Diagnosis and management of pulmonary hypertension in infants with bronchopulmonary dysplasia: a guide for paediatric respiratory specialists

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Shareable abstract (@ERSpublications)
Pulmonary hypertension (PH) can complicate bronchopulmonary dysplasia (BPD). Management of infants with BPD-PH should follow a multidisciplinary approach, focus on optimisation of BPD management, and involve PH-specialist guidance on PH-targeted therapy. https://bit.ly/3CkTgWy

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Abstract

Pulmonary hypertension (PH) can develop in babies with bronchopulmonary dysplasia (BPD). PH is common in those with severe BPD and is associated with a high mortality rate. However, in babies surviving beyond 6 months, resolution of PH is likely. There is currently no standardised screening protocol for PH in BPD patients. Diagnosis in this group relies heavily on transthoracic echocardiography. Management of BPD-PH should be led by a multidisciplinary team and focus on optimal medical management of the BPD and associated conditions that may contribute to PH. PH-targeted pharmacotherapies have been used in BPD-PH. To date, these have not been investigated in clinical trials and evidence of their efficacy and safety is absent.

Educational aims

- To identify those BPD patients most at risk of developing PH.
- To be aware of detection, multidisciplinary management, pharmacological treatment and monitoring strategies for BPD-PH patients.
- To understand the potential clinical course for patients with BPD-PH and that evidence on efficacy and safety of PH-targeted pharmacotherapy in BPD-PH is limited.

Background

Throughout the world, there are an estimated 15 million preterm births annually [1]. Data from the UK National Neonatal Audit Programme show that 33% of babies born at <32 weeks gestational age, and surviving to 36 weeks corrected gestational age (CGA), develop bronchopulmonary dysplasia (BPD) [2]. This amounts to >6500 babies being affected by BPD over the 3-year study period across England and Wales. Babies with severe BPD have higher rates of late in-hospital death, neonatal morbidity and supplemental respiratory support at discharge, when compared to babies without BPD [3].

In recent years, there has been increased recognition of pulmonary hypertension (PH) as an important morbidity associated with BPD. In this review, we summarise the emerging literature and provide a structured approach to the diagnosis and management of PH associated with BPD, including multidisciplinary management, therapeutics, monitoring and outcomes.

TABLE 1 National Institutes of Health (NIH) consensus definition for diagnosis of bronchopulmonary dysplasia (BPD) and assessing severity in infants

	<32 weeks birth GA	⩾32 weeks birth GA
Time of assessment	36 weeks CGA or discharge (whichever comes first)	>28 days but <56 days postnatal age or discharge (whichever comes first)
	Treatment with oxygen >21% for ⩾28 days plus:	
Mild BPD	Room air at 36 weeks CGA or discharge	Room air by 56 days postnatal age or discharge
Moderate BPD	F_{IO_2} <30% at 36 weeks CGA or discharge	F_{IO_2} <30% by 56 days postnatal age or discharge
Severe BPD	F_{IO_2} ⩾30% and/or positive pressure ventilation at 36 weeks CGA or discharge	F_{IO_2} ⩾30% and/or positive pressure ventilation by 56 days postnatal age or discharge

Reproduced and modified from [5] with permission. GA: gestational age; CGA: corrected gestational age; F_{IO_2}: inspiratory oxygen fraction.

What is BPD?

BPD is a chronic lung disease most often seen in preterm infants. In preterm infants, BPD is synonymous with chronic lung disease of prematurity and the terms are used interchangeably [4]. Historically, diagnosis of BPD has been according to the National Institutes of Health (NIH) consensus definition [5]. This defines BPD as an oxygen requirement for ⩾28 days from birth until 36 weeks CGA, with severity defined primarily by oxygen requirement (table 1). In order to reflect modern modalities of neonatal care, a new definition proposed by Jensen *et al.* [6] categorises BPD on the basis of mode of respiratory support at 36 weeks (table 2).

BPD is characterised microscopically by simplified enlarged alveoli and, in severe cases, decreased pulmonary vascular development [5, 7]. BPD is thought to be caused by a variety of antenatal and postnatal insults on the immature lung, clinically manifesting as a requirement for prolonged respiratory support and typical chest radiography findings of patchy hyperinflation with mixed areas of density and hyper-lucency [8].

Despite advances in neonatal care, BPD rates in premature infants have remained consistently high over the past several decades [9]. Rates of moderate/severe BPD steadily increase with falling gestational age, from 44% at 27 weeks to 68% at 24 weeks [10].

Other perinatal risk factors for BPD include low birthweight, intra-uterine growth restriction, and sepsis [11].

What is PH?

PH is defined haemodynamically as a mean pulmonary arterial pressure of ⩾20 mmHg in infants >3 months of age (according to the World Symposium on Pulmonary Hypertension 2018) [12]. The gold standard method for diagnosis of PH is *via* cardiac catheterisation. However, cardiac catheterisation in children with PH carries significant risk [13].

PH can be indirectly detected using transthoracic echocardiography (TTE); systolic pulmonary artery pressure can be estimated using the peak tricuspid regurgitation velocity (TRV) and the estimated right atrial pressure. Additional echocardiographic signs in combination with the TRV can help assess the probability of PH [14]. Discrepancies in measurement of the TRV can affect the values obtained [15]. It is important to interpret TRV with caution in patients with congenital heart disease and to be mindful of other causes of elevated TRV, including anaemia and sepsis [16].

Pulmonary artery pressure may be elevated as a result of increased vascular resistance in the lung, increased postcapillary pressure or increased pulmonary blood flow, analogous to Ohm's law for electrical circuits.

TABLE 2 Proposed definition for bronchopulmonary dysplasia (BPD) diagnosis and severity grading, from Jensen *et al.* [6]

BPD category	Respiratory support requirement at 36 weeks postmenstrual age
No BPD	No support
Grade 1 BPD	Nasal cannula <2 L·min^{-1}
Grade 2 BPD	Nasal cannula >2 L·min^{-1} or noninvasive positive airway pressure
Grade 3 BPD	Invasive mechanical ventilation

Thus, PH is described as being precapillary (caused by reduced pulmonary vessel number, remodelling, or vasoconstriction leading to increased pulmonary vascular resistance) or postcapillary (caused by an increase in pulmonary venous pressure in left-sided heart diseases such as pulmonary vein stenosis) or flow associated (as may be seen in congenital heart disease). These haemodynamic entities can coexist.

The World Symposium on Pulmonary Hypertension divides PH into five groups based on clinical, haemodynamic and pathological similarities: group 1 is pulmonary arterial hypertension (PAH); group 2 is PH due to left-sided heart disease; group 3 is PH due to lung disease or hypoxia; group 4 is chronic thromboembolic PH and other pulmonary artery obstructions; and group 5 is PH with multifactorial mechanisms. PH associated with BPD is currently classified within group 3 PH [17]. The precise pathogenesis of PH associated with BPD remains unknown.

BPD with PH

A systematic review and meta-analysis found that PH is observed in 20% of infants <30 weeks birth gestation (95% CI 14–25%). Importantly, PH risk increases significantly with severity of BPD: 6% of infants with mild BPD are affected by PH, 12% with moderate BPD, and 39% with severe BPD [18]. Increasing gestational age and higher birthweight are inversely related to risk of PH in infants with BPD [19].

Several clinical factors were found to be associated with development of BPD-PH when compared to BPD without PH in systematic review and meta-analysis (table 3) [18–20]. In addition to these associations, in a prospectively screened group of 204 babies, Weismann *et al.* [21] found the presence of atrial septal defects (ASDs) was independently associated with PH in BPD. Meta-analysis also revealed a weak association between the presence of patent ductus arteriosus (PDA), the need for PDA ligation, and PH in BPD patients (risk ratio (RR) 1.3, 95% CI 1.2–1.5) [18]. However, this is not a consistent finding [20].

Outcomes

BPD-PH is a clinically significant association with important implications for the individual patient and for healthcare resourcing. Presence of BPD-PH is associated with a number of complications of prematurity including retinopathy of prematurity, necrotising enterocolitis, and prolonged hospital stays in extremely preterm infants [18]. Furthermore, presence of BPD-PH is associated with a mortality rate of up to 48% within 2 years of PH diagnosis [22]. A meta-analysis of preterm babies (<32 weeks birth gestation) with BPD-PH estimated a mortality rate prior to discharge from hospital of 16%. Mortality rate at longer-term follow-up was estimated at 40%. Infants with BPD-PH were at greater risk of mortality compared to those with BPD and no PH (RR 4.7, 95% CI 2.7–8.3) [18].

Clinical factors associated with mortality in BPD-PH patients have been identified (see table 4) [23, 24]. A small study has also suggested mortality may be increased in patients with trisomy 21 and BPD-PH (42.9%) [25].

In babies surviving beyond 6 months, BPD-PH mainly resolves, with PH resolution rates of 47%, 79% and 94% at 1, 2 and 2.5 years CGA, respectively [23]. Awareness of this likely resolution of PH in BPD-PH infants surviving beyond 6 months is important, for example when planning direction of care for babies with BPD-PH.

TABLE 3 Antenatal and postnatal associations with development of bronchopulmonary dysplasia-pulmonary hypertension [18–20]

Antenatal associations	Postnatal associations
Small for gestation	Sepsis
Oligohydramnios	Early pulmonary hypertension (at <7 days of age)
Maternal diabetes	Systemic steroids
	Ventilation duration
	High-frequency oscillatory ventilation
	Tracheostomy
	Tracheitis
	Retinopathy of prematurity
	Length of hospital stay

TABLE 4 Clinical factors associated with death in bronchopulmonary dysplasia-PH patients [23, 24]

Respiratory	Cardiovascular	Other
Postnatal steroids	Supra-systemic pulmonary arterial pressure	Necrotising enterocolitis
Continuous positive airway pressure dependency at 36 weeks CGA	PH severity	
Ventilator dependency at 36 weeks CGA	Presence of ASD	

PH: pulmonary hypertension; CGA: corrected gestational age; ASD: atrial septal defect.

Associated morbidities

Compared to BPD without PH, BPD-PH is associated with additional respiratory and feeding support requirements, poorer neurodevelopmental outcomes and suboptimal somatic growth. A multicentre, retrospective cohort study by Lagatta *et al*. [24] of 1677 infants born at <32 weeks of gestation with severe BPD showed that, at discharge, compared with BPD without PH, BPD-PH was associated with tracheostomy (27% *versus* 9%; p<0.001), supplemental oxygen use (84% *versus* 61%; p<0.001), and naso-gastric tube feeding (80% *versus* 46%; p<0.001). Through 1 year of corrected age, PH was associated with increased frequency of re-admission (incidence rate ratio 1.38, 95% CI 1.18–1.63; p<0.001) [24]. The retrospective cohort study by Choi *et al*. [26] of 394 extremely preterm infants (<28 weeks birth gestation) showed BPD-PH patients had significantly lower cognitive scores on Bayley-III assessment at 18–24 months CGA compared to those with BPD without PH. Weight and head circumference z-scores were significantly lower in patients with BPD-PH compared to BPD patients without PH [26].

Diagnosing BPD-PH

Clinical signs

The clinical presentation of PH in babies with BPD is not well documented in the literature. Therefore, the diagnosis of PH should be considered in any patient with established BPD. Diagnosis relies on TTE assessment of pulmonary arterial pressure.

TTE

The utility of TTE is in 1) detecting PH, 2) assessing for structural heart disease that can contribute to or cause PH, and 3) stratifying severity of PH. TTE can be technically challenging in BPD-PH patients. The hyperinflated lungs overlying the heart create poor ultrasound windows and can displace the heart such that standard TTE views may need to be adapted.

Assessment of numerous TTE parameters is recommended by the European Pediatric Pulmonary Vascular Disease Network (EPPVDN) and in the Pediatric Pulmonary Hypertension Network (PPHNet) consensus guidelines [27, 28]. These include TRV, interventricular septal flattening, pulmonary regurgitant jet velocity, and ventricular size and function. Both consensus guidelines offer diagnostic thresholds for PH relating to these parameters [27, 28].

TRV is the most often used parameter in TTE assessment of PH. However, it is often not measurable in BPD-PH patients [29] and its absence does not rule out PH. Other cautions when using TRV to estimate PH were described in the earlier section “What is PH?”.

TTE should also always assess for evidence of structural heart abnormalities including pulmonary vein stenosis, common in this group of patients, which may contribute to PH. Pulmonary vein stenosis can evolve over time and is associated with a high mortality rate [30].

TTE should aim to identify and quantify shunt lesions such as ventricular septal defects (VSDs), ASDs, PDA and systemic to pulmonary collaterals. These lesions tend to be poorly tolerated in BPD-PH patients and their early closure may be indicated (discussed in the later section about managing comorbidities). Their presence can have an impact on management strategies; for example, in the case of a large VSD, pulmonary vasodilator therapy may be contraindicated due to the risk of increasing left-to-right shunt, causing high pulmonary blood flow.

Screening for BPD-PH

There are consensus guideline groups that recommend TTE screening for PH in infants with BPD. However, recommendations for screening thresholds vary. In some cases, TTE screening is recommended

for any infant with established BPD [27], while in others, screening is limited to infants with moderate or severe BPD only [31]. Both groups acknowledge that these recommendations are based on expert opinion or small studies only. These recommendations do not meet the widely accepted public health criteria for screening programmes [32]. Furthermore, the impact of this PH screening recommendation on clinical practice and patient outcomes has yet to be assessed.

PPHNet highlights that PH can develop despite a normal TTE at discharge and that older infants can develop PH with acute respiratory infections. They recommend 4–6-monthly TTE for patients with BPD and ongoing oxygen requirement and repeat TTE in any infant who develops increasing oxygen or respiratory support requirements [28]. Recent European Respiratory Society guidelines for BPD and outpatient follow-up do not specify standardised screening for PH in preterm patients with BPD [4].

Variability has also been shown in clinical practice. A survey of North American neonatal consultants showed only 38% of respondents had an institutional screening programme. However, 83% did screen for PH with TTE at 36 weeks CGA for preterm neonates treated with oxygen or ventilatory support [33]. A systematic review showed that the timing of PH screening within the preterm population varied from 28 days, to 36 weeks CGA, to >2 months of age [18].

Differential diagnoses

There are other conditions in infancy whose presenting features can be similar to BPD-PH and these should be considered during the diagnostic phase. Examples include gastro-oesophageal reflux disease with aspiration, congenital lung abnormalities such as congenital cystic adenomatoid malformation, and tracheo-oesophageal fistula. These conditions may coexist with PH and can be important contributory factors. Rarer lung diseases such as alveolar capillary dysplasia and surfactant protein abnormalities can mimic BPD-PH and should also be considered in the differential diagnosis [27].

Further assessment in patients with BPD-PH

Role of chest computed tomography and magnetic resonance imaging

Pulmonary vein stenosis can be causal in PH but it can be challenging to diagnose *via* TTE. Computed tomography (CT) angiography may be used where index of suspicion for pulmonary vein stenosis is high, to provide more detailed imaging. In babies with BPD-PH, CT may also be used to detect and assess severity of lung parenchymal disorders and thromboembolic disease.

Magnetic resonance imaging (MRI) is evolving as an imaging modality in BPD-PH patients, with evidence suggesting MRI can help predict short-term clinical outcomes and need for PH-targeted therapy [34].

Cardiac catheterisation

While cardiac catheterisation remains the gold standard modality for the diagnosis of PH, it is invasive, carries procedural risk, and guidelines on its exact place in the BPD-PH diagnostic and management pathway vary.

The American Heart Association (AHA) and American Thoracic Society guidelines recommend that evaluation for long-term therapy in BPD-PH patients should include cardiac catheterisation to diagnose PH severity and identify potential contributing factors including pulmonary vein stenosis, intra- or extra-cardiac shunting, and left ventricular diastolic dysfunction (class 1, level of evidence B) [31]. PPHNet recommends cardiac catheterisation if patients fail to improve despite optimal management of BPD and comorbidities, or in cases where PH is severe [28]. EPPVDN recommends cardiac catheterisation where PH is refractory to PH-targeted medication or where there is diagnostic uncertainty [27].

These recommendations must be balanced against the risks of catheterisation [13] and the potential for findings to positively affect patient outcome, for example, where there is doubt regarding the severity of PH which would influence use of parenteral prostanoids. The clinical and cost utility of obligatory cardiac catheterisation prior to treatment in this cohort has also been questioned in a modelling study [35]. A recent single-centre study of 135 infants with BPD-PH reported cardiac catheterisation was rarely performed prior to initiation of PH-targeted pharmacotherapy. Instead, cardiac catheterisation was performed further along the management pathway, specifically when patients remained on sildenafil after 1 year [25].

Monitoring

Recommendations for monitoring PH have been published by EPPVDN, AHA and PPHNet [27, 28, 31]. They suggest infants with BPD-PH require close follow-up. Monitoring recommendations include

assessment of pre- and post-ductal oxygen saturations, TTE, and the biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP). The PPHNet consensus guidelines recommend 3–4-monthly multidisciplinary outpatient follow-up for BPD-PH in the context of stable disease [28].

NT-proBNP

Serum BNP and its prohormone, NT-proBNP, are released by cardiomyocytes in response to ventricular wall stress due to pressure overload and/or volume expansion. NT-proBNP value varies widely among individual patients and is dependent on gestational age. Utility of NT-proBNP in longitudinal monitoring of PH has been demonstrated in the paediatric PAH population [36] but has not been studied in BPD-PH. Nevertheless, trend in NT-proBNP is used clinically in combination with TTE for monitoring disease progression and response to treatment in PH associated with BPD. Of note, serum BNP and NT-proBNP levels may also increase due to PDA, renal failure, left ventricular dysfunction, and high systemic blood pressure.

Managing BPD-PH

The following approaches have been recommended in the management of BPD-PH. The primary emphasis should be on optimising BPD treatment and managing comorbidities. This should involve a multidisciplinary approach including the treating neonatal or paediatric team, paediatric respiratory physicians, paediatric cardiology and PH specialists [28]. This is not an exhaustive list: paediatric dieticians, physiotherapists, speech and language therapists, gastroenterologists, general surgeons, cardiothoracic surgeons, occupational therapists, long-term ventilation teams, community nursing teams and palliative care teams may also be involved, depending on comorbidities and disease progression.

Guidance for the management of patients with BPD-PH has been provided by AHA, EPPVDN and PPHNet, as well as by authors from smaller groups. Most recommendations are based on expert opinion, case studies or general standards of care (level of evidence C). The following sections give a summary of the guidance.

Optimising BPD treatment in BPD-PH

Supplemental oxygen has been recommended to avoid hypoxia, which may result in pulmonary vasoconstriction and exacerbate PH. Guidance on target oxygen saturations varies. EPPVDN recommends >93% for suspected BPD-PH and >95% for proven BPD-PH [27]. AHA and PPHNet recommend 92–95% in patients with established BPD-PH [28, 31]. Noninvasive respiratory support and avoidance of mechanical ventilation is recommended where possible [27].

Avoidance of over- or under-inflation of the lungs when providing respiratory support is recommended [27, 28]. This helps to minimise lung injury and ventilation–perfusion mismatch with its associated hypoxia and hypercapnia.

Diuretics, for example, chlorothiazide and spironolactone, can be considered especially when there is evidence of fluid overload [27].

General management measures

The route and volume of feeds should be optimised to encourage growth. Infants with severe BPD have high calorie requirements of up to 160 $kcal \cdot kg^{-1} \cdot day^{-1}$. BPD infants affected by PH are additionally prone to suboptimal growth and have a high prevalence of aspiration [26, 37].

Investigating and managing comorbidities

It is important to investigate for comorbidities and treat them. Examples are obstructive sleep apnoea, gastro-oesophageal reflux with or without aspiration, structural and functional airway problems including subglottic stenosis, tracheobronchomalacia, and vocal cord paralysis [28].

Anatomical cardiac lesions that can lead to increased left-to-right shunting, for example ASDs, VSDs, PDA or systemic to pulmonary collaterals, may not be well tolerated in infants with BPD. There is evidence that repair of ASDs in infants aged <12 months improves symptoms of BPD or shunt-related PH [38]. However, the likelihood of the shunt lesion spontaneously closing or becoming smaller over time, in addition to the anaesthetic and surgical risks, should be carefully considered.

Assessment frequency

Regular clinical re-evaluation is necessary in BPD-PH patients. EPPVDN recommends weekly TTE initially, following diagnosis of suspected or confirmed PH, then one or two TTEs per month thereafter [27]. When serial TTEs reveal normal or near-normal findings, weaning and discontinuation of PH-targeted

medication may be considered. More regular TTE assessments during PH-targeted medication weaning may be necessary.

Pharmacological therapy in BPD-PH

Diuretics

Diuretics such as chlorothiazide and spironolactone may be used in BPD-PH. In a retrospective cohort study of 48 infants with BPD-PH and right ventricular dilatation, symptomatic improvement within 1 week of diuretic commencement was recorded in 90% [39].

Pulmonary vasodilators

Pulmonary vasodilators have proven efficacy in group 1 PAH but there is a lack of evidence on clinical efficacy and safety of PH-targeted medications in infants with BPD-PH and none are approved for use at <1 year of age.

PH-targeted medication (phosphodiesterase type 5 (PDE-5) inhibitors, endothelin receptor antagonists, nitric oxide and prostanoids) may be considered in BPD-PH after careful evaluation and management of BPD and exacerbating factors, and exclusion of associated anomalies such as left-to-right shunts, left ventricular diastolic dysfunction and pulmonary vein stenosis. Recommendations for the use of PH-targeted medication in BPD-PH are based on expert opinion only [27, 28, 31]. In the absence of quality clinical trial data, "off-label" use of PH-targeted medication should be guided by PH experts based on their clinical experience and carefully monitored with timely and regular clinical re-evaluations.

PDE-5 inhibitors

Sildenafil and tadalafil are PDE-5 inhibitors. Sildenafil is licensed in Europe for treatment of children >1 year of age with group 1 PAH. It is not licensed for paediatric use in the USA, due to concerns of unexplained excess mortality in an open-label paediatric study [40]. Despite lack of trial data, sildenafil has been widely used in cohorts of infants with BPD-PH. A retrospective cohort study of 135 BPD-PH patients suggested enteral sildenafil was well tolerated and safe. 45% of patients were able to be weaned off sildenafil due to improvement in PH during the follow-up period; however, there was no control arm in this study [25].

Sildenafil side-effects may include worsening of gastro-oesophageal reflux, priapism and airway spasm, as well as the potential for worsening ventilation–perfusion matching. The same study shows one-quarter of patients required an additional medication added to sildenafil, with a median time to add-on medication of 4 months [25]. There are no data for tadalafil use in BPD-PH.

Endothelin receptor antagonists

Endothelin receptor antagonists, for example bosentan, ambrisentan and macitentan, are not licensed for use in patients with group 3 PH or in infants. However, their use may be considered in BPD-PH (level of evidence C) [31]. Bosentan is most widely used in combination with a PDE-5 inhibitor [27]. Bosentan may result in liver dysfunction and liver function should be monitored at least monthly in children receiving bosentan.

Nitric oxide

Inhaled nitric oxide (iNO) selectively decreases pulmonary vascular resistance and increases systemic venous oxygen saturation by improving ventilation–perfusion matching. AHA suggests that treatment with iNO can be effective for infants with established BPD and symptomatic PH (level of evidence C) [31]. However, the clinical context in which iNO may be used in line with this recommendation is not detailed. Systematic review data show that iNO, when used as rescue therapy in early respiratory failure in preterm infants, does not improve the chance of improved outcomes [41]. This review did not include use of iNO in BPD or BPD-PH. However, PPHNet does recommend iNO for PH crisis in BPD-PH patients [28]. Weaning off iNO needs to be gradual and alternative selective pulmonary vasodilator(s) should be commenced prior to discontinuing iNO in BPD-PH to help avoid rebound PH [28].

Prostanoids

Evidence for inhaled iloprost in BPD-PH is limited to case studies and series only. EPPVDN suggested that very potent intravenous vasodilators, such as epoprostenol, can be considered for the BPD-PH patient [27]. However, evidence is limited to case reports only. Epoprostenol needs to be given through a central venous line (upper body line preferred). Use of epoprostenol may be limited due to adverse effects, with systemic hypotension, potential ventilation–perfusion mismatch and intrapulmonary right-to-left shunting leading to worsening hypoxaemia.

Conclusion

BPD-PH is a significant diagnosis that is common in infants with severe BPD. It is associated with high mortality rates, although resolution is highly likely in those surviving beyond 6 months. Diagnosis of PH in BPD patients relies on TTE, with cardiac catheterisation rarely undertaken in this population of PH patients.

Management should involve a multidisciplinary team and the primary focus should be on optimising BPD management and managing other exacerbating pathologies. There is limited and poor-quality evidence for the safety and efficacy of PH-targeted medications in BPD-PH and their "off-label" use is guided by PH specialists. Research into the prevention and treatment of BPD-PH in this fragile patient group is a high priority area.

Key points

- PH often complicates BPD, is particularly common in severe BPD, and is associated with a high mortality rate.
- Management of BPD-PH focuses on optimising BPD treatment, involves a multidisciplinary team, and relies on TTE for monitoring disease.
- PH-targeted medications have been used in BPD-PH but there are scarce efficacy and safety data and their use should be guided by PH specialists.

Self-evaluation questions

1. Diagnosis of PH in an infant with BPD usually relies on which of the following investigations?
    a) Cardiac catheterisation
    b) TTE
    c) Chest MRI
    d) Clinical history and examination findings alone
2. Which of the following is an appropriate initial step in managing an infant with BPD-PH?
    a) Ensure management of BPD is optimised
    b) Commence PH-targeted medication, for example sildenafil
    c) Request cardiac catheterisation to confirm the diagnosis of PH
    d) Intubate, ventilate and commence inhaled nitric oxide
3. Which of the following statements is true in BPD-PH regarding PH-targeted medications such as PDE-5 inhibitors and endothelin receptor antagonists?
    a) Randomised controlled trial data show PDE-5 inhibitors and endothelin receptor antagonists are safe and effective in the BPD-PH population
    b) Their use is "off-label" in infants with BPD-PH and should be guided by PH specialists
    c) It is common clinical practice to commence dual PH-targeted pharmacotherapy as an initial management step in BPD-PH
    d) Monthly liver function monitoring is necessary for patients on sildenafil
4. Which statement is true of BPD-PH?
    a) Mortality is low and remission is highly likely
    b) Mortality is low but remission is unlikely
    c) Mortality is high but remission in survivors is highly likely
    d) Mortality is high and remission in survivors is unlikely

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References

1 World Health Organization. Preterm birth: key facts. Date last accessed: 7 August 2022. Date last updated: 14 November 2022. www.who.int/news-room/fact-sheets/detail/preterm-birth

2 Royal College of Paediatrics and Child Health (RCPCH). National Neonatal Audit Programme (NNAP) 2020 Annual Report on 2019 Data. London, RCPCH, 2020. www.rcpch.ac.uk/work-we-do/clinical-audits/nnap

3 Jensen EA, Edwards EM, Greenberg LT, *et al.* Severity of bronchopulmonary dysplasia among very preterm infants in the United States. *Pediatrics* 2021; 148: e2020030007.
4 Duijts L, van Meel ER, Moschino L, *et al.* European Respiratory Society guideline on long-term management of children with bronchopulmonary dysplasia. *Eur Respir J* 2020; 55: 1900788.
5 Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001; 163: 1723–1729.
6 Jensen EA, Dysart K, Gantz MG, *et al.* The diagnosis of bronchopulmonary dysplasia in very preterm infants. An evidence-based approach. *Am J Respir Crit Care Med* 2019; 200: 751–759.
7 Hussain NA, Siddiqui NH, Stocker JR. Pathology of arrested acinar development in postsurfactant bronchopulmonary dysplasia. *Hum Pathol* 1998; 29: 710–717.
8 Higano NS, Bates AJ, Gunatilaka CC, *et al.* Bronchopulmonary dysplasia from chest radiographs to magnetic resonance imaging and computed tomography: adding value. *Pediatr Radiol* 2022; 52: 643–660.
9 Islam JY, Keller RL, Aschner JL, *et al.* Understanding the short- and long-term respiratory outcomes of prematurity and bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2015; 192: 134–156.
10 Geetha O, Rajadurai VS, Anand AJ, *et al.* New BPD-prevalence and risk factors for bronchopulmonary dysplasia/mortality in extremely low gestational age infants ⩽28 weeks. *J Perinatol* 2021; 41: 1943–1950.
11 Kalikkot Thekkeveedu R, Guaman MC, Shivanna B. Bronchopulmonary dysplasia: a review of pathogenesis and pathophysiology. *Respir Med* 2017; 132: 170–177.
12 Galiè N, McLaughlin VV, Rubin LJ, *et al.* An overview of the 6th World Symposium on Pulmonary Hypertension. *Eur Respir J* 2019; 53: 1802148.
13 Taylor CJ, Derrick G, McEwan A, *et al.* Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension. *Br J Anaesth* 2007; 98: 657–661.
14 Galiè N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). *Eur Heart J* 2016; 37: 67–119.
15 Kyranis SJ, Latona J, Platts D, *et al.* Improving the echocardiographic assessment of pulmonary pressure using the tricuspid regurgitant signal – the “chin” vs the “beard”. *Echocardiography* 2018; 35: 1085–1096.
16 Dimopoulos K, Condliffe R, Tulloh RMR, *et al.* Echocardiographic screening for pulmonary hypertension in congenital heart disease: *JACC* review topic of the week. *J Am Coll Cardiol* 2018; 72: 2778–2788.
17 Simonneau G, Montani D, Celermajer DS, *et al.* Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019; 53: 1801913.
18 Arjaans S, Zwart EAH, Ploegstra MJ, *et al.* Identification of gaps in the current knowledge on pulmonary hypertension in extremely preterm infants: a systematic review and meta-analysis. *Paediatr Perinat Epidemiol* 2018; 32: 258–267.
19 Nagiub M, Kanaan U, Simon D, *et al.* Risk factors for development of pulmonary hypertension in infants with bronchopulmonary dysplasia: systematic review and meta-analysis. *Paediatr Respir Rev* 2017; 23: 27–32.
20 Sheth S, Goto L, Bhandari V, *et al.* Factors associated with development of early and late pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. *J Perinatol* 2020; 40: 138–148.
21 Weismann CG, Asnes JD, Bazzy-Asaad A, *et al.* Pulmonary hypertension in preterm infants: results of a prospective screening program. *J Perinatol* 2017; 37: 572–577.
22 Khemani E, McElhinney DB, Rhein L, *et al.* Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. *Pediatrics* 2007; 120: 1260–1269.
23 Arjaans S, Haarman MG, Roofthooft MTR, *et al.* Fate of pulmonary hypertension associated with bronchopulmonary dysplasia beyond 36 weeks postmenstrual age. *Arch Dis Child Fetal Neonatal Ed* 2021; 106: 45–50.
24 Lagatta JM, Hysinger EB, Zaniletti I, *et al.* The impact of pulmonary hypertension in preterm infants with severe bronchopulmonary dysplasia through 1 year. *J Pediatr* 2018; 203: 218–224.e3.
25 Cohen JL, Nees SN, Valencia GA, *et al.* Sildenafil use in children with pulmonary hypertension. *J Pediatr* 2019; 205: 29–34.e1.
26 Choi EK, Shin SH, Kim EK, *et al.* Developmental outcomes of preterm infants with bronchopulmonary dysplasia-associated pulmonary hypertension at 18–24 months of corrected age. *BMC Pediatr* 2019; 19: 26.
27 Hansmann G, Sallmon H, Roehr CC, *et al.* Pulmonary hypertension in bronchopulmonary dysplasia. *Pediatr Res* 2021; 89: 446–455.
28 Krishnan U, Feinstein JA, Adatia I, *et al.* Evaluation and management of pulmonary hypertension in children with bronchopulmonary dysplasia. *J Pediatr* 2017; 188: 24–34.e1.
29 Bhat R, Salas AA, Foster C, *et al.* Prospective analysis of pulmonary hypertension in extremely low birth weight infants. *Pediatrics* 2012; 129: e682–e689.
30 Mahgoub L, Kaddoura T, Kameny AR, *et al.* Pulmonary vein stenosis of ex-premature infants with pulmonary hypertension and bronchopulmonary dysplasia, epidemiology, and survival from a multicenter cohort. *Pediatr Pulmonol* 2017; 52: 1063–1070.

31 Abman SH, Hansmann G, Archer SL, *et al.* Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. *Circulation* 2015; 132: 2037–2099.

32 Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva, World Health Organization, 1968. https://apps.who.int/iris/handle/10665/37650

33 Altit G, Lee HC, Hintz S, *et al.* Practices surrounding pulmonary hypertension and bronchopulmonary dysplasia amongst neonatologists caring for premature infants. *J Perinatol* 2018; 38: 361–367.

34 Critser PJ, Higano NS, Tkach JA, *et al.* Cardiac magnetic resonance imaging evaluation of neonatal bronchopulmonary dysplasia-associated pulmonary hypertension. *Am J Respir Crit Care Med* 2020; 201: 73–82.

35 Yang EL, Levy PT, Critser PJ, *et al.* The clinical and cost utility of cardiac catheterizations in infants with bronchopulmonary dysplasia. *J Pediatr* 2022; 246: 56–63.e3.

36 Ploegstra MJ, Zijlstra WMH, Douwes JM, *et al.* Prognostic factors in pediatric pulmonary arterial hypertension: a systematic review and meta-analysis. *Int J Cardiol* 2015; 184: 198–207.

37 Bowman OJ, Hagan JL, Toruno RM, *et al.* Identifying aspiration among infants in neonatal intensive care units through occupational therapy feeding evaluations. *Am J Occup Ther* 2020; 74: 7401205080p1–7401205080p9.

38 Charisopoulou D, Bini RM, Riley G, *et al.* Repair of isolated atrial septal defect in infants less than 12 months improves symptoms of chronic lung disease or shunt-related pulmonary hypertension. *Cardiol Young* 2020; 30: 511–520.

39 Baczynski M, Kelly E, McNamara PJ, *et al.* Short and long-term outcomes of chronic pulmonary hypertension in preterm infants managed using a standardized algorithm. *Pediatr Pulmonol* 2021; 56: 1155–1164.

40 Barst RJ, Beghetti M, Pulido T, *et al.* STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. *Circulation* 2014; 129: 1914–1923.

41 Barrington KJ, Finer N, Pennaforte T. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2017; 1: CD000509.

Suggested answers

1. b.
2. a.
3. b.
4. c.