Predictors of bronchopulmonary dysplasia and pulmonary hypertension in newborn children

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ABSTRACT

INTRODUCTION: Infants with bronchopulmonary dysplasia (BPD) are at high risk of developing cardiovascular sequelae in the form of pulmonary hypertension (PH) which significantly increases morbidity and mortality. The aim of this study was to evaluate the incidence of BPD, to identify characteristics associated with BPD and to identify characteristics associated with PH in infants with BPD.

MATERIAL AND METHODS: A retrospective study was performed. Data were obtained from a regional neonatal database and by reviewing medical records of infants admitted during the 2002-2010 period. A total of 400 infants with a birth weight (BW) < 1,500 g were identified. Eight were excluded and 74 infants met the criteria for BPD. A total of 17 infants with BPD had PH.

RESULTS: We found that the incidence of BPD at the Neonatal Department at Hvidovre Hospital between January 2002 and December 2010 was 18%. Infants with BPD differed significantly from infants without BPD with regard to the following characteristics: Infants with BPD more frequently had a lower gestational age and BW, intubation at birth, mechanical ventilation within 24 hours of birth, a lower Apgar score at one minute and five minutes. The incidence of PH was 23% among infants with BPD. Furthermore, we found a significantly larger frequency of intubation at birth, postnatal infection, longer duration of continuous positive airway pressure treatment and use of oxygen therapy among infants with PH and BPD than among the remaining infants.

CONCLUSION: The incidence of BPD was 18%. Low gestational age was found to be the most important factor associated with development of BPD. Among BPD infants, postnatal infection was significantly associated with PH. Further prospective studies including routine echocardiography are needed to evaluate risk factors for PH.

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Preterm deliveries are those that occur before 37 weeks' of gestational age (GA). In the US, the preterm delivery rate is 12.18% [1]. Today, smaller and more premature infants survive more often than previously owing to technological advances, improved ventilatory strategies and better nursing techniques coupled with the use of prenatal steroids and postnatal surfactant [2]. In these infants, bronchopulmonary dysplasia (BPD) has been characterized on the basis of pathology found in infants dying from the condition [3]. BPD is characterized by less fibrosis, less inflammation, fewer and larger alveoli, and a reduction in the number and size of intra-acinar-pulmonary arteries [3]. These changes cause a significant reduction in the cross-sectional area of the pulmonary vascular bed, which gives rise to increased pulmonary vascular resistance, which, in turn, leads to development of pulmonary hypertension (PH). PH is a severe complication of BPD and it contributes significantly to the increased morbidity. Furthermore, premature infants with BPD and severe PH are at high risk of death, particularly during the first six months after diagnosis of PH [4].

Even though severe PH is a life-threatening complication in neonates, only few studies describing characteristics related to PH in preterm infants with BPD have been published. The aim of the present study was to determine any characteristics associated with the development of PH in infants with BPD and to identify characteristics associated with the development of BPD.

MATERIAL AND METHODS

A retrospective study was conducted by reviewing medical records and data from a neonatal database (NeoBasen) which contains data on all infants admitted to the neonatal department at Hvidovre Hospital, Copenhagen University Hospital, Denmark. All infants with a birth weight (BW) < 1,500 g who were hospitalized between January 2002 and December 2010 were included. Clinical evidence has been provided that significant risk factors associated with BPD in neonates is a BW ≤ 1,500 g. The exclusion criteria were diaphragmatic hernia, congenital pulmonary malformation, congenital cytomegalovirus pneumonia, chromosomal syndromes, malformations or other known explanation for prolonged need of oxygen. Furthermore, infants who died before reaching a post-conceptional age of 36 weeks were excluded.

Definitions

According to the definition refined in the consensus conference of the National Institute of Child Health and Human Development (NICHD) in June 2000, infants depending on supplemental oxygen for a minimum of 28 days suffer from BPD [5]. Prematurely born infants are

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TABLE 1

Definitions

	Definition
Gestational age	Gestational age was based on maternal last menstrual period or early prenatal ultrasound
Patent ductus arteriosus	Patent ductus arteriosus was diagnosed in the presence of clinical findings and documented by cardiac echocardiography
Retinopathy of prematurity	Retinopathy of prematurity was defined according to the International Classification [6]
Intraventricular haemorrhage	Intraventricular haemorrhage was diagnosed by ultrasound scan
Haemorrhages	Haemorrhages were graded in 1-4 according to the criteria of *Papile et al* [7]
Necrotizing enterocolitis	Necrotizing enterocolitis was diagnosed based on the criteria of *Bell et al* [8]
Postnatal infection	Postnatal infection was defined as positive bacterial or fungal blood or cerebrospinal fluid or urine culture or positive culture from endotracheal secretions

classified as having moderate or severe BPD according to their respiratory support requirement a GA of 36 weeks [5]. Our retrospective design bars us from using this method since the percentage of supplemental oxygen is not rigorously described in the medical records. Regardless of these limitations, in order to classify severity, we used the need for supplemental oxygen at a GA of 36 weeks as a measure of moderate/severe disease and the need for supplemental oxygen for 28 days as a measure of mild BPD. For more definitions, see **Table 1**.

Definition of pulmonary hypertension

The diagnosis of PH was made by echocardiography based on the following criteria: dilatation of right-sided chambers or right-sided ventricular hypertrophy or flattening and left deviation of the septum or triscuspid incompetence (TI) gradient > 30 mmHg or steep pulmonary artery flow curve with an acceleration time (AT)/ejection time (ET) ratio < 0.3. The same criteria for PH were applied to all cases. Routine echocardiography was not provided. Echocardiography was only provided on clinical demand such as a heart murmur or increasing need for oxygen.

Statistical analysis

Continuous data were analyzed using the two-tailed Student t-test. Binary outcomes were analyzed using the χ^2-test and Fisher's exact test. Furthermore, multivariable logistic regression analysis was conducted with backward selection. The variables included in the multivari-

TABLE 2

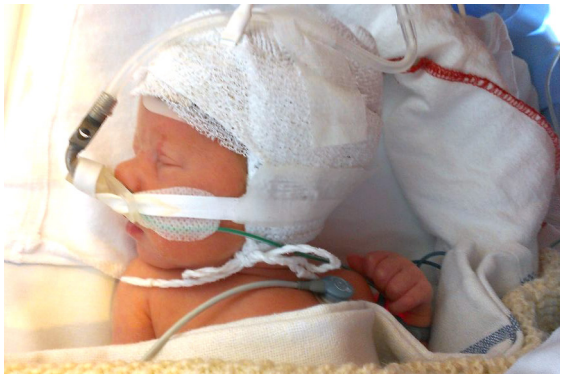
Characteristics of infants with and without bronchopulmonary dysplasia.

	BPD (n = 74)	Non-BPD (n = 318)	p-value[a]	OR	95% CI
Gestational age, weeks, mean	26.7	30.4	0.0000	–	–
Birth weight, g, mean	904	1,222	0.0000	–	–
Male, n (%)	39 (53)	151 (47)	0.4185	1.2324	0.7425-2.0455
Multiple pregnancies, n (%)	21 (28)	119 (37)	0.1438	0.6626	0.3807-1.1531
Emergency caesarean, n (%)	45 (61)	212 (67)	0.1833	0.7759	0.4605 – 1.3073
Vaginal birth, n (%)	24 (32)	55 (17)	0.0003	2.2953	1.3021 – 4.0461
Surfactant, n (%)	34 (46)	61 (19)	0.0000	3.5811	2.0959 – 6.1187
Tracheal intubation at birth, n (%)	28 (38)	19 (6)	0.0000	9.5789	4.9503 – 18.535
Mechanical ventilation < 24 h after birth, n (%)	35 (47)	42 (13)	0.0000	5.8974	3.3685 – 10.324
Duration of CPAP, days, mean	60	11	0.0000	–	–
Duration of intubation, days, mean	6	0.5	0.0000	–	–
APGAR 1, mean	6.6	7.9	0.0002	–	–
APGAR 5, mean	8.9	9.3	0.0242	-	-
ROP, operation, n (%)	11 (15)	3 (1)	0.0000	18.3333	4.9716-67.605
PDA, operation, n (%)	4 (5)	0 (0)	0.0000	40.6596	2.1642-763.86
PDA, indomethacin, n (%)	29 (39)	6 (2)	0.0000	33.5111	13.1828.85.18
Postnatal infection, n (%)	28 (38)	19 (6)	0.0000	9.5789	4.9503-18.535
IVH, n (%)	10 (14)	23 (7)	0.0796	2.0041	0.9095-4.4162
NEC, n (%)	4 (5)	15 (5)	0.8038	1.1543	0.3717-3.5846
Weight at discharge, g, mean	2,936	2,470	0.0086	–	–

APGAR = appearance (skin colour), pulse (heart rate), grimace (reflex irritability), activity (muscle tone); BPD = bronchopulmonary dysplasia; CI = confidence interval; CPAP = continuous positive airway pressure; IVH = intraventricular haemorrhage; NEC = necrotizing enterocolitis; OR = odds ratio; PDA = persistent ductus arteriosus; ROP = retinopathy of prematurity.
a) Definition of statistical significance: $p < 0.05$.

ate analyses for BPD in the whole cohort were GA, BW, emergency caesarean, surfactant and duration of intubation. The variables included in the multivariate analyses for PH were patent ductus arteriosus (PDA)(operation), surfactant, duration of continuous positive airway pressure (CPAP), mechanical ventilation < 24 h after birth, tracheal intubation at birth, duration of intubation, emergency caesarean, multiple pregnancy, GA, BW, sex and postnatal infection. A stepwise regression was utilized and in all analyses; $p < 0.05$ was considered significant.

Trial registration: not relevant.



Nasal continuous positive airway pressure is a Danish system widely used in Scandinavia, but not in the rest of the world. It is not unpleasant for the child, and the mouth can be used for a pacifier, drops of milk, etc.

RESULTS

Results of analyses for bronchopulmonary dysplasia in the whole cohort

A total of 400 preterm infants were born with a BW < 1,500 g; 82 of the infants met our criteria for BPD and eight of these infants were excluded due to missing or incomplete medical records. A total of 74 preterm infants were included in the final cohort of infants with BPD. The incidence of BPD among infants with a BW < 1,500 g was 18.5%.

The premature infants with BPD (BPD infants) had a significantly lower GA and BW than those without BPD (non-BPD infants) (**Table 2**). The mean GA at birth was 26.7 weeks, and the mean BW was 904 g for BPD infants. There were significant differences between BPD infants and non-BPD infants with respect to vaginal birth, surfactant, tracheal intubation at birth, mechanical ventilation < 24 hours after birth, duration of CPAP treatment, duration of intubation, Apgar score after one minute and five minutes, treatment for retinopathy of prematurity (ROP), surgical management and treatment with indomethacin for PDA, postnatal infection and weight at discharge (Table 2). Based on the multivariate logistic regression analysis, GA was the only factor significantly associated with the development of BPD.

The proportion of BPD infants among the live born infants increased along with the general increase in the survival rate of the neonates born at < 1,500 g of BW between 2002 and 2010.

BPD infants born in 2006-2010 had a lower mean GA ($p = 0.0016$) and BW ($p = 0.0256$) than those born in 2002-2005. The mean GA at birth was 26.2 weeks and the mean BW was 851 g for infants born in the 2006-2010 period compared with the mean GA of 27.5 weeks and the mean BW of 981 g of infants born in 2002-2005.

Results of analyses for pulmonary hypertension in the bronchopulmonary dysplasia cohort

Seventeen infants with BPD met the criteria for PH. The mean GA at birth for infants with PH was 26.4, and the mean BW was 836 g; 82% of infants with PH had moderate/severe BPD (p-value 0.0023). The duration of oxygen supplementation was significantly longer in the PH group (mean 97 days) than in the non-PH group (mean 58 days). The duration of CPAP was longer in the PH group than in the non-PH group (87 days versus 51 days, $p < 0.0000$). The PH group counted more infants who had undergone tracheal intubation at birth than the non-PH group (65% versus 30%, $p = 0.0107$). There was a significantly ($p = 0.0420$) higher incidence of postnatal infection in the PH group (59%) than in the non-PH group (32%) (**Table 3**).

Based on the multivariate logistic regression analysis, postnatal infection was significantly ($p = 0.0100$) and positively correlated with PH in preterm infants with BPD.

The prevalence of PH among the entire sample of preterm infants with BPD was 23%.

DISCUSSION

In the present regional cohort study of premature infants born in Denmark during the 2002–2010 period, BPD was a serious complication to prematurity and was diagnosed in 18.5% of the surviving infants. The characteristics associated with BPD are well-known [9] and were also confirmed in our study. Prematurity is a primary determinant of an infant's risk of developing BPD due to poor development of the airways in the premature lung.

The incidence of BPD in the literature ranges from 4.6% to 72% [10-12]. This broad range may be explained by the heterogeneity of the studied populations, or by varying management practices or disease definitions. The BPD incidence observed in our cohort was expected from the literature and was very close to that reported by Cunha et al [13] who found the global incidence of BPD among very low birth weight (VLBW) newborns to be 19.7% .Our result was lower than that reported in the study published by the Neocosur Group [14] who found the incidence to be 23%, and those of two other large

TABLE 3

Comparison between bronchopulmonary dysplasia infants with and without pulmonary hypertension.

	PH (n = 17)	Non-PH (n = 57)	p-value[a]	OR	95% CI
Gestational age, weeks, mean	26.4	26.9	0.2983	–	–
Birth weight, g, mean	836	924	0.2023	–	–
Male, n (%)	8 (47)	31 (54)	0.5954	0.7455	0.2517-2.2078
Multiple pregnancies, n (%)	2 (12)	19 (33)	0.0834	0.2667	0.0552-1.2882
Emergency cesarean, n (%)	11 (65)	34 (60)	0.7078	1.2402	0.4019-3.8267
Vaginal birth, n (%)	4 (23)	20 (35)	0.3716	0.5692	0.1638-1.9782
Surfactant, n (%)	6 (35)	28 (49)	0.3175	0.5649	0.1839.1.735
Tracheal intubation at birth, n (%)	11 (65)	17 (30)	0.0107	4.3137	1.3724-13.558
Mechanical ventilation < 24 h after birth, n (%)	11 (65)	24 (42)	0.1014	2.5208	0.8183-7.7658
Duration of CPAP, days, mean	87	51	0.0000	–	–
Duration of intubation, days, mean	6.5	6.3	0.9584	–	–
Duration of O_2, days, mean	97	58	0.0001	–	–
Moderate/severe BPD, n (%)	14 (82)	23 (40)	0.0023	6.8986	1.7802-26.733
Treatment with diuretics, n (%)	12 (71)	18 (32)	0.0040	5.2	1.5925-16.98
APGAR 1, mean	5.9	6.7	0.2735	–	–
APGAR 5, mean	8.3	9.1	0.0865	–	–
ROP, operation, n (%)	4 (24)	7 (12)	0.2533	2.1978	0.5575-8.6638
PDA, operation, n (%)	2 (12)	2 (4)	0.1913	3.6667	0.4761-28.240
PDA, indomethacin, n (%)	9 (53)	20 (35)	0.1859	2.0813	0.695-6.2325
Postnatal infection, n (%)	10 (59)	18 (32)	0.0420	3.0952	1.0142-9.446
IVH, n (%)	2 (12)	8 (14)	0.8101	0.8167	0.1562-4.2693
NEC, n (%)	0 (0)	4 (7)	0.6087	0.3397	0.0174-6.6292
Weight at discharge, g, mean	3,226	2,842	0.1468	–	–

APGAR = appearance (skin colour), pulse (heart rate), grimace (reflex irritability), activity (muscle tone); BPD = bronchopulmonary dysplasia; CI = confidence interval; CPAP = continuous positive airway pressure; IVH = intraventricular haemorrhage, NEC = necrotizing enterocolitis; OR = odds ratio; PDA = persistent ductus arteriosus; PH = pulmonary hypertension; ROP = retinopathy of prematurity.
a) Definition of statistical significance: $p < 0.05$.

data banks in Canada and the United States which have published a BPD incidences of 26% [15] and 23% [16], respectively, in VLBW newborns. The difference between the incidence rates of the cited studies and our study may be due to the higher rate of healthy infants in our cohort. Infants who are very sick get transferred to a more specialized hospital in Denmark.

Although causation is multifactorial in BPD, the prenatal and postnatal factors for disrupted alveolar growth remain fairly well defined. Prematurity (GA < 37 weeks) remains the primary determinant of an infant's risk of developing BPD [9]. Our results are in accordance with international results. A low GA was found to be the most important factor associated with the development of BPD in our study.

In the present study, we aimed to evaluate possible characteristics associated with PH in BPD infants. The prevalence of PH among the entire sample of preterm infants with BPD was 23% in our cohort. Retrospective studies report that PH may occur in up to 17-43% of preterm infants with BPD [4, 17-19]. In the present study, most of the infants diagnosed as having PH had underlying moderate/severe BPD. Furthermore, the duration of oxygen supplementation was significantly longer in the PH group than in the non-PH group. These findings are consistent with previous findings by An et al [17] and Kim et al [18].

In a large retrospective study, An et al [17] obtained data by reviewing the medical records of all infants < 32 weeks GA born between 2004 and 2008. A total of 116 preterm infants with BPD ware included. The study showed that PH occurred initially at a median age of 65 days (range: 7-232 days). Severe BPD, BW < 800 g, long-term ventilator care and oxygen supplementation, a high ventilator setting, infection and a PDA were related to PH based on univariate analysis ($p < 0.05$). The severity of BPD was graded according to the fraction of inspired oxygen (FiO_2) or positive pressure ventilation (PPV) as follows: mild BPD, breathing room air; moderate BPD, requiring oxygen supplementation (FiO_2 of < 0.30); and severe BPD, requiring an FiO_2 of ≥ 0.30 or PPV at 36 weeks GA. The infants who received oxygen supplementation for a longer period were significantly more likely to have PH (odds ratio, 18.5; 95% confidence interval (CI), 4.1-84.6; $p < 0.001$). Kim et al [18] performed a retrospective review of data from 295 infants with a GA < 32 weeks born during the 2005-2009 period. Of the 295 infants enrolled in the present study, 145 (49%)

were diagnosed with BPD. A total of 25 preterm infants (17 males and eight females) with BPD had PH. PH was diagnosed in 52.5% (21/40) of infants with severe BPD, in 6.9% (4/58) of infants with moderate BPD and in 0% (0/47) of infants with mild BPD. BPD and its severity were defined using treatment with oxygen for at least 28 days with division into the following three subgroups at 36 weeks' PCA: 1) mild (breathing room air); 2) moderate (need for a < 30% FiO_2), and 3) severe (need for > 30% FiO_2 and/or positive pressure support). They found that infants with PH had more severe cases of BPD and underwent longer oxygen therapy, conventional or high-frequency ventilation, and hospitalization than those without PH. Low 5-min Apgar scores (≤ 6; relative risk (RR) 6.2; 95% CI 1.4-28.0; p = 0.017) were found to be significant risk factors for PH according to multivariate analysis. There was a tendency towards a lower 5-min Apgar in the PH group, but this finding was not significant in our cohort.

This study was limited by its retrospective design, which resulted in incomplete data collection. Not every BPD-infant underwent echocardiography during the study period. As the use of echocardiography was selective, we were only able to determine a minimal estimate of PH in BPD infants. This may have led to undiagnosed PH in our BPD group without PH. Cardiac catheterization is today accepted as the gold standard for diagnosing PH. However, since this procedure is very invasive and is not easily performed in preterm infants, echocardiography is recommended as the main tool to screen for PH despite its several limitations [20]. Even though it is likely that echocardiography tends to be ordered for the sickest infants, routine use of echocardiography may lead to earlier diagnosis, altered treatment strategy and more knowledge of the development of pulmonary hypertension. Regular screening for PH has also been suggested by other authors [17-19].

Postnatal infection was very broadly defined in our study. We did not have a prospective design, which makes it impossible to determine whether postnatal infections increase the risk of developing PH, or whether infants with PH have more complications during hospitalization in terms of infections than non-PH infants do.

In conclusion, the incidence of BPD at Hvidovre hospital was 18%. A low GA was found to be the most important factor associated with the development of BPD. The findings of this study confirmed our expectation that the variables of BW and GA were risk factors strongly associated with BPD. These data emphasize the fact that BPD continues to be a significant public health concern that is linked to the improved survival of extremely premature newborns. Among BPD infants, postnatal infection was the only factor associated with PH in the final multivariate analysis. To further evaluate risk factors for the development of BPD and PH, a prospective study with routine echocardiography is needed. Improved screening for and increased recognition of PH may allow for earlier treatment and improved clinical outcomes. Identification of both prenatal and postnatal risk factors for the development of PH may allow for targeting of therapy and resources for those at the highest risk.

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