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 620–910 g). Fifty-seven (60.6%) received postnatal steroids 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.

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.3–8

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, or beyond, 38 weeks corrected gestational age.

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RESULTS

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.

What is already known on this topic?

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What this study adds?

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well-established centre for paediatric rare disease surveillance, using their methodologies. 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 ≥2L/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 X² 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’ GA.

Incidence
Using national population estimates, 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).

Disputes 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.

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 0–6, 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

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).

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Nasal CPAP/BiPAP and high flow were both extensively used (96.7% and 91.3%, respectively, table 2). Flow high 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.
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%) pneumonias, 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

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**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 (>24hours) | 46/153 (30.1%) |
| Placenta |  |  |  |
| Evidence of chorioamnionitis | 21/153 (13.7%) | Other abnormality | 21/153 (13.7%) |
| Appgar scores | 5min | 7 (5–8) | 10min | 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 (34.0%) |
| 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
extremely vulnerable subgroup, at high-risk of death, respiratory and neurodevelopmental morbidity. 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.

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.

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. 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.

**Table 2** Respiratory support and medications received pre-discharge

| Respiratory support                          | Number of infants | Starting age (days) | Starting CGA (weeks) | Total duration (days) | Postnatal age last received (days) |
|----------------------------------------------|-------------------|--------------------|----------------------|-----------------------|-----------------------------------|
| 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)                   |

*Outcomes reported for infants with complete data only.

**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)  |
| Perventriculal 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 (LTi)       | 22/94 (23.4) |
| Death or major neurodevelopmental impairment (NDI) | 28/75 (37.3)* |
| Death or major morbidity (LTi, major NDI or readmission for respiratory support within 1st year) | 42/94 (44.7) |

*Data presented as number (%) or median (IQR).
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.

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.18–22 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. Nosocomial infections are implicated in the pathogenesis of BPD. Neither have proven efficacy in prevention or treatment of BPD. Neither have proven efficacy in prevention or treatment of BPD. Neither have proven efficacy in prevention or treatment of BPD. Neither have proven efficacy in prevention or treatment of BPD. Neither have proven efficacy in prevention or treatment of BPD. Neither have proven efficacy in prevention or treatment of BPD.

Results of univariate analysis reported as number (%) or median (IQR); results of regression analysis reported as aOR (95% CI).

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

### Association with outcomes on univariate analysis

| Death/NDI (n=28) | No death/NDI (n=47) | Death/LTV (n=22) | No death/LTV (n=70) |
|------------------|---------------------|-------------------|--------------------|
| **Gestational age (weeks)** | 27.0 (24.1–27.7) | 26.1 (24.7–28.3) | 27.0 (25.1–28.7) | 26.8 (24.3–28.4) |
| **Birth weight (g)** | 705 (570–869) | 755 (621–930) | 750 (610–892) | 775 (604–1048) |
| **Birth weight <10th centile** | 7 (46.7%) | 29 (37.7%) | 510 (35.7%) | 22 (46.8%) |
| **Male sex** | 7 (46%) | 48 (62%) | 256 (57.1%) | 30 (63.8%) |
| **Received antenatal steroids** | 15 (100%) | 68 (88.3%) | 160 (71.4%) | 105 (62.9%) |
| **Received postnatal steroids** | 12 (80%) | 43 (55.8%) | 200 (53.6%) | 150 (44.2%) |
| **Duration postnatal steroids (days)** | 31 (10–53) | 8 (0–27) | 29 (9–53) | 4 (0–24) |
| **Age first steroid (days)** | 23 (7–63) | 11 (0–10) | 23 (7–63) | 10 (0–35) |
| **Starting dose dexamethasone (µg/kg/day)** | 87.5 (15–142.5) | 25 (0–120) | 50 (0–120) | 10 (0–120) |
| **Maximum dose dexamethasone (µg/kg/day)** | 120 (30–120) | 0 (0–120) | 60 (0–150) | 0 (0–120) |
| **Diuretics** | 0.269 | 0.257 | 0.269 | 0.257 |
| **Antenatal steroids** | 0.269 | 0.257 | 0.269 | 0.257 |
| **Male sex** | 0.269 | 0.257 | 0.269 | 0.257 |
| **Received antenatal steroids** | 0.16 | 0.15 | 0.16 | 0.15 |
| **Received postnatal steroids** | 0.20 | 0.19 | 0.20 | 0.19 |
| **Duration postnatal steroids (days)** | 0.029 | 0.020 | 0.029 | 0.020 |
| **Age first steroid (days)** | 0.081 | 0.081 | 0.081 | 0.081 |
| **Starting dose dexamethasone (µg/kg/day)** | 0.081 | 0.081 | 0.081 | 0.081 |
| **Maximum dose dexamethasone (µg/kg/day)** | 0.081 | 0.081 | 0.081 | 0.081 |

### Association with outcomes on binomial logistic regression analysis

| Death | (95% CI) | P value | Death/NDI | (95% CI) | P value | Death/LTV | (95% CI) | P value |
|-------|----------|---------|-----------|----------|---------|-----------|----------|---------|
| Gestational age (weeks) | 1.42 (0.95 to 2.37) | 0.183 | 1.06 (0.66 to 1.74) | 1.08 | 1.33 (0.87 to 2.05) | 0.188 |
| Birth weight (g) | 1.0 (0.99 to 1.00) | 0.419 | 1.0 (1.00 to 1.0) | 1.08 | 1.33 (0.87 to 2.05) | 0.188 |
| 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 (0.01 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 ≥36 weeks | 11.73 (3.31) | 0.019 | 15 (53.6%) | 20 (42.6%) | 0.355 | 10 (45.5%) | 0.143 |
| Any high flow ≥38 weeks | 8 (53.3%) | 0.005 | 20 (71.4%) | 45 (97.5%) | 0.004 | 14 (63.6%) | 0.280 |
| Received inhaled nitric oxide | 7 (46.7%) | 0.24 | 23 (9–53) | 14 (29–63) | 0.242 | 10 (0–150) | 0.093 |
| Received HFOV | 10 (80%) | 0.036 | 39 (50.6%) | 26 (55.3%) | 0.648 | 14 (63.6%) | 0.061 |
| Pulmonary hypertension* | 12 (80%) | 0.005 | 18 (7%) | 10 (6%) | 0.002 | 13 (59.1%) | 0.001 |
| Received sildenafil* | 10 (66.7%) | 0.001 | 11 (39.3%) | 8 (64%) | 0.317 | 14 (63.6%) | 0.007 |

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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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Contributors
SH and JB contributed equally. SH and JB conceptualised and designed the study. RN, SR, SH and JB collected data. RN, SH and JB analysed and interpreted the data. JR reviewed the statistical analysis. RN drafted the initial manuscript. SH, JB, JR and RN reviewed and revised the initial manuscript.

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Competing interests
None declared.

Patient consent for publication
Not required.

Ethics approval
Approved by the North East Tyne and Wear South Research Ethics Committee (reference 16/NE/0343). Permission to access data obtained from the Health Research Authority via Section 251 Confidentiality Advisory Group, and the Public Benefit and Privacy Panel for Health and Social Care in Scotland.

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Data availability statement
Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplemental information.

Supplemental material
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