



Bronchopulmonary dysplasia: incidence, risk factors and resource utilization in a population of South American very low birth weight infants

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Abstract

Objective: To determine the incidence of bronchopulmonary dysplasia, its risk factors and resource utilization in a large South American population of very low birth weight infants.

Methods: Prospectively collected data in infants weighing 500 to 1,500 g born in 16 NEOCOSUR Network centers from 10/2000 through 12/2003. Multivariate relative risk and 95% confidence intervals were estimated by Poisson regression with robust error variance to find factors that affected the risk of bronchopulmonary dysplasia.

Results: 1,825 very low birth weight infants survivors were analyzed. Mean birth weight and gestational age were 1085±279 g and 29±3 weeks respectively. Bronchopulmonary dysplasia incidence averaged 24.4% and survival without bronchopulmonary dysplasia augmented with increasing gestational age. A higher birth weight and gestational age and a female gender all decreased the risk for bronchopulmonary dysplasia. Factors that independently increased that risk were surfactant requirement, mechanical ventilation, airleak, patent ductus arteriosus, late onset sepsis and necrotizing enterocolitis. Bronchopulmonary dysplasia infants had more days of hospitalization (91±27 vs. 51±19), of mechanical ventilation (19±20 vs. 4±7) and oxygen therapy (72±30 vs. 8±14) in comparison with non BPD infants.

Conclusions: Bronchopulmonary dysplasia incidence was 24.4% in a large South American population and is related to greater resource utilization. Population and is related to greater resource utilization. Risk factors for bronchopulmonary dysplasia in this study were: surfactant requirement, mechanical ventilation, airleak, patent ductus arteriosus, late onset sepsis and necrotizing enterocolitis. These studies may provide useful information in the design of effective preventive perinatal strategies.

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Introduction

Advances in perinatal care over the past decades have improved the survival of very low birth weight infants (VLBWI). However, long-term morbidity is frequent and bronchopulmonary dysplasia (BPD) is one of the most important chronic complications in these very premature survivors. The reported incidence of BPD, although variable, has not declined, affecting 20-30% of the surviving VLBWI.¹⁻⁵ Therefore, at the present time there are a growing number of infants at risk for long-term pulmonary morbidity.

BPD infants often require prolonged hospitalization and greater financial and emotional cost.⁶ They are also exposed to several different drug therapies such as diuretics and postnatal steroids. This last therapy has been related to adverse long term neurological outcomes.⁷

BPD is a disease whose etiology has not yet been fully established, resulting from multiple factors that can injure the immature lung.⁸⁻¹⁰ Identifying factors that affect the risk of BPD may be important for the development of preventive strategies. Low birth weight and gestational age, RDS and mechanical ventilation have been the most common described risk factors.^{3,11} More recently, other factors such as neonatal infection and patent ductus arteriosus (PDA) have been recognized.¹² Also, undernutrition may interact with other causative factors in the pathogenesis of BPD, and growth failure is common in infants with this condition.¹³

There are not many analyses of risk factors in large population studies.

The aims of this study are to determine the incidence of BPD, its risk factors and resource utilization in a large South American population of VLBWI.

Methods

All inborn live infants with BW 500 g to 1,500 g born from 10/2000 through 12/2003 at the 16 NEOCOSUR Network participating centers from Argentina, Chile, Paraguay, Peru and Uruguay were included in this study. Biodemographic information and outcome data are prospectively and routinely collected across the Network using predefined diagnostic criteria and online data entry.

Bronchopulmonary dysplasia (BPD) was defined as oxygen requirement at 28 days of life and chronic radiographic changes. Oxygen dependency at 36 weeks postmenstrual age was defined as a separate diagnostic criterion. Respiratory distress syndrome (RDS) was diagnosed according to clinical and radiology findings. Pulmonary air leak (PAL) diagnoses were confirmed by chest X-Ray. Late onset sepsis (LOS) diagnoses were confirmed by isolation of the organism in blood or cerebrospinal fluid by cultures taken at more than 72

hours of life. Patent ductus arteriosus (PDA) was diagnosed clinically and whenever available confirmed by echocardiography. Necrotizing enterocolitis (NEC) was confirmed by radiological (pneumatosis and/or perforation) or surgical findings.

Total incidence of BPD at 28 days was calculated for survivors of the total VLBWI population. Death and survival with and without BPD were determined for each week of gestational age. Average days on mechanical ventilation, on oxygen therapy, length of stay and weight gain in the first weeks of life were compared for BPD versus non-BPD infants.

The chi-square test was used to compare categorical variables and the t-test to compare continuous variables. ANOVA for repeated measures was used to compare differences in weight between BPD and non-BPD infants.

Poisson regression with robust error variance was used to identify factors associated with BPD. A step-wise procedure was used to select those factors that independently contribute to explain the outcome. The effect of each factor was expressed as relative risk (RR) and 95% confidence intervals.

p values ≤ 0.05 were considered significant. Statistical analyses were conducted using SAS.

Results

One thousand, eight hundred and forty infants survived (73.8%), from a total of 2,785 born during the study period weighing 500 to 1,500 g. Complete chart information from 1,825 of these was available for data analysis. The incidence of BPD in survivors averaged 24.4%, with a range of 8.6 to 44.6%.

The characteristics of the sample population and of resource utilization are detailed in Table 1. Infants who developed BPD had lower birth weights and gestational ages. They also had lower incidence of cesarean section and lower Apgar scores. On average, BPD infants spent more days hospitalized (91 ± 27 vs. 51 ± 19), on mechanical ventilation (19 ± 20 vs. 4 ± 7) and on oxygen therapy (72 ± 30 vs. 8 ± 14) than non BPD infants. In a Poisson regression adjusted by birth weight the association between BPD and more days on oxygen therapy, mechanical ventilation and in hospital remained highly significant ($p < 0.0001$).

At discharge 22.8% of the BPD infants were still oxygen-dependent.

Figure 1 shows percentages for death, BPD, and survival without BPD for each week of gestational age. There is a significant increase in survival without BPD with increasing gestational age ($p < 0.001$).

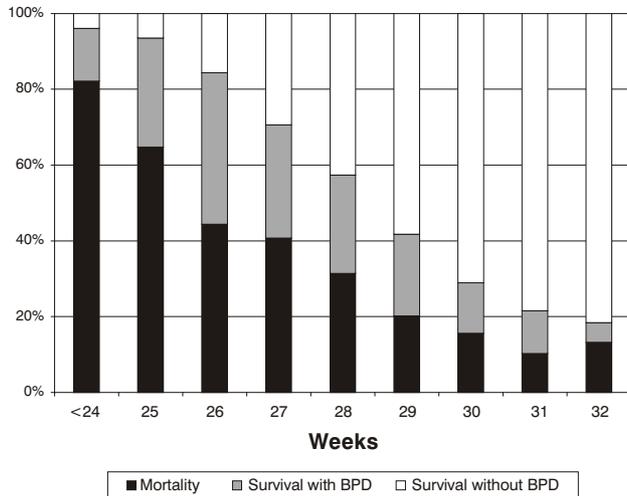


Figure 1 - Mortality and survival in very low birth weight infants with and without bronchopulmonary dysplasia

Risk factors for BPD calculated with a Poisson regression multivariate model can be observed in Table 2. Factors that independently increased that risk were: surfactant requirement, the need for mechanical ventilation, the appearance of PAL, the presence of PDA, the development of a LOS and NEC. Other factors included in the model were prenatal steroid use, route of delivery, 1st minute APGAR score and maternal hypertension, but showed no effect.

These risk factors similarly affected the risk for oxygen dependency at 36 weeks of corrected gestational age (Table 2).

A significantly (p value < 0.001) lower weekly weight gain was observed in BPD infants when compared with those with no BPD over the first 5 weeks of life (Figure 2).

Postnatal steroid administration to BPD infants decreased during the study period from 46% in 2000 to 16% in 2003 ($p < 0.05$).

Discussion

The present study is based on a large South-American population from 16 centers that vary in size, populations served and resources. This diversity may be a better setting to inquire for risk factors for a common morbidity in VLBWI.

The incidence of BPD is comparable to a similar study in the region and to our previous report from this network.^{5,14}

As expected, survival without BPD increases with GA. Reaching 32 weeks or more and over-representing infants with growth retardation, mortality increases. Several studies indicate that growth retarded VLBWI have a worse outcome compared to appropriate for gestational age infants.¹⁵

In this study VLBWI with BPD had more resource utilization counting days of oxygen therapy, mechanical

Table 1 - Characteristics of the VLBWI population, with and without bronchopulmonary dysplasia

Characteristic	DBP n = 446	No DBP n = 1,379	Total n = 1,825	p-value
BW (g) mean (SD)	950 (235)	1280 (209)	1210 (243)	< 0.001
GA (weeks) mean (SD)	28 (2.3)	31 (2.2)	30 (2.6)	< 0.001
Male gender	243 (55%)	638 (46%)	881 (48%)	0.003
Multiple pregnancy	68 (15%)	268 (20%)	336 (19%)	0.04
Prenatal steroids	329 (75%)	1003 (76%)	1332 (75%)	0.96
Vaginal delivery	172 (39%)	360 (26%)	532 (29%)	< 0.001
Apgar < 3 at 1 minute	60 (14%)	62 (5%)	122 (7%)	< 0.001
Apgar < 3 at 5 minute	12 (3%)	7 (0.5%)	19 (1%)	< 0.001
Intubation at birth	264 (60%)	316 (23%)	580 (32%)	< 0.001
Days on O ₂ mean (SD)	72 (30)	8 (14)	25 (34)	< 0.001
Hospital days mean (SD)	91 (27)	51 (19)	61 (28)	< 0.001
Days on IMV mean (SD)	19 (20)	4 (7)	9 (14)	< 0.001

VLBWI = very low birth weight infants; BPD = bronchopulmonary dysplasia; BW = birth weight; SD = standard deviation; GA = gestational age; IMV = intermittent mandatory (mechanical) ventilation.

ventilation and hospital days. These associations remained highly significant after correcting by birth weight. Therefore, preventing BPD may also be of significant financial benefit.

Among the risk factors for BPD, lower BW and GA are both to be expected and difficult to prevent. Male gender also increases the risk for BPD and in other studies has also increased the risk of death in low birth weight populations.¹⁶ The association of BPD with the need for intubation at birth and mechanical ventilation can be explained because these are interventions indicated for more critical infants and clearly related to the pathogenesis of BPD. There is also evidence in animal models that manual ventilation with high tidal volumes at birth may damage immature lungs.¹⁷ The association of BPD with AL may well be reflecting a more aggressive mechanical ventilation with high tidal volumes that have been related to BPD.¹⁸

The association between surfactant requirement and increased risk of BPD may appear conflicting. Exogenous surfactant administration clearly reduces the severity of respiratory distress syndrome (RDS) and consequently the need for aggressive ventilation and prolonged oxygen therapy.¹⁹ However, surfactant is required by the more critical infants who present with RDS. Surfactant therapy and antenatal steroids have markedly increased the survival of the smallest infants who present a higher risk of BPD.²⁰ There has also been a change in the pathogenesis and the presentation of BPD. While the classical form of BPD was mainly the consequence of barotrauma and oxygen toxicity, the “new” BPD seen in the surfactant era results from the interaction of many

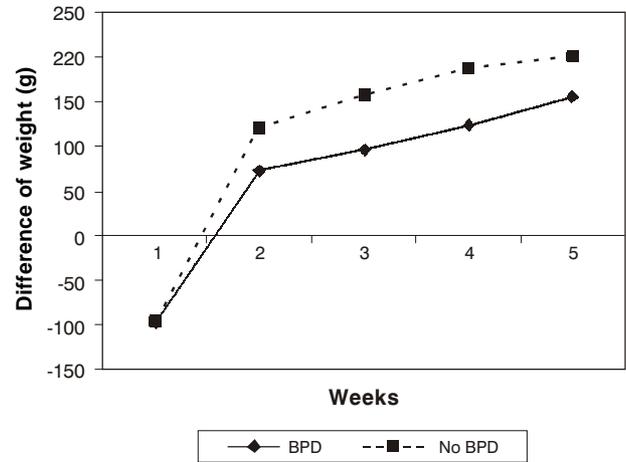


Figure 2 - Weight change per week over the first 5 weeks of life in very low birth weight infants with and without bronchopulmonary dysplasia

factors that lead to prolonged mechanical ventilation and colonization of the airway with pathogens that may trigger an inflammatory cascade.^{8-10,19,20}

In agreement with previous publications we found a significant association between LOS and BPD.^{12,21} The mechanisms by which infection leads to BPD is unclear but may involve an inflammatory process, which results in damage to lung tissue. Infection also increases ductal dilatory prostaglandins and therefore the risk of late ductal reopening and PDA closure failures.²¹ PDA increases pulmonary blood flow and interstitial edema, with a

Table 2 - RR (95% CI) for BPD at 28 days and at 36 weeks' corrected gestational age

Variable	BPD 28 days	BPD 36 weeks
GA (for each week)	0.91 (0.88-0.95)	0.98 (0.94-1.03)
BW (for every 100 g)	0.86 (0.83-0.90)	0.84 (0.80-0.87)
Gender (female)	0.75 (0.66-0.86)	0.67 (0.57-0.78)
IMV	3.36 (2.19-5.15)	3.81 (2.37-6.13)
Surfactant	1.44 (1.13-1.83)	1.40 (1.08-1.82)
Late onset sepsis	1.19 (1.03-1.37)	1.22 (1.03-1.45)
NEC	1.30 (1.06-1.59)	1.36 (1.10-1.69)
PAL	1.30 (1.07-1.58)	1.40 (1.12-1.76)
PDA	1.42 (1.23-1.63)	1.53 (1.29-1.82)

RR = relative risk; CI = confidence interval; BPD = bronchopulmonary dysplasia; GA = gestational age; BW = birth weight; IMV = intermittent mandatory (mechanical) ventilation; NEC = necrotizing enterocolitis; PAL = pulmonary air leak; PDA = patent ductus arteriosus.

subsequent decrease in lung compliance and increase in lung resistance,²² thereby increasing the need for mechanical ventilation and supplemental oxygen. These interrelated factors may explain the association between PDA, and the additive effect of PDA with concurrent infection, with an increased risk of developing BPD.

To our knowledge the association between NEC and BPD has not been previously reported. One explanation to our finding is that NEC presents in the more critical infants. There is also evidence that several inflammatory mediators play an important role in the development of NEC,²³ and in this way may increase the likelihood of BPD.

LOS, PDA and NEC are at least potentially preventable, and may represent opportunities to plan strategies for BPD prevention.

Possible beneficial interventions that need further study are early surfactant and or CPAP intended to decrease the need for mechanical ventilation and thus pulmonary injury.^{24,25}

The observation that infants who developed BPD had a lower weight gain in the first weeks of life may be explained because these infants had a lower GA. However, it may also be reflecting the relation between nutrition and BPD. Deficiency in specific nutrients may play a role in the development of BPD in VLBWI.²⁶

The decrease over time in the use of postnatal steroids in our premature population is satisfactory, as it is in line with published evidence and current recommendations:²⁷ The use of corticosteroids should be limited to exceptional clinical circumstances. We should aim to a further reduction in their use across our network.

There are several limitations to this study. We could not study factors such as severity of the initial RDS or fluid intake in the first days of life or PaCO₂ levels, all of which have been associated with BPD in other studies, because these are not included in our database.^{3,28}

In conclusion, several risk factors for BPD require our efforts to decrease their impact. Decreasing prematurity is probable the most important although difficult challenge of perinatal medicine. Prevention or early identification of PDA, LOS and NEC are warranted. There is a need for controlled interventions in chronic nutrition and respiratory outcomes.

Large population studies may provide useful information and help in the design of effective preventive perinatal strategies and/or interventions that will impact on the outcome of VLBWI survivors.

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