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# Pulmonary hypertension in infants with bronchopulmonary dysplasia: risk factors, mortality and duration of hospitalisation

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#### **Abstract**

**Objectives:** Pulmonary hypertension (PH) is a complication of bronchopulmonary dysplasia (BPD) and associated with increased mortality and morbidity. Our aim was to identify, in infants with BPD, the effect of PH on health-care utilisation and health related cost of care.

**Methods:** An electronic data recording system was used to identify infants ≤32 weeks of gestation who developed BPD. PH was classified as early (≤28 days after birth) or late (>28 days after birth).

**Results:** In the study period, 182 infants developed BPD; 22 (12.1%) developed late PH. Development of late PH was associated with a lower gestational age [24.6 (23.9–26.9) weeks, p=0.001] and a greater need for positive pressure ventilation on day 28 after birth (100%) compared to infants without late PH (51.9%) (odds ratio (OR) 19.5, 95% CI: 2.6–148), p<0.001. Late PH was associated with increased mortality (36.4%) compared those who did not develop late PH (1.9%) after adjusting for gestational age and

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ventilation duration (OR: 26.9, 95% CI: 3.8–189.4), p<0.001. In infants who survived to discharge, late PH development was associated with a prolonged duration of stay [147 (118–189) days] compared to the infants that did not develop late PH [109 (85–149) days] (p=0.03 after adjusting for gestational age). Infants who had late PH had a higher cost of stay compared to infants with BPD who did not develop late PH (median £113,494 vs. £78,677, p=0.016 after adjusting for gestational age).

**Conclusions:** Development of late PH was associated with increased mortality, a prolonged duration of stay and higher healthcare cost.

**Keywords:** bronchopulmonary dysplasia; neonate; premature; pulmonary hypertension.

## Introduction

The survival rates of extremely premature infants have improved significantly in the last few decades, but are associated with long term morbidities [1–3]. Bronchopulmonary dysplasia (BPD) is the most common adverse outcome and can result in complications which may extend into adulthood [4]. One of the significant contributory factors for morbidity and mortality in infants with BPD is the development of pulmonary hypertension (PH) [5].

The incidence of pulmonary hypertension in infants with BPD ranges from 17 to 37% [6–8]. The pathogenesis of pulmonary vascular disease associated with BPD is multifactorial and can be attributed to the interaction of maternal, genetic and postnatal factors. Inhibition of angiogenesis has been associated with decreased alveolarization and pulmonary vascular growth in an animal model [9]. The arrest of vascular growth and the reduction in the alveolar-capillary surface result in impaired gas exchange. Thus, the lungs are exposed to prolonged ventilation and high oxygen levels along with hemodynamic and inflammatory stressors. This causes pulmonary arterial remodelling leading to fibrosis of the vessel walls [10]. The risk factors associated with the development of pulmonary hypertension include intrauterine growth restriction, preeclampsia, maternal

substance abuse, lower gestational age and birthweight, patent ductus arteriosus (PDA) requiring treatment and sepsis [8, 11–14].

The gold standard to diagnose pulmonary hypertension is cardiac catheterization, but this is often difficult to perform in BPD infants who may have significant vascular and haemodynamic complications [15]. Two-dimensional echocardiography, however, is a valuable tool for screening and diagnosis of PH in such patients [10]. Various studies have investigated the risk factors, outcomes [5-8, 11, 14, 16-21] and evolution of pulmonary hypertension in BPD infants [7, 8, 14, 19-21]. The identified risk factors include early pulmonary hypertension, postnatal steroid administration, tracheostomy and tracheitis [5, 16, 17]. Outcomes associated with PH in BPD infants include increased mortality and morbidity including a prolonged duration of invasive ventilation, increased occurrence of severe IVH and prolonged hospitalization [5, 7, 8, 14, 19–21]. Our aim was to identify, in infants with BPD, the effect of PH on health-care utilisation and the health related cost of care.

# Materials and methods

#### Study subjects

An observational study was conducted of infants admitted to the neonatal unit at a London hospital, United Kingdom (UK) between January 2017 and December 2020. Badgernet, an electronic patient record database, was used to identify study subjects. The criteria for inclusion were (i) infants born at or prior to 32 weeks' gestation (ii) birthweight less than 1,500 g and (iii) development of BPD (oxygen requirement for at least 28 days from birth) [22]. Infants who died before 36 weeks of gestation, but required oxygen for at least 28 days were included in the study [23].

Infants had an echocardiogram when there was a clinical suspicion of pulmonary hypertension as evidenced by different preductal and post-ductal saturations, a persistently high oxygen requirement above 60% and/or requiring increased mean airway pressures to maintain oxygenation. Some infants had an echocardiogram for assessment of whether they had a patent ductus arteriosus (PDA). Infants whose echocardiogram reports were not available, who were admitted for short surgical procedures such as inguinal hernia and laser photocoagulation and those with major respiratory and cardiac anomalies were excluded from the study.

#### Ethical approval

The study was registered with the local Clinical Governance and Audit Department and did not require informed parental consent.

## Assessment of pulmonary hypertension

The echocardiograms of the infants were reviewed by one author, a neonatologist trained in echocardiography and further reviewed by a paediatric cardiologist. The presence of PH was defined based on quantitative or qualitative assessments. Quantitative assessment included the presence of tricuspid regurgitant jet velocity (TRJV)>3 m/s (right ventricular systolic pressure (RVSP)>36 mm Hg). In the absence of tricuspid regurgitation, qualitative assessment was used to detect PH using the following parameters: (i) flattened or left deviated intraventricular septum in ventricular systole (ii) right to left shunting across a patent foramen ovale, atrial septal defect, ventricular septal defect or patent ductus arteriosus, if present (iii) right ventricular hypertrophy or dysfunction [15].

#### **Definitions and risk factors**

BPD was defined as per the Jobe and Bancalari criteria [22]. Early PH was defined as PH diagnosed within 28 days after birth, while late PH diagnosed after 28 days [16]. Severe intraventricular haemorrhage was defined as Grade 3 or 4 as described by Papile [24].

The last echocardiogram during the admission was used to identify the presence of PH at discharge or death. Risk factors for late PH assessed included maternal preeclampsia, substance abuse, small for gestational age (SGA) (defined as birthweight less than 10th percentile or less than –1.28 standard deviation for gestational age [25]), positive pressure ventilation (PPV) at 28 days after birth, medically or surgically treated patent ductus arteriosus (PDA), sepsis (positive blood culture requiring intravenous antibiotics) and presence of early PH.

#### **Outcomes**

We assessed the mortality in the cohort and the total duration of stay in the survivors. Additionally, the total cost of stay was calculated based on national average costs of neonatal unit stay. We also compared the length and cost of stay in infants whom PH resolved prior to discharge against the ones in whom PH did not resolve prior to death or discharge. The average daily cost ranges from £437 to £1,218 was graded based on the intensity of care coded as intensive care, high dependency and special care (Table 1) [26]. The duration of care at each level of care was extracted from Badgernet and used to estimate the total cost of stay in the neonatal unit.

#### Statistical analysis

On testing for normality using Shapiro-Wilk test, the data was found to be non-normally distributed. Therefore, the Mann-Whitney U test was used for comparing the continuous variables and Chi-square test for dichotomous variables. Multiple logistic or linear regression was used to adjust for confounding variables. All the risk factors were adjusted

**Table 1:** National schedule of reference costs in neonatal units in IIK.

Level of intensity	National average unit cost per day (interquartile range)		
Intensive care	£1,218 (£959–£1,399)		
High dependency	£872 (£746-£984)		
Special care	£560 (£455–£645)		

for gestational age, birthweight z score and 10 min Apgar score. The effect on mortality and duration of hospitalisation were further adjusted for gestational age and the duration of invasive ventilation. The effect of total cost of stay was further adjusted for gestational age. IBM SPSS Statistics for Windows, Version 25.0 (SPSS Inc. Chicago, IL) was used to analyse the data.

## Results

A total of 428 premature infants were admitted to the neonatal unit during the study period, 211 (49.3%) subsequently developed BPD; 189 infants were included in the analysis and 29 infants were excluded (Figure 1).

The included infants had a median (interquartile range) gestational age of 25.9 (24.9-27.7) weeks and birthweight of 769 (667–930) grams (Table 2). Twenty-one (11.5%) infants had early PH of which six (28.5%) subsequently developed late PH. Twenty-two (12%) infants had late PH. Amongst the 22 infants with late PH, pulmonary hypertension resolved in 10 infants, four had pulmonary hypertension at discharge from neonatal care and eight died with pulmonary hypertension (Figure 2).

The characteristics of infants who developed early PH, late PH, both early and late and no PH have been detailed in Table 3. The infants who developed both early and late PH had a lower (median) gestational age (24.4 weeks) compared to those who had only early PH (25.7 weeks), late PH (24.6 weeks) or no PH (26.1 weeks, p=0.02). Furthermore, infants who developed both early and late PH had a lower (median) birthweight (603 g) compared to those who had early PH (780 g), late PH (673 g) or no PH (818 g, p<0.001).

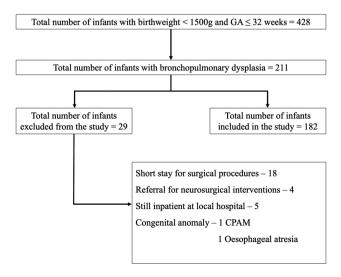


Figure 1: Flowchart of selected cases.

**Table 2:** Demographics of the study population.

	Median (interquartile range)	n (%)
Gestational age	25.9	
oostationat age	(24.9–27.7)	
Birthweight	769 (667–930)	
Small for gestational age	, ,	36 (19.8)
Sex		Male: 94 (51.6)
Ethnicity (maternal)		White: 71 (39)
, ,		Black: 64 (35.2)
		Asian: 14 (7.7)
		Mixed: 3 (1.6)
		Other: 7 (3.8)
Mode of delivery		Emergency
		caesarean: 75 (41.2)
		Elective caesarean: 6
		(3.3)
		Spontaneous vaginal:
		97 (53.3)
		Instrumental: 4 (2.2)
Antenatal steroids (at least		169 (92.9)
one dose)		
Pre-eclampsia		30 (16.5)
Maternal substance abuse		4 (2.2)
Clinical chorioamnionitis		9 (4.9)
Early PH		21 (11.5)
Late PH		22 (12.1)
PH at death or discharge		12 (6.6)
Positive pressure ventila-		105 (57.7)
tion on day 28		
Inhaled nitric oxide		54 (29.7)
Inotrope administration		100 (54.9)
PDA requiring treatment		73 (40.1)
Culture proven sepsis		78 (42.9)
Surgical NEC		18 (9.9)
Severe IVH		44 (24.2)
Severe ROP		34 (18.7)
Mortality		11 (6.0)

PH, pulmonary hypertension; PDA, patent ductus arteriosus.

The infants who developed late PH had a lower gestational age (24.6 vs. 26.1 weeks, p=0.002) and lower birthweight (642.5 vs. 816.5 g, p<0.001) compared to those who did not have late PH. The infants who developed late PH were more often mechanically ventilated on day 28 after birth compared to the ones who did not develop late PH [100 vs. 51.9%, p<0.001; OR: 19.5 (CI: 2.6–148)]. The infants who developed late PH had a longer median duration of mechanical ventilation compared to the infants without late PH (53.5 vs. 27.5 days, p<0.001) [Table 4].

Eleven infants (6%) died in the study population. Eight had pulmonary hypertension at death, of those eight, six had developed PH within 28 days after birth (Figure 2). The presence of late PH was independently associated with

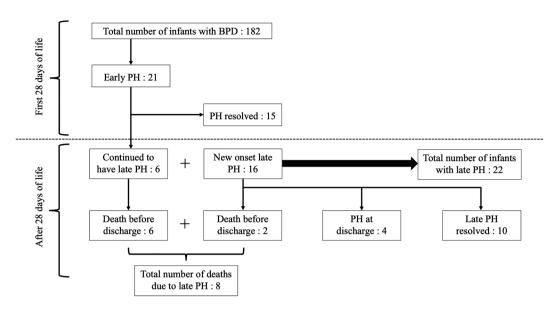


Figure 2: Development and evolution of pulmonary hypertension during neonatal stay.

**Table 3:** Demographics of infants by early PH, late PH, both early + late and no PH.

Characteristics	Early PH (n=15), n (%) or median (IQR)	Late PH (n=16), n (%) or median (IQR)	Early + late PH (n=6), n (%) or median (IQR)	No PH (n=145), n (%) or median (IQR)	p- Value
Gestational age, weeks	25.7 (25.0–28.1)	24.6 (24.2–26.5)	24.4 (23.5–27.4)	26.1 (25–27.9)	0.02
Birthweight, grams	780 (704-890)	673 (627-769)	603 (535–650)	818 (692.5-962)	<0.001
Birthweight z scores	-0.6 (-1.2 to 0.23)	-0.6 (-1.4 to 0.31)	-0.7 (-2.5 to 0.04)	-0.3 (-1.1 to 0.19)	0.66
Apgar at 10 min	8 (7-9)	8 (7-9)	8 (8-9)	9 (8–10)	0.15
Small for gestational	2 (19)	4 (25.0)	2 (33.3)	28 (19.3)	0.71
age					
Sex, male	8 (53.3)	8 (50.0)	4 (66.7)	74 (51.0)	0.90
Antenatal steroids	13 (86.7)	16 (100)	5 (83.3)	135 (93.1)	0.40
Pre-eclampsia	3 (20.0)	3 (18.8)	0	24 (16.6)	0.71
Maternal substance abuse	1 (6.7)	0	0	3 (2.1)	0.59

PH, pulmonary hypertension; IQR, interquartile range.

increased mortality [OR: 21.4 (4.1–111.3), adjusted p=0.001]. Similarly, the presence of late PH in surviving infants was independently associated with a longer duration of hospital stay [147 vs. 109 days, adjusted p: 0.03] (Table 5).

The total cost of stay for the 182 infants was £17,164,290 (\$23,957,659). The median (IQR) total cost of stay in infants with late PH was £113,494 (72,650–169,798) compared to £78,677 (48,476–115,483) in infants with BPD, but no late PH after adjusting for gestational age (p=0.016) [Table 5]. The median cost of stay in infants with BPD and PH was approximately £35,000 higher (44% higher) compared to that of infants with BPD without PH.

The median length of hospitalisation was similar in infants whom PH resolved before discharge [147 (118–189) days] compared to the infants in whom PH did not resolve

before discharge or died with PH [147 (72–259) days, p=0.81]. The total cost of stay was not significantly different in infants in whom PH resolved before discharge [£85,992 (67,524–121,939)] compared to the infants in whom PH did not resolve before discharge [£148,458 (80,185–252,455), p=0.07].

### **Discussion**

We have demonstrated late PH was associated with a higher mortality and a longer duration of stay compared to infants with BPD without PH. Furthermore, we found that the total cost of stay for infants with late PH and BPD was higher compared to those who did not develop late PH.

Table 4: Demographics of infants by late PH status.

Characteristics	Late PH (n=22), n (%) or median (IQR)	No late PH (n=160), n (%) or median (IQR)	p- Value
Gestational age,	24.6 (23.9–	26.1 (25–27.9)	0.002
weeks	26.9)		
Birthweight, grams	642.5 (610.3-	816.5 (696.3-	<0.001
	718.9)	960)	
Birthweight z scores	-0.6 (-1.4 to	-0.34 (-1.1 to	0.38
	0.13)	0.2)	
Apgar at 10 min	8 (7-9)	9 (8–10)	0.084
Small for gestational age	6 (27.2)	30 (18.8)	0.35
Sex, male	12 (54.5)	82 (51.2)	0.77
Antenatal steroids	21 (95.5)	148 (92.5)	0.61
Pre-eclampsia	3 (13.6)	27 (16.9)	0.70
Maternal substance abuse	0	4 (2.5)	0.45
Positive pressure ventilation on day 28	22 (100)	83 (51.9)	<0.001
PDA requiring treat- ment (medical/ surgical)	12 (54.5)	61 (38.1)	0.141
Duration of invasive ventilation, days	53.5 (42–65.8)	27.5 (8-48)	<0.001
Culture proven sepsis	13 (59.1)	65 (40.6)	0.08
Presence of early PH	6 (27.3)	15 (9.4)	0.19
Surgical NEC	2 (9.1)	16 (10)	0.89
Severe IVH	6 (27.3)	38 (23.8)	0.72

PH, pulmonary hypertension; IQR, interquartile range; PDA, patent ductus arteriosus.

Our study showed that while the incidence of overall mortality was 6% in the study population, the presence of late PH was associated with a 36% increase in mortality. Studies have described the association of PH and mortality with an incidence ranging from 10 to 38% [7, 8, 14, 17, 18, 27]. Notably, among the eight infants who died with pulmonary hypertension, six of them had developed PH within 28 days (Figure 2). Two studies have shown that early PH increases the risk for severe BPD and development of late PH in infants with BPD, but did not describe the impact of this on mortality [16, 17]. This highlights the need for early as well as regular screening for pulmonary hypertension via echocardiographic assessment in infants with BPD.

One study reported the healthcare utilization of infants with PH associated with BPD presenting after two months of age into a BPD clinic and found that the infants were hospitalised for a longer duration and had more respiratory morbidity than infants with BPD but no PH [28]. Our study reported on the total cost of stay based on national average in infants with BPD and PH and to our knowledge this is the first study which specifically looked into the effect of pulmonary hypertension in infants with bronchopulmonary dysplasia on health care costs.

Our study has strengths and some limitations. In our study population we used echocardiography to identify pulmonary hypertension; echocardiography is considered to be an effective and reliable screening tool for detection of pulmonary hypertension in infants with BPD [29]. A limitation, however, was that the infants had echocardiograms at various time intervals according to clinical need rather than at specific intervals, but this makes our results generalisable to clinical practice.

In conclusion, infants with late PH had a longer duration of hospitalization and increased mortality compared to the infants without late PH. The presence of late PH in infants with BPD resulted in increased healthcare costs.

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Table 5: Late PH and mortality and total cost of stay.

	Late PH (n=22), n (%) or median (IQR)	No late PH (n=160), n (%) or median (IQR)	p- Value	Odds ratio (95% CI)	Adjusted p-value	Adjusted OR (95% CI)
Mortality	8 (36.4)	3 (1.9)	<0.001	29.9 (7.1–125.6)	0.001	26.9 (3.8–189.4)
Length of hospital- isation, days	147 (118–189)	109 (85–149)	0.002		0.034	
Total cost of hospital stay	£113,494 (72,650–169,798)	£78,677 (48,476–115,483)	0.018		0.016	

PH, pulmonary hypertension; IQR, interquartile range.

analysis of the data. All authors were involved in the preparation of the manuscript and approved the final

**Competing interests:** Authors state no conflict of interest. **Informed consent:** Not applicable.

**Ethical approval:** The study was registered with the King's College Hospital NHS Foundation Trust Clinical Governance and Audit Department and did not require informed parental consent.

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