



# Late respiratory outcomes after preterm birth

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## KEYWORDS

Prematurity;  
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dysplasia;  
Lung function;  
Airways obstruction

## Abstract

Chronic respiratory morbidity is common following premature birth, particularly if complicated by bronchopulmonary dysplasia (BPD) development. Affected patients can remain oxygen dependent for many months, but unusually beyond two years. Those requiring supplementary oxygen at home have increased healthcare utilisation, even during the preschool years when no longer oxygen dependent. More than 50% of "BPD" patients require readmission in the first two years, particularly for respiratory infections. Prematurely born children, especially those who had BPD, are more likely to suffer frequent troublesome symptoms at school age and in adolescence than term born controls. This is associated with evidence of airways obstruction. Although lung function improves as the clinical condition improves, abnormalities can be detected even in young adults who had severe BPD. Nowadays, severe BPD is uncommon, but those with "new" BPD may have abnormal antenatal lung growth, whether they achieve appropriate catch up lung growth needs careful investigation.

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## 1. Introduction

Chronic respiratory morbidity is a common outcome of neonatal intensive care, particularly in infants who developed bronchopulmonary dysplasia (BPD). BPD occurs frequently in infants born very prematurely, affecting more than 40% of infants born prior to 29 weeks of gestation in one series [1]. Various criteria have been used to diagnose BPD including oxygen dependency beyond 28 days or 36 weeks postmenstrual age (PMA) with or without chest radiograph abnormalities at those times. At a National Institute of Child Health and Human Development sponsored (NICHD) workshop [2] a consensus was reached that BPD should be

diagnosed if an infant remained oxygen dependent for at least 28 days. Infants are then reassessed at a later date to determine whether they had mild, moderate or severe BPD [2] (Table 1). This consensus definition compared to previous definitions of BPD more accurately correlates with a spectrum of risk for adverse pulmonary and neurodevelopmental outcomes in early infancy [3]. A major problem in diagnosing BPD is that there has been no agreement regarding the criteria for instituting supplementary oxygen. A survey of the Vermont Oxford Network highlighted that pulse oximetry saturation thresholds for instituting supplementary oxygen varied from lower than 84% to lower than 96% with only 41% of the respondents using the same criteria (<90%) [4]. Many institutions, however, have now introduced an oxygen reduction test to enable more accurate diagnosis of an ongoing supplementary oxygen requirement.

In the past, infants who developed BPD often had had severe respiratory failure in the neonatal period and, at postmortem, fibrosis and airway smooth muscle hypertrophy

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**Table 1** Classification of severity of BPD in infants born at less than 32 weeks of gestation and assessed at 36 weeks PMA

Mild BPD	Breathing room air
Moderate BPD	Need for <30% oxygen at 36 weeks PMA
Severe BPD	Need for >30% oxygen and/or positive pressure support (IPPV or nCPAP)

Modified from the NICHD workshop report [2].

were prominent. Such infants are described as suffering from “classical” BPD. Nowadays, infants may become chronically oxygen dependent despite minimal or even no respiratory distress immediately after birth and are described as suffering from “new” BPD. The few pathological reports of new BPD [5] highlight dilation of the distal gas exchange units and decreased alveolarisation, but minimal small airway injury and less inflammation and fibrosis. It has been proposed that “new” BPD is not the injury/repair paradigm of traditional BPD, but a maldevelopment sequence resulting from interference/interruption of normal signalling for terminal maturation of alveolarisation of the lungs of very prematurely born infants [3].

This review describes the long-term respiratory outcome of prematurely born infants, particularly those who developed BPD. It should be noted that the reports of older children and adults usually include patients who had classical BPD. The long-term outcome of new BPD is not known, as new BPD has only relatively recently been diagnosed. The data from affected preschool children, however, demonstrate they too suffer chronic respiratory morbidity [6]. A concern is whether they will fail to achieve appropriate catch-up lung growth postnatally [7] and thus may suffer worsening problems with increasing age.

## 2. Late respiratory outcomes

### 2.1. Supplementary oxygen at home—“home oxygen”

Prematurely born infants may require supplementary oxygen at home for many months. Lung growth and remodelling, however, results in progressive improvement in pulmonary function and few BPD patients remain oxygen dependent beyond two years of age [6]. Infants are usually sent home on oxygen when they have no other medical problem, but some units allow infants who require nasogastric tube feeding home on supplementary oxygen, if there is appropriate support in the community [8]. That policy allows earlier discharge and, in a four centre study, no increase in subsequent admissions was demonstrated; indeed, it was associated with a lower total cost of care [8]. Nevertheless, overall infants who require home oxygen compared to other BPD infants require twice the number of hospital readmissions in the first two years [9] and even when they are no longer oxygen dependent they still have more outpatient attendances and are more likely to wheeze and require an inhaler with a doubling of the cost of care between years two to five [6]. Although use of home oxygen allows earlier discharge from the neonatal unit, it can adversely impact on

families. Use of a parental completed quality of life questionnaire revealed that, after controlling for gestational age, postnatal age, birthweight and type of residence, parents of infants on home oxygen compared to those whose infants no longer required home oxygen or had never required it, had less desire to go out, saw their friends and family less often and were more likely to complain of fatigue [10].

### 2.2. Rehospitalisation

More than 50% of infants with BPD require readmission to the hospital during early childhood. In one series of 235 BPD infants, only 27% were never readmitted during the first two years after birth and another 27% had at least three readmissions; the maximum was twenty [9]. The readmission rate is highest in those infants who have had a respiratory syncytial virus (RSV) infection and/or required supplementary oxygen at home. The high rate of hospitalization declines during the second year with few readmissions in the third year after birth [6]. Indeed, at 14 years, hospitalisation was found to be infrequent in prematurely born children regardless of whether they had or had not had BPD [11].

### 2.3. Respiratory symptoms

At least 50% of very prematurely born (<32 weeks of gestation) infants are symptomatic in the first year and 35% in the preschool years. They are much more likely to be symptomatic than children born at term of similar age. In one series [12], infants born prior to 33 weeks of gestation were five times more likely to wheeze than term born controls. Risk factors for wheeze were prolonged oxygen dependency, a family history of atopy, siblings at home and maternal smoking [12]. Not only are prematurely born infants likely to be symptomatic at follow up, but they are likely to suffer frequent symptoms. Follow-up of 492 infants born prior to 29 weeks of gestational age 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]. The symptoms were troublesome as indicated by the need for medication; 14% of the infants 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 risk factor for every adverse respiratory outcome [13]. Even during the preschool years, 28% of a BPD cohort coughed more than once a week and 7% wheezed more than once a week, this was associated with on average 10 (maximum 68) visits to the general practitioner during the three year period [6].

At school age, prematurely born infants, particularly if they had BPD are more likely to be symptomatic than their classroom colleagues born at term. In a cohort of seven to eight 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 [14]. In addition, review of eight to nine year olds in another study [15], demonstrated that those born very low birthweight were more likely to use inhalers, be absent from school or require admission for respiratory illness. There is also evidence that this adverse respiratory outcome may persist into adulthood [16]. Northway et al. [16] reported that 23% of young adults who had BPD currently had respiratory symptoms, wheezing and need for

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