very prematurely born infants wheezing at follow up – lung function and risk factors. *Arch Dis Child* 2007;92: 776–780.
- 23 Doyle LW; the Victorian Infant Collaborative Study Group: Respiratory function at age 8–9 years in extremely low birthweight/very preterm children born in Victoria in 1991–1992. *Pediatr Pulmonol* 2006;41:570–576.
- 24 Pelkonen AS, Hakulinen AL, Turpeinen M: Bronchial lability and responsiveness in school children born very preterm. *Am J Respir Crit Care Med* 1997;156:1178–1184.
- 25 Filippone M, Sartov M, Zachello F, Banaldi E: Flow limitation in infants with BPD and respiratory function at school age. *Lancet* 2003;361:753–754.
- 26 Mitchell SH, Teague WG, Robinson A: Reduced gas transfer at rest and during exercise in school age survivors of bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 1998;157:1406–1412.
- 27 Koumbourlis AC, Motoyama EK, Mutich RL, Mallory GB, Walczak SA, Fertal K: Longitudinal follow up of lung function from childhood to adolescence in prematurely born patients with neonatal chronic lung disease. *Pediatr Pulmonol* 1996;21:28–34.
- 28 Allen J, Zwerdling R, Ehrenkranz R, Gaultier C, Geggel R, Greenough A, Kleinman R, Klijanowicz A, Martinez F, Ozdemir A, Panitch HB, Nickerson B, Stein MT, Tomezsko J, Van Der Anker J; for the American Thoracic Society: Statement on the care of the child with chronic lung disease of infancy and childhood. *Am J Respir Crit Care Med* 2003;168:356–396.
- 29 Santuz P, Baraldi E, Zaramella P, Filippone M, Zachello F: Factors limiting exercise performance in long term survivors of bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 1995;152:1284–1289.
- 30 Willer KE, Jobe AH, Ikegami M, Newnham J, Brennan S, Sly PD: Antenatal endotoxin and glucocorticoid effects on lung morphology in preterm lambs. *Pediatr Res* 2000;48: 782–788.
- 31 Broughton S, Bhat R, Roberts A, Zuckerman M, Rafferty GF, Greenough A: Diminished lung function, RSV infection and respiratory morbidity in prematurely born infants. *Arch Dis Child* 2006;91:26–30.
- 32 Hofhuis W, Huysman MW, Van Der Wiel EC, Holland WP, Hop WC, Brinkhorst G, de Jongste JC, Merkus PJ: Worsening of VMax FRC in infants with chronic lung disease in the first year of life: a more favourable outcome after high frequency oscillation ventilation. *Am J Respir Crit Care Med* 2002;166: 1539–1543.
- 33 Hoo AF, Dezateux C, Henschen M, Costeloe K, Stocks J: Development of airway function in infancy after preterm delivery. *J Pediatr* 2002;141:652–658.