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Life-threatening bronchopulmonary dysplasia: a British Paediatric Surveillance Unit Study

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ABSTRACT

Objectives To assess the minimum incidence of life-threatening bronchopulmonary dysplasia (BPD), defined as need for positive pressure respiratory support or pulmonary vasodilators at 38 weeks corrected gestational age (CGA), in infants born <32 weeks gestation in the UK and Ireland; and to describe patient characteristics, management and outcomes to 1 year.

Methods Prospective national surveillance study performed via the British Paediatric Surveillance Unit from June 2017 to July 2018. Data were collected in a series of three questionnaires from notification to 1 year of age.

Results 153 notifications met the case definition, giving a minimum incidence of 13.9 (95% CI: 11.8 to 16.3) per 1000 live births <32 weeks' gestation. Median gestation was 26.1 (IQR 24.6–28) weeks, and birth weight 730 g (IQR 620–910 g). More affected infants were male (95 of 153, 62%; p<0.05). Detailed management and outcome data were provided for 94 infants. Fifteen died at median age 159 days (IQR 105–182) or 49.6 weeks CGA (IQR 43–53). Median age last receiving invasive ventilation was 50 days (IQR 22–98) and total duration of pressure support for surviving infants 103 (IQR 87–134) days. Fifty-seven (60.6%) received postnatal steroids and 22 (23.4%) pulmonary vasodilators. Death (16%) and/or major neurodevelopmental impairment (37.3%) or long-term ventilation (23.4%) were significantly associated with need for invasive ventilation near term and pulmonary hypertension.

Conclusions This definition of life-threatening BPD identified an extremely high-risk subgroup, associated with serious morbidity and mortality. Wide variability in management was demonstrated, and future prospective study, particularly in key areas of postnatal steroid use and pulmonary hypertension management, is required.

What is already known on this topic?

- Bronchopulmonary dysplasia (BPD) is a common complication of preterm birth with significant respiratory and neurodevelopment consequences.
- Little is known about the outcomes of infants with the most severe BPD, particularly infants requiring positive pressure support near term.
- There is limited evidence to guide treatment of established BPD, and management strategies vary.

What this study adds?

- We defined 'life-threatening' BPD in preterm infants requiring positive pressure respiratory support or pulmonary vasodilators at, or beyond, 38 weeks corrected gestational age.
- Mortality and morbidity were high, and significant variation in practice was demonstrated.
- Invasive ventilation near term and presence of pulmonary hypertension were identified as key factors significantly associated with adverse outcomes within this cohort.

INTRODUCTION

Significant bronchopulmonary dysplasia (BPD), defined as need for oxygen or positive pressure respiratory support at 36 weeks corrected gestational age (CGA), affected 37% of infants born <32 weeks gestation in the UK in 2019, and is the most common major complication of preterm birth.[1] BPD is associated with adverse respiratory and neurodevelopmental outcomes throughout childhood and into adult life, and despite significant progress in neonatal respiratory care in recent decades, rates continue to increase.[2–4]

BPD is traditionally classified according to respiratory support or oxygen requirement at 36 weeks CGA,[5] but it is increasingly recognised that the predictive value of this classification is limited, and need for pressure support more closely associated with longer term morbidity.[6–8]

Although extensively studied as a broad group, there is little data on treatment and outcomes of infants with the most severe BPD, making management decisions, counselling and identification of research priorities difficult. This study aimed to identify the minimum incidence of 'life-threatening BPD', defined as a need for positive pressure respiratory support or pulmonary vasodilators at 38 weeks CGA in the UK and Ireland, and to describe infant characteristics, management strategies, and outcomes to 1 year. This pragmatic definition was chosen to capture infants with the most severe lung disease and include a feasible number of infants to survey in this manner, providing a novel detailed description of this group.

METHODS

This was an observational, descriptive surveillance study in the UK and Ireland, carried out via the British Paediatric Surveillance Unit (BPSU), a

well-established centre for paediatric rare disease surveillance, using their methodologies.[9] All paediatricians are sent monthly electronic reporting cards to notify cases or confirm they have seen none. Surveillance was undertaken for 13 months from 1 July 2017 to 31 July 2018 as standard for BPSU Studies.

Clinicians then completed up to three questionnaires using medical records: questionnaire 1 at notification (demographics, pregnancy and delivery details), questionnaire 2 at 8 weeks post-term (neonatal care and outcome at discharge/death), and questionnaire 3 at 1 year of age (post-discharge data). Presence of major or minor neurodevelopmental concerns at 1 year was reported from medical records. Up to three reminders were sent for each questionnaire by email and post.

Case definition

Life-threatening BPD was defined in any infant born at <32 weeks gestation, without significant congenital anomaly, requiring positive pressure support (ventilation, continuous/bilevel positive airway pressure (CPAP/BiPAP), or high flow ≥2 L/min) or pulmonary vasodilators at 38 weeks CGA, without intercurrent illness to explain this need.

Statistics

Descriptive statistics with measures of central tendency and dispersion were used. Categorical variables were compared using X^2 or Fisher's exact tests, and continuous, non-parametric variables using Mann-Whitney U test. A p value of <0.05 was considered significant. Binomial logistic regression was used to evaluate predictors of outcomes. Models included gestational age (GA), birth weight and sex, plus variables with p<0.1 on univariate analysis not showing multicollinearity. All analyses were performed using IBM SPSS V.26.

RESULTS

Case reporting

During the study period, overall monthly BPSU surveillance reporting was 94.7%. In total, 329 notifications were received; 90 were excluded as they did not fulfil inclusion criteria (n=68) or were duplicates (n=22). For a further 86 notifications, no data were provided despite multiple requests. One hundred fifty-three confirmed cases were finally included with detailed data up to discharge (questionnaire 2) provided for 94 infants and data to 1 year or death (questionnaire 3) for 77 infants (figure 1). All infants met the case definition by virtue of requiring positive pressure support at 38 weeks' CGA.

Incidence

Using national population estimates,[10–13] minimum incidence of life-threatening BPD during the surveillance period was 13.9 (95% CI 11.8 to 16.3) per 1000 live births <32 weeks gestation, or 0.17 (0.15 to 0.2) per 1000 of all live births, based on 153 confirmed cases.

Demographics

Cases were reported from 57 hospitals, with individual units reporting 0–12 cases. Median GA was 26.1 weeks (IQR 24.6–28), and birth weight 730 g (IQR 620–910 g). More affected infants were male (95 of 153, 62%; p<0.05) and most (120 of 153, 78%) white British (online supplemental table 1). No differences in baseline characteristics were identified between infants with and without discharge data (online supplemental table 2).

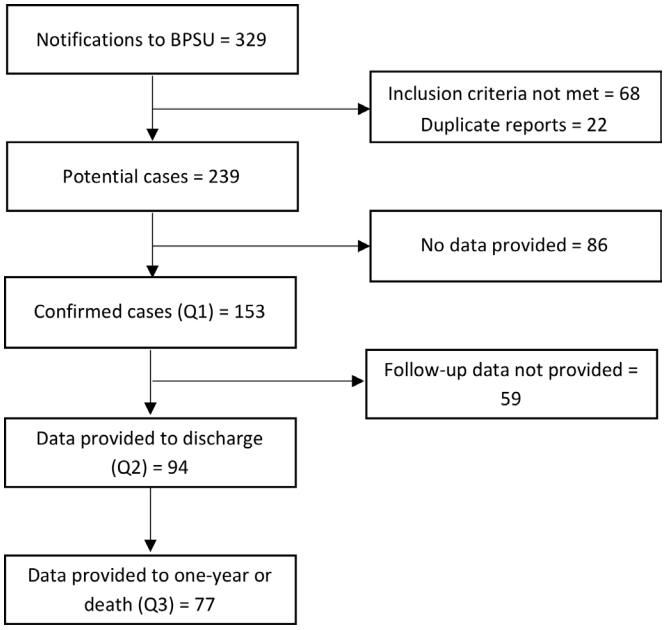

Figure 1 Cases reported to the BPSU. Q1/Q2/Q3=eligible questionnaire returned. BPSU, British Paediatric Surveillance Unit.

Antenatal steroids were given in 139 of 153 (90.8%) cases, with the last dose received a median of 2 days (IQR 1–6) before delivery (table 1).

Respiratory support

Episodes of respiratory support were considered separate if transfer to another device was achieved for >24 hours. Two of 94 cases provided incomplete respiratory data due to multiple postnatal transfers. Ninety-one (98.9%) infants received invasive ventilation: 85 of 91 (92.4%) on the first day of life and the remaining 6 within 72 hours. Infants were ventilated for median 29 days (IQR 17–51) in 2 (IQR 1–3) episodes, and median age last receiving invasive ventilation was 50 days (IQR 22–98).

All ventilated infants received surfactant, with a median first dose of 182 mg/kg (IQR 144–211) given at 11 min (IQR 7–23) of age. High-frequency oscillatory ventilation (HFOV) was used in 53 of 94 (56.4%); 30 of 94 (31.9%) received inhaled nitric oxide, and 4 of 94 (4.3%) had a pneumothorax.

Nasal CPAP/BiPAP and high flow were both extensively used (96.7% and 91.3%, respectively, table 2). High flow was generally started later and given for a significantly longer duration than CPAP (40.5 vs 27 days; p<0.05). Median duration of positive pressure support for infants discharged alive, off support was 103 days (IQR 87–134; max 258), which was discontinued at a median 41.3 weeks CGA (IQR 39.4–45.4; max 65.14). Seven infants required long-term ventilation post-discharge, all of whom survived to 1 year.

Postnatal steroids

Postnatal steroids were used for BPD in 57 of 94 (60.6%) infants, starting at a median age of 26 days (IQR 14–48). Initial steroid received was dexamethasone in the majority (52 of 57; 91.2%). Median steroid courses (defined as separate if >72 hours deliberately elapsed between doses) per infant was 1 (IQR 0–2, max 6). In total, infants in the study received 109 courses of steroid: 90 (82.6%) dexamethasone, 10 (9.2%) prednisolone, 5 (4.6%) methylprednisolone and 4 (3.7%) hydrocortisone. Two infants

Table 1 Demographic, antenatal and delivery details

Demographics	
Gestational age at delivery (weeks)	26.1 (24.6–28)
Birth weight (g)	730 (620–910)
Birth weight <10th centile	57/153 (37.3%)
Male	95/153 (62.1%)
Female	58/153 (37.9%)
Antenatal steroids	
Received any steroid	139/153 (90.8%)
Incomplete course only	16/139 (11.5%)
One complete course	109/139 (78.4%)
Two complete courses	13/139 (9.4%)
Courses not known	1/139 (0.7%)
None	13/153 (8.5%)
Not known	1/153 (0.7%)
Antenatal steroid received	
Betamethasone	66/139 (47.5%)
Dexamethasone	65/139 (46.8%)
Betamethasone and dexamethasone	1/139 (0.7%)
Not known	7/139 (5.0%)
Mode of delivery	
Caesarean section	85/153 (55.6%)
Vaginal	64/153 (41.8%)
Not known	4/153 (2.6%)
Rupture of membranes	
Prelabour	65/153 (42.5%)
Prolonged (>24 hours)	46/153 (30.1%)
Placenta	
Evidence of chorioamnionitis	21/153 (13.7%)
Other abnormality	21/153 (13.7%)
Apgar scores	
5 min	7 (5–8)
10 min	8 (7–9)
Surfactant	
Doses received	
None	1/153 (0.7%)
One	58/153 (37.9%)
Two	50/153 (32.7%)
≥Three	33/153 (21.6%)
Not known	11/153 (7.2%)
Respiratory support at 36 weeks' CGA	
Invasive ventilation	13/94 (13.8%)
CPAP/BiPAP	32/94 (34%)
High flow	43/94 (45.7%)
Not known	6/94 (6.4%)
Respiratory support at 38 weeks' CGA	
Invasive ventilation	13/94 (13.8%)
CPAP/BiPAP	20/94 (21.3%)
High flow	56/94 (59.6%)
Not known	5/94 (5.3%)

Data presented as number (%) or median (IQR).
BiPAP, bilevel positive airway pressure; CGA, corrected gestational age; CPAP, continuous positive airway pressure.

received Mini-Dex investigational medicinal product, one of whom also received open-label dexamethasone.[14]

Dexamethasone was given at a median starting dose of 135 µg/kg/day (IQR 50–150), and maximum dose 150 µg/kg/day (IQR 100–200) for 10 days (IQR 10–16) per course. Median total duration of steroid treatment was 23 days (IQR 14–44, range 2–163), and nine remained on steroid at discharge.

Management of patent ductus arteriosus

Medical therapy for patent ductus arteriosus (PDA) was used in 36 of 94 (38.3%) infants, and 8 (8.4%) received repeat courses (table 2). Seventeen (18.1%) underwent PDA ligation at median age of 43 days (IQR 37–78): 11 following medical therapy and 6 primary closures. Immediately before ligation, 9 of 17 (52.9%) infants were invasively ventilated.

Infections

Culture-positive sepsis occurred in 42 of 94 (44.7%) infants, most commonly coagulase-negative staphylococcus. Forty-nine (52.1%) experienced ≥1 episode of culture-negative sepsis, and 32 of 94 (34.0%) pneumonia, most commonly *Klebsiella* or *Staphylococcus aureus* (online supplemental table 3). Median number of treated infections was 2 (IQR 1–4), and age of first reported infection 7 days (IQR 1–28).

Pulmonary hypertension

Echocardiographic evidence of pulmonary hypertension (PHT) was identified in 32 of 94 (34%) infants. Sildenafil was used in 22 of 94 (23.4%) at a maximum dose of 3 mg/kg/day (IQR 1.6–4.3). One infant also received bosentan.

Other medications

Diuretics were frequently used (82 of 94, 87.2%), while inhaled steroids and bronchodilators were less common and started much later during admission (table 2).

Outcomes

Key outcomes are reported in table 3. By 1 year of age, 15 of 94 (16%) infants died; 14 before discharge, at median age 159 days (IQR 105–182) or 49.6 weeks CGA (IQR 43–52.9). Reported cause of death was BPD in 11 of 15 (73.3%), pulmonary stenosis in 1 of 15 (6.7%), and not known in 3 of 15 (20%).

Of 79 surviving infants, 1 (1.3%) remained an inpatient at 1 year. Median age of discharge home was 143 (IQR 117–185) days, or 46.6 (IQR 43–52.9) weeks CGA. Eighteen infants were transferred to respiratory paediatrics before discharge. At final discharge, 60 of 79 (75.9%) infants were documented as receiving low-flow oxygen, and 7 of 79 (8.9%) required long-term positive pressure support at home. Five had a tracheostomy at a median age of 260 days (range 177–278). Post-discharge, two infants required new invasive ventilation, one required CPAP and eight required high flow during readmissions in the first year of life.

One-year neurodevelopmental assessment was available for 60 of 79 (76%) surviving infants. No concerns were reported for 37 (61.7%), minor concerns in 10 (16.7%) and major concerns in 13 (21.7%) infants.

Characteristics of infants who died with and without major neurodevelopmental impairment (NDI) or required long-term ventilation are compared in table 4. Presence of PHT and need for any invasive ventilation at or beyond 38 weeks were significantly associated with these adverse outcomes on regression analysis.

DISCUSSION

Broad definitions of BPD do not facilitate focus on the most severely affected infants who merit separate approaches to their care. Infants requiring pressure support near term are an

Table 2 Respiratory support and medications received pre-discharge

	Number of infants	Starting age (days)	Starting CGA (weeks)	Total duration (days)	Postnatal age last received (days)
Respiratory support					
Invasive ventilation	91/92 (98.9%)	0 (0–0; 0–2)	26.4 (24.6–28.1; 23.3–31.3)	29 (17–51; 1–238)	50 (22–98)
Nasal CPAP/BiPAP	89/92 (96.7%)	20 (6–39; 0–152)	29.6 (27.7–32.1; 24.3–48.7)	27 (14–45; 2–297)	84 (49–103)
Nasal high flow	84/92 (91.3%)	49.5 (28–84; 0–161)	33.6 (31.1–37.1; 27.7–50.7)	40.5 (22–64; 4–156)	109 (89.5–143)
Medications					
PDA closure	36/94 (38.6%)	7.5 (5–14.5; 0–34)	26.3 (25.3–27.1; 23.9–31.9)	–	–
Ibuprofen	33 (91.7%)				
Paracetamol	4 (11.1%)				
Postnatal steroid	57/94 (60.6%)	26 (14–48; 0–185)	29.7 (27.9–33.4; 24.6–55.9)	23 (14–44)	91 (57–150)
Diuretics	82/94 (87.2%)	32 (17–51; 3–204)	31.1 (29.1–34.5; 25.4–34.5)	90 (49–123)	128 (101–169)
Inhaled steroid	16/94 (17.0%)	96.5 (60–126; 9–231)	39.4 (35.0–46.5; 26.4–61.1)	21 (5–74)	132 (104–183)
Inhaled bronchodilators	8/94 (8.5%)	124.5 (120–192; 100–231)	45.4 (42.4–56.6; 40.9–61.1)	14 (5–27)	148 (134–209)
Sildenafil	22/94 (23.4%)	–	–	44 (18–132)	–

Data presented as number (%) or median (IQR; ±range). Ages and duration displayed for infants who received intervention only.
BiPAP, bilevel positive airway pressure; CGA, corrected gestational age; CPAP, continuous positive airway pressure; PDA, patent ductus arteriosus.

extremely vulnerable subgroup, at high-risk of death, respiratory and neurodevelopmental morbidity.[6 15] This study describes in detail the demographics, management and clinical outcomes of infants with 'life-threatening' BPD; a group we defined based on assessment at 38 weeks to capture those with the most severe disease.

Table 3 Discharge details and outcomes

Outcomes	Number (%)
Status at 1 year	
Discharged home	76/94 (81)
Died	15/94 (16)
Remained inpatient	1/94 (1.1)
Not known	2/94 (2.1)
Age of discharge home (days)	143 (117–185)
CGA of discharge home (weeks)	46.6 (43–52.9)
Age of death (days)	159 (105–182)
CGA of death (weeks)	49.6 (42.6–52.6)
Respiratory support at discharge	
Air	8/79 (10.1)
Low-flow oxygen	60/79 (75.9)
Long-term ventilation (ventilation, CPAP, high flow)	7/79 (8.9)
Not known	4/79 (5.1)
Comorbidities	
Retinopathy of prematurity requiring treatment	26/94 (27.7)
Laser	20/94 (21.3)
Avastin	3/94 (3.2)
Both	3/94 (3.2)
Periventricular leukomalacia	7/94 (7.4)
Ventriculoperitoneal shunt inserted	5/94 (5.3)
Gastrostomy inserted	7/94 (7.4)
Tracheostomy	5/94 (5.3)
Neurological assessment at 1 year	
Normal	37/60 (61.7)
Minor concerns	10/60 (16.7)
Major concerns	13/60 (21.7)
Death or long-term ventilation (LTV)	22/94 (23.4)
Death or major neurodevelopmental impairment (NDI)	28/75 (37.3)*
Death or major morbidity (LTV, major NDI or readmission for respiratory support within 1st year)	42/94 (44.7)

Data presented as number (%) or median (IQR).
*Outcomes reported for infants with complete data only.
CGA, corrected gestational age; CPAP, continuous positive airway pressure.

There are certain limitations to this study. The well-established BPSU methodology was chosen to provide a collated overview of a condition seen rarely in individual units, with a high level of detail not possible using other methodologies. Compliance with reporting is high, but ascertainment and follow-up limited by clinician's responses. Our study of three questionnaires was designed to maximise data collected but, despite multiple reminders, attrition occurred at each stage, meaning detailed information was provided for 94 of 153 confirmed (or 239 potential) cases. Although a potential source of bias, baseline characteristics of infants with and without additional data were similar, and a detailed description of highly informative cases from 57 different centres is provided. Minimum incidence of life-threatening BPD was calculated using 153 confirmed cases, however true incidence is likely higher due to under-reporting. Finally, as cases were reported at 38 weeks CGA, deaths occurring before this time point or without meeting the case definition were not captured, therefore true BPD-related mortality is higher.

Our minimum annual incidence of life-threatening BPD is 13.9 (95% CI 11.8 to 16.3) per 1000 live births <32 weeks gestation. The associated high mortality, morbidity and significant resource use during a protracted neonatal admission make further study important. Furthermore, incidence is likely to increase as progressively more immature infants are supported from birth, and survival at the lowest gestation increases.[16]

By definition, infants received very prolonged pressure support (median 103 days). Most were ventilated on the first day of life, and it is unclear whether a more proactive approach to non-invasive support from birth would have a positive impact in this cohort.[17] Need for any invasive ventilation at or beyond 38 weeks CGA was significantly associated with death and major morbidity in this cohort (also significant when retrospectively assessed at 36 weeks). This is consistent with Jensen *et al* reporting significantly higher rates of death, serious respiratory and NDI in infants requiring invasive rather than non-invasive support at 36 weeks CGA, and supports the distinct classification of infants requiring invasive ventilation near term as an extremely high-risk subgroup.[6]

Table 4 Comparison of infants with and without outcomes of death, death/major neurodevelopmental impairment (NDI) and death/long-term ventilation (LTV) at 1 year

Association with outcomes on univariate analysis

	Died (n=15)	Alive (n=77)	P value	Death/NDI (n=28)	No death/NDI (n=47)	P value	Death/LTV (n=22)	No death/LTV (n=70)	P value
Gestational age (weeks)	27.0 (24.1–27.7)	26.1 (24.7–28.3)	0.816	26.4 (24.6–27.4)	27.0 (25.1–28.7)	0.179	26.8 (24.3–28.4)	26.1 (25–28.1)	0.826
Birth weight (g)	705 (570–869)	755 (621–930)	0.316	750 (610–892)	775 (604–1048)	0.511	706 (579–874)	775 (611–960)	0.385
Birth weight <10th centile	7 (46.7%)	29 (37.7%)	0.513	10 (35.7%)	22 (46.8%)	0.347	9 (40.9%)	27 (38.6%)	0.845
Male sex	7 (46%)	48 (62%)	0.257	16 (57.1%)	30 (63.8%)	0.565	11 (50%)	44 (62.9%)	0.283
Received antenatal steroids	15 (100%)	68 (88.3%)	0.346	24 (85.7%)	46 (97.9%)	0.061	20 (90.9%)	63 (90%)	1.0
Received postnatal steroids	12 (80%)	43 (55.8%)	0.081	20 (71.4%)	25 (53.2%)	0.119	17 (77.3%)	38 (54.3%)	0.055
Duration postnatal steroids (days)	31 (10–53)	8 (0–27)	0.029	23 (0–54)	0 (0–32)	0.030	29 (8–53)	4 (0–24)	0.009
Age first steroid (days)	23 (7–63)	11 (0–30)	0.081	13 (0–120)	0 (0–27.3)	0.134	18 (2–46)	10 (0–28)	0.093
Starting dose dexamethasone (µg/kg/day)	87.5 (15–142.5)	25 (0–120)	0.093	50 (0–120)	0 (0–120)	0.242	100 (0–150)	0 (0–120)	0.033
Maximum dose dexamethasone (µg/kg/day)	120 (30–120)	0 (0–120)	0.032	60 (0–150)	0 (0–120)	0.095	120 (0–200)	0 (0–120)	0.011
Duration initial ventilation (days)	23 (9–43)	16 (5–34)	0.269	22 (7–42)	11 (3–24)	0.069	24 (6–44)	16 (5–30)	0.213
Duration total ventilation (days)	23 (11–42)	30 (18–54)	0.215	23 (11–42)	34 (18–52)	0.108	24 (11–43)	33 (18–53)	0.145
Any ventilation ≥36 weeks	12 (80%)	24 (31.2%)	<0.001	17 (60.7%)	13 (27.7%)	0.005	15 (68.2%)	21 (30%)	0.001
Any ventilation ≥38 weeks	12 (80%)	18 (23.4%)	<0.001	15 (53.6%)	9 (19.1%)	0.002	14 (63.6%)	16 (22.9%)	<0.001
Any CPAP/BiPAP ≥38 weeks	11 (73.3%)	31 (40.3%)	0.019	15 (53.6%)	20 (42.6%)	0.355	10 (45.5%)	10 (14.3%)	0.052
Any high flow ≥38 weeks	8 (53.3%)	71 (92.2%)	0.001	20 (71.4%)	45 (95.7%)	0.004	14 (63.6%)	28 (40%)	0.002
Received inhaled nitric oxide	7 (46.7%)	23 (29.9%)	0.236	12 (42.9%)	14 (29.8%)	0.25	9 (40.9%)	20 (28.6%)	0.141
Received HFOV	12 (80%)	39 (50.6%)	0.036	17 (60.7%)	26 (55.3%)	0.648	14 (63.6%)	65 (92.9%)	0.061
Pulmonary hypertension*	12 (80%)	18/74 (24.3%)	<0.001	16 (57.1%)	10/46 (21.7%)	0.002	13 (59.1%)	46 (65.7%)	<0.001
Received sildenafil*	10 (66.7%)	12/75 (16%)	<0.001	11 (39.3%)	8/46 (17.4%)	0.037	14 (63.6%)	8/68 (11.8%)	<0.001

Association with outcomes on binomial logistic regression analysis

	Death aOR (95% CI)	P value	Death/NDI aOR (95% CI)	P value	Death/LTV aOR (95% CI)	P value
Gestational age (weeks)	1.42 (0.85 to 2.37)	0.183	0.96 (0.66 to 1.42)	0.849	1.33 (0.87 to 2.05)	0.188
Birth weight (g)	1.0 (0.99 to 1.00)	0.439	1.00 (1.0 to 1.0)	0.183	1.00 (1.0 to 1.0)	0.758
Male sex	0.40 (0.09 to 1.87)	0.242	0.70 (0.20 to 2.38)	0.562	0.40 (0.11 to 1.43)	0.159
Received antenatal steroids	–	–	0.02 (0.001 to 0.40)	0.010	0.71 (0.11 to 4.68)	0.721
Received postnatal steroids	3.42 (0.55 to 21.16)	0.186	4.33 (0.96 to 19.52)	0.057	2.91 (0.66 to 12.78)	0.158
Any ventilation ≥38 weeks	10.95 (1.97 to 60.79)	0.006	5.73 (1.45 to 22.70)	0.013	5.95 (1.51 to 23.46)	0.011
Received HFOV	2.52 (0.42 to 15.03)	0.309	0.47 (1.22 to 1.81)	0.273	1.33 (0.34 to 5.15)	0.681
Pulmonary hypertension	6.88 (1.47 to 32.28)	0.015	3.71 (1.001 to 13.72)	0.049	5.58 (1.61 to 19.40)	0.007

Results of univariate analysis reported as number (%) or median (IQR); results of regression analysis reported as aOR (95% CI).
*Reported for infants with complete data only.
aOR, adjusted OR; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; HFOV, high-frequency oscillatory ventilation.

HFOV was common (56.4%) and associated with increased risk of death, presumably reflecting use as 'rescue' therapy. Similarly, inhaled nitric oxide use was higher than the general preterm population (31.9% vs 16.6%), indicating severe respiratory disease, and knowledge of such associations with poorer outcomes may facilitate risk stratification for future treatment intervention studies.[18]

Although most infants received both CPAP and high flow (97% and 92%, respectively), high flow was generally started later and continued for a significantly longer duration. A number of retrospective studies have reported increased BPD, longer respiratory support and hospitalisation since introduction of high flow, although this is not universal.[19–21] Randomising infants with evolving BPD to weaning via CPAP only or CPAP and high flow to explore this relationship further would be helpful.

Postnatal dexamethasone reduces BPD, but optimal timing, dosing and duration of postnatal steroids to prevent and treat BPD are unknown.[22 23] Only 61% of infants received any postnatal steroid, despite the severity of their BPD, and significant variability in use demonstrated. Treatment commenced at an average age of 26 days, but recent retrospective studies suggest benefit from earlier treatment in the second postnatal week.[24] Risk stratification and prospective assessment of the optimal steroid regimes both to prevent BPD in high-risk infants and to treat established BPD should be a priority.

Diuretics were widely used (87%) despite no convincing evidence for long-term respiratory benefit and frequent side-effects.[25 26] Inhaled steroids and bronchodilators were used uncommonly (17% and 8.5%, respectively) and later in the inpatient course, likely reflecting a shift to treatment of established BPD. Neither have proven efficacy in prevention or treatment of BPD but evidence is scarce, and further work to clarify the role of these medications is needed.[27–29]

Nosocomial infections are implicated in the pathogenesis of BPD, and colonisation with *Ureaplasma* spp specifically associated with >2-fold risk of BPD on meta-analysis.[30] *Ureaplasma* was only isolated in one infant, but screening for atypical organisms, and conditions such as cytomegalovirus were not surveyed; an area for potential development addressed by the ongoing AZTEC Study (ISRCTN11650227).

Abnormalities of pulmonary vascular structure and function are common in BPD, with a subset of infants developing

clinical PHT proportional to BPD severity.[31 32] In our cohort, 34% had confirmed PHT, however screening rates were not surveyed, so this may be an underestimation. Recognised PHT was significantly associated with death, major NDI and/or long-term ventilation, highlighting this as an important prognostic factor potentially amenable to treatment.[33] Retrospective studies have associated sildenafil use with haemodynamic improvement and reduced mortality, although efficacy data are limited, and prospective studies to establish optimal PHT screening and treatment regimens required.[33 34]

By 1 year of age, 16% infants died, however this cohort did not include BPD-related deaths before 38 weeks, so overall mortality is higher. Ultimately, 81% infants were discharge home at a median 46.6 weeks CGA. While most were weaned to low-flow oxygen, 9% required long-term ventilation and major NDI was evident at 1 year in one of five survivors; significantly higher than the general preterm population.[35] The associated substantial ongoing healthcare resource use and impact on families make this condition a priority for future investment.

CONCLUSIONS

Life-threatening BPD occurred in 13.9 per 1000 infants born at <32 weeks gestation during the study period, with death or major morbidity in 45% of affected infants. There is little evidence to guide management of severe BPD, and we demonstrate significant variation in practice. Optimisation of non-invasive respiratory support, targeted postnatal corticosteroid use and universal screening for PHT are recommended priority actions. We have identified an extremely high-risk subgroup not discernible using current definitions of BPD, and better identification, possibly through a dedicated register, and research focus on this group of infants is urgently needed.

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Supplemental Data

Gestation	Number (%)
23^{+0}-24^{+6}	50/153 (32.7%)
25^{+0}-27^{+6}	62/153 (40.5%)
28^{+0}-29^{+6}	33/153 (21.6%)
30^{+0}-32^{+0}	7/153 (4.6%)
Not known	1/153 (0.7%)
Birth Weight	
<500g	9/153 (5.9%)
500-749g	66/153 (43.1%)
750-999g	47/153 (30.7%)
≥1000g	27/153 (17.6%)
Not known	4/153 (2.6%)
Birth Weight Centile	
≤0.4	18/153 (11.8%)
2	16/153 (10.5%)
9	23/153 (15.0%)
25	39/153 (25.5%)
50	40/153 (26.1%)
≥75	12/153 (7.8%)
NK	5/153 (3.3%)
Ethnicity	
White British	120/153 (78.4%)
Pakistani	11/153 (7.2%)
African	7/153 (4.6%)
Indian	4/153 (2.6%)
Other	10/153 (6.5%)
Not known	1/153 (0.7%)
Reporting Country	
England	129/153 (84.3%)
Scotland	13/153 (8.5%)
Wales	3/153 (2%)
Northern Ireland	5/153 (3.3%)
Ireland	3/153 (2%)

Supplementary Table 1: Additional Demographic Data

	All	Additional Data Provided to Discharge	Additional Data Not Provided	p
Gestation (weeks)	26.1 (24.6-28)	26.3 (24.6-28.1)	25.6 (24.7-28)	0.40
Birth weight (g)	730 (620-910g)	715 (601-912)	755 (630-898)	0.77
Male sex	95/153 (62%)	56/94 (60%)	39/59 (66%)	0.42
Birth weight <10th centile	57/153 (37%)	37/94 (39%)	20/59 (34%)	0.49
Received antenatal steroids	138/153 (91%)	85/94 (90%)	53/58 (91%)	0.84
C-section delivery	85/149 (57%)	54/93 (58%)	31/56 (55%)	0.75
5-minute Apgar score	7 (5-8)	7 (5-8)	6 (5-8)	0.90
10-minute Apgar score	8 (7-9)	8 (7.8-9)	8 (7-9)	0.83

Supplementary Table 2: Demographics of infants with and without additional discharge data provided.

	Blood Culture/PCR Positive	Pneumonia
Gram Positive		
CONS	35	1
Enterococcus faecalis	8	1
S. aureus	6	5
GBS	2	-
Corynebacterium	2	-
Gram Negative		
E. coli	7	2
Enterobacter	2	1
Pseudomonas	1	3
Klebsiella	1	5
Serratia	1	-
Stenotrophomonas	-	2
Proteus	-	2
Ureaplasma	-	1
Viruses		
HSV-2	1	-
Rhinovirus	-	3
CMV	-	1
Parainfluenza	-	1
RSV	-	1
Fungi		
Candida	1	-

Supplementary Table 3: Organisms identified