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## Chronic respiratory morbidity following premature delivery – prediction by prolonged respiratory support requirement?

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**Abstract** Neonatal chronic lung disease (CLD) is usually diagnosed if an infant remains oxygen dependent beyond 36 weeks postconceptional age (PCA). Our aim was to determine whether a shorter duration of respiratory support accurately predicted subsequent respiratory morbidity. A total of 103 infants, median gestational age 29 weeks (range 23–35), were followed prospectively for 5 years. They had a birth weight of <1500 g or, if a birth weight of between 1500 and 2000 g, had required neonatal ventilatory support. Parents completed diary cards; their child had positive symptom status if, in any one year, they coughed and/or wheezed on at least 3 days per week for a 4-week period or for at least 3 days following each upper respiratory tract infection. Subsequent respiratory morbidity, positive symptom status in years 1 and 2 or all 5 pre-school years, was related to various definitions of prolonged respiratory support: intermittent positive pressure ventilation dependence >7 days; oxygen dependence >28 days and oxygen dependence >36 weeks PCA. In years 1 and 2, 25 children were symptomatic and 22 in all 5 years. The patients with subsequent respiratory morbidity were distinguished from those without by requiring longer respiratory support ( $P < 0.05$ ). Logistic regression analysis demonstrated only oxygen dependence beyond 28 days was independently related to subsequent respiratory morbidity ( $P < 0.01$ ). The positive predictive values and likelihood ratios (95% confidence intervals) for positive symptom status in all 5 years were for intermittent positive pressure ventilation >7 days 35% (16–53) and 19.5 (1.01–3.76), for oxygen dependency >28 days 42% (23–61) and 2.20 (1.45–5.02) and for oxygen dependency >36 weeks PCA 35% (13–58) and 1.67 (0.65–4.31).

**Conclusion** Oxygen dependency at 28 days of age remains a useful criterion on which to diagnose “neonatal” chronic lung disease.

**Key words** Chronic lung disease · Prematurity

**Abbreviations** CLD Chronic lung disease · PCA Post conceptional age

### Introduction

Chronic lung disease (CLD) following premature birth has been variously defined [13]. Oxygen dependency beyond 36 weeks post conceptional age (PCA), however, is presently the most frequently used definition. That

criterion was adopted following a review of the records of 605 very low birth weight infants which demonstrated that, whereas oxygen dependency at 28 days had a positive predictive value of only 38% for abnormal pulmonary findings at follow up. This value improved to 63% if oxygen dependency beyond 36 weeks PCA was

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used [11]. There are, however, limitations to that study [11]. Certain of the criteria for diagnosis of abnormal pulmonary outcome were non-specific and, therefore, could have encompassed infants with non-respiratory problems. Secondly, a combination of short- and long-term outcome criteria were used which would tend to increase the predictive value. Thirdly, the period of follow up of 2 years was relatively short, particularly when one considers that a significant proportion of children born prematurely remain symptomatic throughout the pre-school years [7]. Interestingly, when positive symptom status throughout the first 5 years was used to define abnormal respiratory outcome [7], then oxygen dependency beyond 36 weeks PCA did not relate significantly to it. There is also a practical problem in using oxygen dependency beyond 36 weeks as a criterion on which to diagnose CLD and that is if an infant is born at 24 weeks of gestation he or she is 3 months of age before the diagnosis can be made. This may not matter if the occurrence of CLD is simply being used to audit new strategies, but a possibly important delay will have been introduced if the diagnosis of CLD is being used as a criterion on which to introduce therapies with the hope of influencing long-term outcome. The aim, therefore, of this study was to determine whether a shorter duration of respiratory support could be used to accurately predict abnormal respiratory status in the first 5 years of life, when diagnosed using specific respiratory adverse sequelae.

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## Patients and methods

### Methods

Analysis was made of the results of prematurely born infants with a birth weight <1500 g and a birth weight between 1500 g and 2000 g and requiring mechanical ventilation recruited into a previously reported prospective follow up study [7]. The infants were born between February 1989 and February 1992. Once discharged from the neonatal unit, patients were kept under regular clinical review at least at 6-monthly intervals and their respiratory symptoms documented. At each review, parents were asked about their child's symptoms during the period from the previous review. This was cross checked against the information they recorded prospectively, that is, parents were asked to record symptoms in a standardised diary card in the month prior to each review. The diary cards were assessed independently of the child's case notes. Children were defined as symptomatic in any one year, if they wheezed and/or coughed for more than 3 days a week over a 4-week period or if they wheezed and/or coughed for at least 3 days following upper respiratory tract infections [6, 15].

### Patients

A total of 164 infants survived until discharge during the study period, 3 died during follow up, 30 moved out of the area and 28 did not return for follow up. The remainder, 103 infants (54 males), median gestational age 29 weeks (range 23–35) and birth weight 1248 g (range 506–1950) were followed [7]. Of the mothers, 19 had received antenatal steroids and five infants postnatal surfactant. Their median duration of mechanical ventilation was 2 days (range 0–75) and of oxygen dependency 5 days (range 0–720). Some

infants (26) were ventilated for longer than 1 week, 26 were oxygen-dependent beyond 28 days and 17 beyond 36 weeks PCA. Infants were nursed in sufficient ambient oxygen to maintain their oxygen saturation between 90% and 96%. The prospective follow up study was approved by King's College Hospital Ethics Committee and parents gave informed consent for their child to take part.

### Analysis

Three definitions of a prolonged duration of respiratory support were compared: mechanical ventilation >7 days, oxygen dependency >28 days and oxygen dependency >36 weeks PCA. The definitions were then related to subsequent respiratory morbidity, that is positive symptom status in years 1 and 2 or all 5 years. Differences between infants with and without subsequent respiratory morbidity were assessed for statistical significance using the Mann Whitney U-test or Chi-squared test. The sensitivity, specificity, positive and negative predictive values and positive likelihood ratios of each definition of prolonged respiratory support were calculated for each of the adverse outcomes. Logistic regression analysis was then undertaken to determine which definition of prolonged respiratory support related most significantly to subsequent respiratory morbidity.

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## Results

Twenty-five children were symptomatic in years 1 and 2 and 22 in all 5 years. Patients symptomatic in years 1 and 2 differed significantly from those who were asymptomatic regarding their duration of ventilatory support ( $P < 0.05$ ) and oxygen dependency ( $P < 0.05$ ). In addition, more were oxygen-dependent at 28 days ( $P < 0.01$ ) and 36 weeks PCA ( $P < 0.05$ ) (Table 1). Children who were symptomatic in all 5 years differed significantly from the rest of the cohort with regard to requiring a longer duration of ventilatory support ( $P < 0.01$ ) and oxygen dependency ( $P < 0.05$ ), in addition more were oxygen-dependent at 28 days ( $P < 0.01$ ). Oxygen dependency >28 days had the highest positive predictive values and positive likelihood ratios for positive symptom status in all 5 years (Table 2). Logistic regression analysis demonstrated only oxygen dependency beyond 28 days was independently related to either definition of subsequent respiratory morbidity ( $P < 0.01$ ).

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## Discussion

Oxygen dependency at 28 days, but not at 36 weeks PCA, was independently related to subsequent respiratory morbidity. This contrasts with previous findings [11]. It had been suggested [11] that the 28-day criterion was useful for infants more mature than 30 weeks gestational age and an increasingly poor predictor of subsequent pulmonary outcome as gestation decreased. Our results do not confirm those findings, as our population included infants as immature as 23 weeks of gestational age. We do not feel differences in steroid usage were responsible for the conflicting results. The earlier study [11] was carried out before the meta-analysis of

**Table 1** Comparison of infants with and without subsequent respiratory morbidity. (IPPV intermittent positive pressure ventilation)

	Symptom status years 1 and 2	
	<i>n</i>	
Results are expressed as <i>n</i> or median (range)		
<i>n</i>	25	78
Birth weight (g)	1092 (566–1950)	1275 (506–1800)
Gestational age (weeks)	28 (24–34)	29 (23–35)
Antenatal steroids	1	18
IPPV (days)	5 (0–49)	1 (0–75)
Oxygen dependency (days)	14 (0–720)	4 (0–390)
IPPV > 1 week	9	17
Oxygen dependency > 28 days	12	14
Oxygen dependency > 36 weeks	8	9
Symptom status all 5 years		
<i>n</i>	+	–
<i>n</i>	22	81
Birth weight (g)	1100 (566–1800)	1270 (506–1920)
Gestational age (weeks)	28 (24–35)	29 (23–34)
Antenatal steroids	1	18
IPPV (days)	5 (0–49)	1 (0–75)
Oxygen dependency (days)	23 (0–720)	4 (0–390)
IPPV > 1 week	9	17
Oxygen dependency > 28 days	11	15
Oxygen dependency > 36 weeks	6	11

**Table 2** Prediction of subsequent respiratory morbidity. (The 95% confidence intervals for each value are given in brackets)

	Sensitivity	Specificity	Positive predictive	Negative values	Positive likelihood ratio
Positive symptom status in years 1 and 2					
IPPV > 1 week	36% (17–55)	78% (69–87)	35% (16–53)	79% (70–88)	1.74 (0.9–3.39)
Oxygen dependency > 28 days	48% (28–68)	82% (74–91)	46% (27–65)	83% (75–91)	2.82 (1.52–5.25)
Oxygen dependency > 36 weeks PCA	32% (14–50)	89% (81–96)	47% (23–71)	80% (72–89)	2.56 (1.07–6.15)
Positive symptom status in all 5 years					
IPPV > 1 week	41% (20–61)	79% (70–88)	35% (16–53)	83% (75–91)	1.95 (1.01–3.76)
Oxygen dependency > 28 days	50% (29–71)	81% (73–90)	42% (23–61)	86% (78–94)	2.20 (1.45–5.02)
Oxygen dependency > 36 weeks PCA	27% (9–46)	86% (79–94)	35% (13–58)	81% (73–90)	1.67 (0.65–4.31)

antenatal steroid therapy was published [2] and, as no data regarding steroid use were given [11], it seems likely this therapy may have been little or even not used. Although, the efficacy of antenatal steroid administration was well appreciated in our institution [4], only approximately 20% of the present population received that treatment. Both our and the previous study [11] had relatively limited samples and thus chance variation should be considered as a possible explanation of the differences. We related the three definitions of prolonged respiratory support to positive symptom status in all 5 pre-school years, but even when we restricted the period under scrutiny to 2 years, as in the earlier report [11], our results were not altered. We, therefore, feel that inclusion of non-specific outcome criteria in the previous study [11] may have biased their results. We feel that positive symptom status is an appropriate criterion on which to diagnose chronic morbidity. Our population were defined as symptomatic if they wheezed and/or coughed

for more than 3 days a week over a 4-week period or following upper respiratory tract infections [15]. We chose that definition as we have previously shown symptomatic infants so defined have worse lung function abnormalities at follow up [16] require treatment [15] even with inhaled steroids [17]. The nature of the patients' symptoms and their lung function abnormalities, that is a raised airway resistance and low functional residual capacity/thoracic gas volume ratio, indicating gas trapping [16] are suggestive these children have asthma-like abnormalities. That hypothesis is supported by their response to "anti-asthma" medication [15, 17]. Premature birth per se increases the risk of positive symptom status at follow up [5]. It is clear, however, that "CLD" regardless of the definition employed, is associated with an increased risk of such morbidity at follow up. It is obviously important, if interventions are to be targeted effectively, to be able to accurately define the highest risk group. We have demonstrated oxygen

dependency beyond 28 days rather than 36 weeks PCA or ventilator dependence beyond 1 week is the most accurate predictor of abnormal respiratory status at follow up.

Only a small proportion of our population received postnatal surfactant, as the study group were recruited prior to routine administration of exogenous surfactant. Exogenous surfactant administration has been suggested to improve lung function at follow up [19] but this has been disputed [1]. In addition, meta-analyses have failed to show it reduces the incidence of CLD [9] and follow up studies have suggested at least bovine surfactant [1] may have little long-term effect on lung function in terms of the recurrence of asthma, pneumonia, wheezing or total number of required hospitalisations. Our findings therefore are of relevance to a population routinely treated with surfactant.

Although oxygen dependency beyond 28 days significantly related to positive symptom status in the first 5 years, its positive predictive value was low. The other definitions of prolonged respiratory support also performed poorly (Table 2). Our results are supported by those of Palta et al. [10] who found oxygen dependency at 30 days and particularly oxygen dependency at 36 weeks PCA had low predictive values for a requirement for bronchodilators and/or steroids up to 2 years, asthma beyond the age of 2 and hospitalization after discharge for respiratory disorders. A bronchopulmonary dysplasia severity score which took into account blood gases as well as respiratory support requirement at about 1 month of age fared no better. Assessment of the radiograph appearance at approximately 4 weeks by the scale of Weinstein et al. [14] was most predictive [10]. As found previously [12], however, adding respiratory support requirement to the radiographic criterion did not improve the predictive value.

Prolonged dependency on respiratory support is a simple criterion on which to define CLD and therefore attractive to employ, but we and others [10] show it is poorly predictive of subsequent respiratory morbidity, limiting its usefulness. Although with a predictive value of over 40%, it could be of value in a multicentre study of an intervention considered to be of low risk. Assessment of the radiograph appearance at present appears most predictive [10]. There are, however, a number of chest radiograph scoring systems/assessments [3, 8, 12, 14, 18] which, to date, have rarely been compared [20]. Further work is necessary, particularly in cohorts routinely exposed to antenatal steroids and postnatal surfactant, to identify the most accurate criterion on which to both diagnose CLD and predict subsequent morbidity. Our results suggest oxygen dependency at 28 days is at least as useful as oxygen dependency beyond 36 weeks PCA in predicting chronic respiratory morbidity following premature delivery.

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