Progress in Pediatric Cardiology 54 (2019) 101135

Contents lists available at ScienceDirect

Progress in Pediatric Cardiology

journal homepage: www.elsevier.com/locate/ppedcard

Review

Lung disease and pulmonary hypertension in the premature infant

Lori A. Christ[a], Jennifer M. Sucre[b], David B. Frank[c,d,*]

[a] Division of Neonatology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, United States of America
[b] Mildred Stahlman Division of Neonatology, Department of Pediatrics, Vanderbilt University, Nashville, TN, United States of America
[c] Division of Pediatric Cardiology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, United States of America
[d] Penn-CHOP Lung Biology Institute and Penn Cardiovascular Institute, University of Pennsylvania, Philadelphia, PA, United States of America

ARTICLE INFO

Keywords:
Lung development
Pulmonary hypertension
Bronchopulmonary dysplasia
Chronic lung disease

ABSTRACT

The premature infant is born into the world unprepared to naturally thrive in a foreign environment. Lung development entails immense growth, structural remodeling and differentiation of specialized cells during the normal term perinatal and postnatal periods. Thus, the premature infant presents with a lung deficient for appropriate respiration. Disruption of lung development seen in bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD) results in not only impaired airway growth but also a deficiency in the accompanying vasculature including the capillary system required for gas exchange. Deficient vascular area can lead to elevated pulmonary vascular resistance and the development of pulmonary hypertension (pH). Unlike PH seen in children and adults with pulmonary arterial hypertension (PAH), treatment with conventional pulmonary vasodilators can be limited in developmental lung disease-associated PH because there are fewer blood vessels to dilate. In this brief review, we highlight some of the knowledge on PH in the premature infant presented at the Proceedings of the 22nd Annual Update on Pediatric and Congenital Cardiovascular Disease.

1. Introduction

The use of surfactant combined with the technological and medical care advancements made by neonatologists have led to improved survival in the extremely low birth weight and premature neonate. However, sequelae such as bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD) of prematurity result in significant morbidity and mortality. BPD is clinically defined by gestational age and the presence and duration of oxygen-dependence and/or positive pressure ventilation in the postnatal period [1,2]. BPD in the surfactant era differs from previous classifications of pre-surfactant BPD in that it now is predominantly disrupted normal lung development in the context of premature birth [3]. While the use of surfactant therapy and gentle ventilation techniques has decreased the severity and prevalence of fibrosis in BPD, interstitial fibrosis remnant of “old BPD” does continue in the modern era as demonstrated by autopsy in infants with the most severe manifestations of BPD [4,5].

2. Epidemiology of PH and lung disease of the premature infant

Despite improved care, recent studies in the surfactant era reveal a steady prevalence and incidence of BPD in premature infants [6–11]. With this, co-morbidities such as pulmonary hypertension have become an increasingly common manifestation with BPD. Epidemiological studies in premature infants indicate that up to 25% of premature infants with BPD develop PH [6,12–16]. In addition, BPD severity correlates positively with the risk for developing PH, and infants with both BPD and PH have an increased risk of mortality [17]. Furthermore, data examining PH-related hospitalizations reveals that a co-diagnosis of BPD is associated with increased mortality, length of stay, and hospital charges [18].

3. Lung development and its relevance to neonatal lung disease pathogenesis

Disruption of the normal development of the lung in the setting of prematurity continues to be a leading mechanism for BPD/CLD. Lung development is typically classified in five stages that include embryonic, pseudoglandular, canalicular, saccular, and alveolar stages. Within these stages of lung development, there is a tightly regulated process of lung cellular specification, growth and branching morphogenesis, and structural remodeling to form a complex modality consisting of tissue interactions to produce conducting airways, vasculature, stroma, and alveoli for gas exchange. For a detailed description

* Corresponding author at: Children's Hospital of Philadelphia, 3401 Civic Center Boulevard, 8NW, Division of Pediatric Cardiology, Philadelphia, PA 19104, United States of America.
E-mail address: frankd@email.chop.edu (D.B. Frank).

https://doi.org/10.1016/j.ppedcard.2019.101135
Received 20 May 2019; Received in revised form 19 July 2019; Accepted 30 July 2019
Available online 31 July 2019

of lung development, we instruct the reader to a number of reviews on lung development [19–23].

Briefly, lung identity and specification occur during organogenesis in both mouse and human lung development [19]. Following inductive cues from the surrounding mesoderm, the foregut endoderm expresses the pioneering transcription factor, NKX2-1, that gives lung identity to the foregut endoderm. Soon after, the extension of two lung buds occurs followed by a period of rapid growth to finish the embryonic stage. Around 12 weeks of gestational age in humans, the fetal lungs initiate branching morphogenesis and growth to produce a more complex organ system. Concomitantly, there is patterning of the lung airway into proximal and distal fates marked by expression of the transcription factors, SOX2 and SOX9/ID2, respectively. In addition, this specification into proximal and distal fates determines the future conducting airway and alveolus of the lung, respectively. This period of branching morphogenesis is accompanied by growth and remodeling of the pulmonary vascular plexus so that the proximal pulmonary arterial tree follows the branching pattern of the lung epithelium. The process of vascular growth occurs throughout both the pseudoglandular and canalicular stages and ends near 24–26 weeks of gestation. Congenital defects that can arise during these stages of early development include branching, lobation, and specification defects observed in congenital pulmonary airway malformations (CPAMs) and congenital diaphragmatic hernia (CDH) that may result in pulmonary hypoplasia and PH [19].

Defects such as BPD and later CLD result in functional pulmonary hypoplasia as well, but they arise due to premature birth during the saccular stage of lung development. This stage of development is important in that cell specification into terminal fates occurs in the proximal and distal lung and is accompanied by structural remodeling of the distal lung into a thin-walled primitive alveolus and capillary network for gas exchange. While alveolar epithelial cell fate has been classically defined to occur at sacculation, recent evidence indicates that alveolar epithelial cell fate occurs much earlier in lung development during branching morphogenesis [24]. These data are congruent with recent clinical advances allowing the successful resuscitation of premature infants < 24 weeks and suggest that alveolar development occurs early [10,25]. Nevertheless, the alveoli and capillary and arterial vasculature are limited as development of the majority of the pulmonary vasculature including capillaries and arteries occurs following the saccular stage during alveologenesis and years into the postnatal period [26,27]. In addition to vascular growth, alveologenesis involves significant structural remodeling via a process of secondary septation of the primitive alveolus resulting in a marked increase in surface area for gas exchange. In patients with BPD, there is a marked reduction in secondary septation resulting in alveolar simplification, loss of capillary bed, and aberrant pulmonary arteriole remodeling (Fig. 1).

4. Pathophysiology of PH in lung disease in the premature infant

In addition to disrupted lung development after preterm birth, injury can occur during resuscitation and postnatal care, exacerbating the limitation of lung growth. Perinatal and postnatal infection, aspiration, atelectasis, barotrauma from ventilation, and oxidative stress all contribute to lung inflammation and can lead to further damage to the lung [28]. Cellular interactions consisting of epithelial-endothelial-mesenchymal communication are important and rely on reciprocal signaling among the three cell lineages. Thus, disruption in development of the airway epithelium in BPD also results in deficits of mesenchymal and arterial, venous, and capillary endothelial growth. This reciprocal signaling is nicely demonstrated in studies that have manipulated the important vascular pathway mediated by vascular endothelial growth factor (VEGF). Both deletion of VEGF production in the lung epithelium in mice as well as inhibition of the VEGF receptor using chemical inhibitors or blocking antibodies result in significant deficiencies not only in the pulmonary vasculature but also the distal airway/alveolar epithelial region [29–31].

A deficient capillary bed and pulmonary arterial and venous hypoplasia in the setting of BPD can lead to severe loss of vascular area and increased resistance in the lung and PH. Resistance calculations on dog models in the 1960s suggest that all three vascular compartments contribute to a normally low resistant circuit in the lung. Interestingly, the allocation of resistance to each vascular bed was portioned at 46% for arterial, 34% for capillary, and 20% for venous circulations [32]. In addition, recruitment of the capillary bed has been implicated as an important component of maintaining a low PVR in the setting of increased cardiac output in exercise and at rest, which can be impaired in certain disease states [33–36]. As such, BPD/CLD pathology with a severe reduction in capillary area would lead to an elevated PVR and subsequent aberrant pulmonary arterial remodeling and PH.

5. Evaluation and treatment of lung disease and PH in the premature infant

Diagnosis and treatment of PH in the BPD/CLD patient involve a multidisciplinary approach. Recent guidelines have provided practical recommendations for screening and treatment of PH related to BPD/CLD [37,38], however, practice varies between institutions [39]. Despite this, an algorithm has been defined that outlines screening and treatment of PH related BPD/CLD (Fig. 2) [37]. While the severity of PH tends to correlate with more severe lung disease, some infants with mild BPD have severe PH [40], making screening protocols essential for

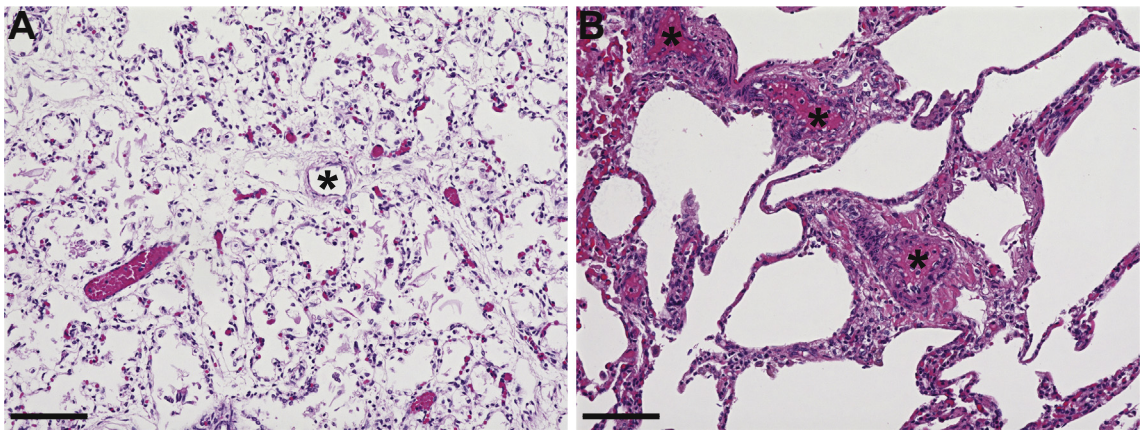

Fig. 1. Pathology observed in bronchopulmonary dysplasia. Hematoxylin and eosin staining of tissue sections from a term infant (A) and 55 weeks corrected gestational age patient with bronchopulmonary dysplasia. Note severe alveolar simplification concomitant with medial wall thickening of pulmonary arteries in B compared to A. Asterisks define pulmonary arteries. Scale bar = 10 μm.

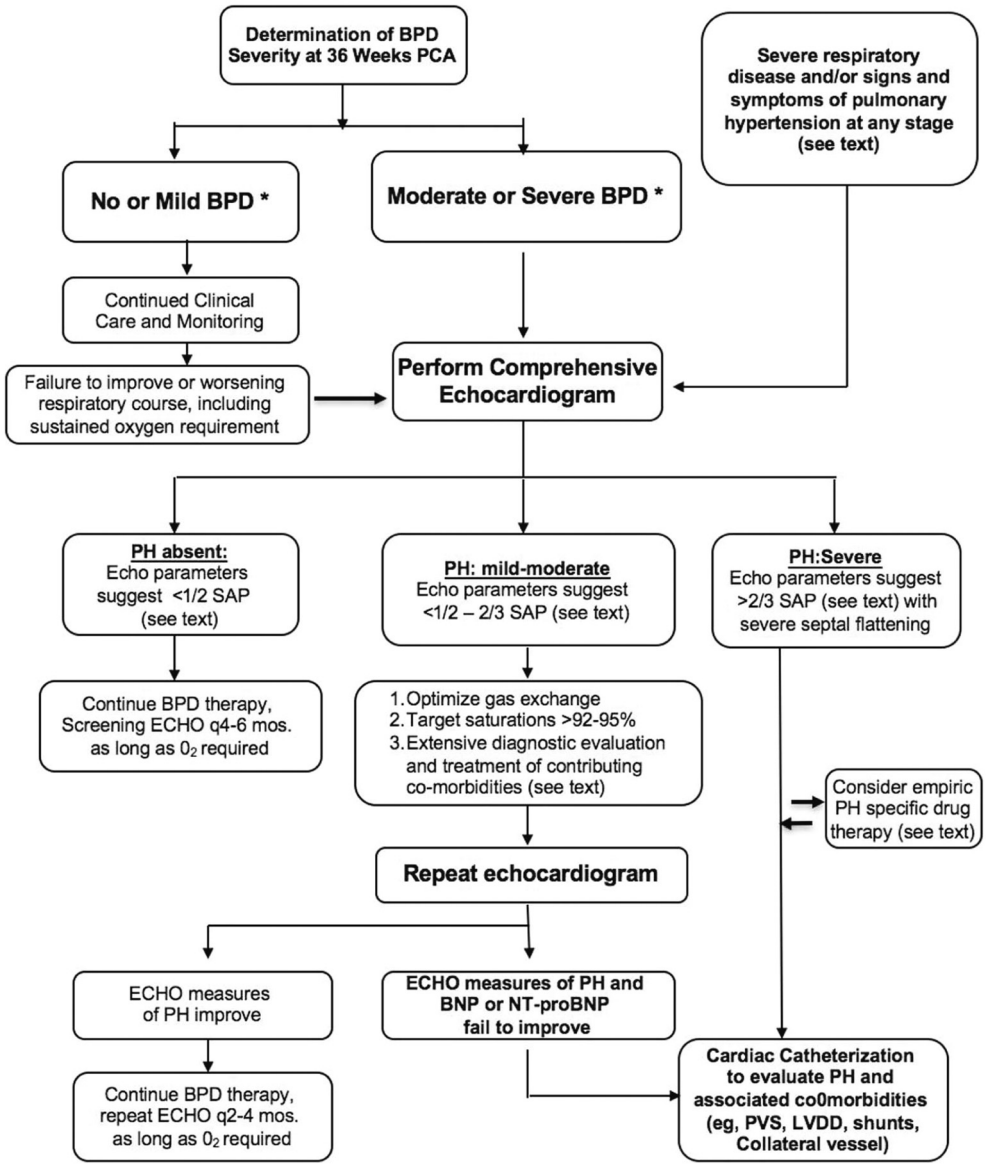

Fig. 2. Clinical algorithm for the evaluation and treatment of pulmonary hypertension in bronchopulmonary dysplasia. ECHO, echocardiogram; SAP, systemic arterial pressure; LVDD, left ventricular diastolic dysfunction, O_2, oxygen. Permission obtained, 5.17.2019: Reprinted from The Journal of Pediatrics, Vol. 188, Krishnan U et al., Evaluation and Management of Pulmonary Hypertension in Children with Bronchopulmonary Dysplasia, 24–34. Copyright (2017), with permission from Elsevier.

identification and treatment of PH. Screening echocardiograms play an important role in not only diagnosis but also evaluation of response to therapies, especially in those with severe BPD/CLD. After initial screening, a cardiac catheterization remains the gold standard and can be used prior to initiation of pulmonary vasodilator therapy to assess the responsiveness of the pulmonary vasculature. But given the tenuous condition of patients with severe BPD/CLD and PH, an echocardiogram may be a preferable given a requirement for continuous critical care and potential complications of general anesthesia.

The use of pulmonary vasodilators is becoming more common in the neonatal population, but there remains very little data on the efficacy and safety of these drugs in the long term. The use of vasodilator therapy other than inhaled nitric oxide (iNO) predominantly includes sildenafil, and data on sildenafil use is limited to small retrospective studies or retrospective administrative databases [41–43]. However, sildenafil use should be adjunctive and secondary to lung protective strategies that reduce the risk of developing BPD, limit further lung injury, and promote lung development and growth to improve vascular area.

5.1. Lung protective strategies

Lung protective strategies are employed throughout the intensive care admission for preterm infants to minimize the risk of BPD. Over the last few decades, several strategies have been identified through randomized controlled trials and meta-analyses. These therapies focus largely on improving lung compliance, minimizing ventilator-induced barotrauma and volutrauma, and promoting lung growth and recovery. Observational studies have identified intubation in the delivery room, male gender, younger gestational age, and prolonged mechanical ventilation (> 7 days) as risk factors for severe BPD [44]. Non-invasive support in the delivery room and early surfactant have been identified as protective factors.

Antenatal corticosteroids are one of the best-studied interventions for preterm infants. Antenatal corticosteroids promote fetal lung maturation by upregulating expression of surfactant proteins in the fetal

lung, thereby improving lung compliance after preterm delivery. The administration of steroids before anticipated preterm birth was first described by Liggins and Howie in 1972, in which a randomized controlled trial found that betamethasone phosphate/acetate reduced respiratory distress syndrome and mortality in premature infants < 32 weeks gestation [45]. Subsequent randomized controlled trials reported similar findings with dexamethasone [46]. Meta-analyses by Crowley [47] and Roberts [48] support these conclusions and highlight additional benefits of antenatal corticosteroids including a reduction in IVH, NEC, need for mechanical ventilation, and systemic infections in the first 48 h of life. Interestingly, though antenatal corticosteroids prevent several serious co-morbidities, alone they are not associated with a reduction in BPD [48], highlighting the multifactorial etiology of BPD.

Exogenous surfactant administration is another mainstay of early respiratory management of preterm infants. Surfactant decreases alveolar surface tension and improves lung compliance, reducing the need for prolonged mechanical ventilation. Despite the recent focus on non-invasive ventilation for preterm infants, the rate of non-invasive failure remains high, and up to 65% of extremely preterm infants will require surfactant administration for respiratory distress syndrome [49]. A meta-analysis by Soll noted a significant reduction in the risk of BPD when exogenous artificial surfactant was administered to preterm infants with RDS [50]. When surfactant is given, it is most effective when administered within 2 h of life [51]. Newer studies focus on strategies for administering surfactant. The technique of INtubation, SURfactant administration during brief mechanical ventilation, followed by Extubation (INSURE) was introduced with a goal of minimizing exposure to mechanical ventilation. A meta-analysis by Stevens found that compared with selective, late administration of surfactant, an early INSURE approach was associated with less BPD in addition to fewer air leak syndromes and a decreased need for mechanical ventilation [52]. In addition, instillation of surfactant into the trachea using a thin catheter while infants are spontaneously breathing may avoid invasive ventilation altogether for preterm infants, but evaluation of this technique remains ongoing [53].

Initial observational studies comparing the rates of BPD at different centers noted that centers with the highest rates of non-invasive ventilation by nasal continuous airway pressure (nCPAP) reported the lowest rates of BPD [54]. The use of nCPAP facilitates alveolar recruitment and maintains a constant mean airway pressure to prevent atelectrauma, which results from alveolar expansion and collapse. In addition, nCPAP can avoid barotrauma and volutrauma inherent to mechanical ventilation. Several large, multi-center randomized controlled trials examined the role of early delivery room stabilization on nCPAP versus prophylactic surfactant administration and/or mechanical ventilation [55–57]. While there are methodological differences between these studies, a trend toward lower rates of BPD was noted in the early nCPAP groups. Various meta-analyses have noted a lower association of the combined outcome of data or BPD in those infants with early nCPAP stabilization [58].

When premature infants require mechanical ventilation due to a combination of hypercarbia, hypoxia, and apnea of prematurity, a thoughtful approach is necessary to avoid barotrauma and volutrauma. Continuous-flow, time-cycled, pressure-limited ventilators have become standard in NICUs throughout the developed world. Volume-targeted ventilation delivers more stable tidal volumes than pressure-limited ventilation, and it maintains adequate minute ventilation in the face of changing lung compliance, thereby avoiding overdistension. The benefits of volume-targeted ventilation were supported in a meta-analysis that demonstrated reduced death or BPD in infants receiving volume-targeted ventilation [59]. High frequency ventilation provides a constant distending mean airway pressure and avoids atelectrauma and volutrauma from under- and over-distended alveoli respectively. However, a meta-analysis of trials from the last two decades demonstrated that high frequency ventilation is comparable to conventional ventilation with regard to the outcomes of mortality and BPD [60].

Caffeine is one of the most commonly prescribed and cost-effective medications used in the NICU. Caffeine is a methylxanthine that reduces central nervous system adenosine signaling. In animal and human studies, caffeine increased diaphragmatic excursion and improved normoxic respiratory drive, and clinically facilitates ventilator weaning in extremely premature infants [61,62]. The Caffeine for Apnea of Prematurity (CAP) randomized, controlled trial demonstrated that compared with placebo, caffeine citrate reduced the rate BPD at 36 weeks post menstrual age as well as improved neurodevelopmental outcomes at 18 to 22 months chronological age in infants < 1250 g at birth [63,64]. Additional studies support this finding when caffeine is initiated in the first 72 h of birth [65].

Dexamethasone, a potent glucocorticoid, has been discussed extensively in the neonatal literature to facilitate ventilator weaning and prevention of BPD. Its initial use early in postnatal life and at high doses readily facilitated weaning of respiratory support but was later demonstrated to contribute to adverse neurodevelopmental outcomes. In more recent years, investigators have attempted to identify a dosing regimen for dexamethasone that balances the short-term goal of ventilator weaning with the effect on neurodevelopmental outcome [66]. A meta-analysis concluded that late (> 7 days of life) postnatal treatment with steroids facilitated ventilator weaning, reduced extubation failure, and reduced BPD. However, the included trials were not powered sufficiently to detect adverse effects on neurodevelopment, and therefore, the benefits of steroid therapy may not outweigh the risks [67]. A meta-regression by Doyle attempted to quantify the risk-benefit ratio with regards to death or cerebral palsy. The benefit of steroids depended on the risk of BPD in the enrolled population such that when steroids are used in a population with the highest risk of BPD, the risk of death or CP is reduced [68].

5.2. Nutritional support for lung growth

Nutritional considerations are vital to all aspects of neonatal care, not least of which is lung development. Lower caloric intake in the first 14 days of life was significantly associated with the development of BPD [69]. Infants born small for gestational age or who develop extra uterine growth failure are also more likely to develop BPD [70]. Vitamin A has been identified as a key factor in lung maturation, and its deficiency may contribute to impaired lung healing, increased loss of cilia, a decreased number of alveoli, and an increased susceptibility to infection [71]. A randomized controlled trial by Tyson in 1999 found that extremely low birthweight infants supplemented with vitamin A IM reduced the primary outcome of death or BPD with a number needed to treat of 14 to 15 to prevent one case of BPD [72].

6. Conclusion

Technological and medical care advancements will likely lead to an increasing prevalence of PH and lung disease in the premature infant. Our understanding of lung development is increasing and indicates that survival is possible for the increasingly premature infant. However, with these advancements, the burden of care will also escalate. Although there is some evidence of benefit in some patients, current pharmacological therapy can be potentially futile in the patient with a limited vascular bed. Until discovery of novel therapeutics to improve lung growth are available, care and therapy should continue to be directed toward reducing further insult and injury, allowing for the lung to “heal” and advance through normal development and improve vascular area.

Funding

National Institutes of Health, K08-HL140129 and the Parker B. Francis Foundation (DBF); National Institutes of Health, K12-

HD087023 and the Parker B. Francis Foundation (JMS).

Declaration of Competing Interest

None.

References

[1] Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723–9.
[2] Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics 2005;116:1353–60.
[3] Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med 2007;357:1946–55.
[4] Benjamin JT, Smith RJ, Halloran BA, Day TJ, Kelly DR, Prince LS. FGF-10 is decreased in bronchopulmonary dysplasia and suppressed by toll-like receptor activation. Am J Physiol Lung Cell Mol Physiol 2007;292:L550–8.
[5] McCulley D, Wienhold M, Sun X. The pulmonary mesenchyme directs lung development. Curr Opin Genet Dev 2015;32:98–105.
[6] Stroustrup A, Trasande L. Epidemiological characteristics and resource use in neonates with bronchopulmonary dysplasia: 1993-2006. Pediatrics 2010;126:291–7.
[7] Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The diagnosis of bronchopulmonary dysplasia in very preterm infants: An evidence-based approach. Am J Respir Crit Care Med 2019. [epub ahead of print].
[8] Kollee LA, Cuttini M, Delmas D, Papiernik E, den Ouden AL, Agostino R, et al. Obstetric interventions for babies born before 28 weeks of gestation in Europe: results of the MOSAIC study. BJOG 2009;116:1481–91.
[9] Doyle LW, Carse E, Adams AM, Ranganathan S, Opie G, Cheong JLY, et al. Ventilation in extremely preterm infants and respiratory function at 8 years. N Engl J Med 2017;377:329–37.
[10] Rysavy MA, Li L, Bell EF, Das A, Hintz SR, Stoll BJ, et al. Between-hospital variation in treatment and outcomes in extremely preterm infants. N Engl J Med 2015;372:1801–11.
[11] Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. Jama 2015;314:1039–51.
[12] Slaughter JL, Pakrashi T, Jones DE, South AP, Shah TA. Echocardiographic detection of pulmonary hypertension in extremely low birth weight infants with bronchopulmonary dysplasia requiring prolonged positive pressure ventilation. J Perinatol: official journal of the California Perinatal Association 2011;31:635–40.
[13] Khemani E, McElhinney DB, Rhein L, Andrade O, Lacro RV, Thomas KC, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics 2007;120:1260–9.
[14] Bhat R, Salas AA, Foster C, Carlo WA, Ambalavanan N. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. Pediatrics 2012;129:e682–9.
[15] An HS, Bae EJ, Kim GB, Kwon BS, Beak JS, Kim EK, et al. Pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. Korean Circ J 2010;40:131–6.
[16] Lagatta JM, Hysinger EB, Zaniletti I, Wymore EM, Vyas-Read S, Yallapragada S, et al. The impact of pulmonary hypertension in preterm infants with severe bronchopulmonary dysplasia through 1 year. J Pediatr 2018;203:218–24 e3.
[17] Arjaans S, Zwart EAH, Ploegstra MJ, Bos AF, Kooi EMW, Hillege HL, 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;32:258–67.
[18] Frank DB, Crystal MA, Morales DL, Gerald K, Hanna BD, Mallory Jr. GB, et al. Trends in pediatric pulmonary hypertension-related hospitalizations in the United States from 2000-2009. Pulmonary circulation 2015;5:339–48.
[19] Swarr DT, Morrisey EE. Lung endoderm morphogenesis: gasping for form and function. Annu Rev Cell Dev Biol 2015;31:553–73.
[20] Whitsett JA, Kalin TV, Xu Y, Kalinichenko VV. Building and regenerating the lung cell by cell. Physiol Rev 2019;99:513–54.
[21] Cardoso WV. Lu J. Regulation of early lung morphogenesis: questions, facts and controversies. Development 2006;133:1611–24.
[22] Morrisey EE, Hogan BL. Preparing for the first breath: genetic and cellular mechanisms in lung development. Dev Cell 2010;18:8–23.
[23] Morrisey EE, Cardoso WV, Lane RH, Rabinovitch M, Abman SH, Ai X, et al. Molecular determinants of lung development. Ann Am Thorac Soc 2013;10:S12–6.
[24] Frank DB, Penkala IJ, Zepp JA, Sivakumar A, Linares-Saldana R, Zacharias WJ, et al. Early lineage specification defines alveolar epithelial ontogeny in the murine lung. Proceedings of the National Academy of Sciences of the United States of America. 2019.
[25] Mehler K, Oberthuer A, Keller T, Becker I, Valter M, Roth B, et al. Survival among infants born at 22 or 23 weeks' gestation following active prenatal and postnatal care. JAMA Pediatr 2016;170:671–7.
[26] Hislop AA, Pierce CM. Growth of the vascular tree. Paediatr Respir Rev 2000;1:321–7.
[27] Schachtner SK, Wang Y, Scott Baldwin H. Qualitative and quantitative analysis of embryonic pulmonary vessel formation. Am J Respir Cell Mol Biol 2000;22:157–65.
[28] Mourani PM, Abman SH. Pulmonary hypertension and vascular abnormalities in bronchopulmonary dysplasia. Clin Perinatol 2015;42:839–55.
[29] Yamamoto H, Yun EJ, Gerber HP, Ferrara N, Whitsett JA, Vu TH. Epithelial-vascular cross talk mediated by VEGF-A and HGF signaling directs primary septae formation during distal lung morphogenesis. Dev Biol 2007;308:44–53.
[30] Yun EJ, Lorizio W, Seedorf G, Abman SH, Vu TH. VEGF and endothelium-derived retinoic acid regulate lung vascular and alveolar development. Am J Physiol Lung Cell Mol Physiol 2016;310:L287–98.
[31] Le Cras TD, Markham NE, Tuder RM, Voelkel NF, Abman SH. Treatment of newborn rats with a VEGF receptor inhibitor causes pulmonary hypertension and abnormal lung structure. Am J Physiol Lung Cell Mol Physiol 2002;283:L555–62.
[32] Brody JS, Stemmler EJ, DuBois AB. Longitudinal distribution of vascular resistance in the pulmonary arteries, capillaries, and veins. J Clin Invest 1968;47:783–99.
[33] Vonk Noordegraaf A, Chin KM, Haddad F, Hassoun PM, Hemnes AR, Hopkins SR, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. Eur Respir J 2019;53.
[34] Presson RG, Jr., Baumgartner WA, Jr., Peterson AJ, Glenny RW, Wagner WW, Jr. Pulmonary capillaries are recruited during pulsatile flow. J Appl Physiol (1985). 2002;92:1183–90.
[35] Dupuis J, Goresky CA, Rouleau JL, Bach GG, Simard A, Schwab AJ. Kinetics of pulmonary uptake of serotonin during exercise in dogs. J Appl Physiol (1985) 1996;80:30–46.
[36] Dupuis J, Goresky CA, Ryan JW, Rouleau JL, Bach GG. Pulmonary angiotensin-converting enzyme substrate hydrolysis during exercise. J Appl Physiol (1985) 1992;72:1868–86.
[37] Krishnan U, Feinstein JA, Adatia I, Austin ED, Mullen MP, Hopper RK, et al. Evaluation and management of pulmonary hypertension in children with bronchopulmonary dysplasia. J Pediatr 2017;188:24–34. [e1].
[38] Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation 2015;132:2037–99.
[39] Altit G, Lee HC, Hintz S, Tacy TA, Feinstein JA, Bhombal S. Practices surrounding pulmonary hypertension and bronchopulmonary dysplasia amongst neonatologists caring for premature infants. J Perinatol: official journal of the California Perinatal Association 2018;38:361–7.
[40] Berkelhamer SK, Mestan KK, Steinhorn RH. Pulmonary hypertension in bronchopulmonary dysplasia. Semin Perinatol 2013;37:124–31.
[41] Backes CH, Reagan PB, Smith CV, Jadcherla SR, Slaughter JL. Sildenafil treatment of infants with bronchopulmonary dysplasia-associated pulmonary hypertension. Hosp Pediatr 2016;6:27–33.
[42] Wardle AJ, Wardle R, Luyt K, Tulloh R. The utility of sildenafil in pulmonary hypertension: a focus on bronchopulmonary dysplasia. Arch Dis Child 2013;98:613–7.
[43] Mourani PM, Sontag MK, Ivy DD, Abman SH. Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. J Pediatr 2009;154(379–84):84 e1–2.
[44] Rutkowska M, Hozejowski R, Helwich E, Borszewska-Kornacka MK, Gadzinowski J. Severe bronchopulmonary dysplasia - incidence and predictive factors in a prospective, multicenter study in very preterm infants with respiratory distress syndrome. J Matern Fetal Neonatal Med 2019;32:1958–64.
[45] Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972;50:515–25.
[46] Effect of antenatal dexamethasone administration on the prevention of respiratory distress syndrome. Am J Obstet Gynecol 1981;141:276–87.
[47] Crowley PA. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. Am J Obstet Gynecol 1995;173:322–35.
[48] Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2017;3:CD004454.
[49] Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ 2013;347:f5980.
[50] Soll RF. Synthetic surfactant for respiratory distress syndrome in preterm infants. Cochrane Database Syst Rev 2000:CD001149.
[51] Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev 2012;11:CD001456.
[52] Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database Syst Rev 2007:CD003063.
[53] More K, Sakhuja P, Shah PS. Minimally invasive surfactant administration in preterm infants: a meta-narrative review. JAMA Pediatr 2014;168:901–8.
[54] Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birth weight infants: spontaneous breathing or intubation? Pediatrics 1999;103:961–7.
[55] Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, Howard D, et al. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics 2011;128:e1069–76.
[56] Network SSGotEKSNNR, Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 2010;362:1970–9.
[57] Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB, et al. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008;358:700–8.
[58] Subramaniam P, Ho JJ, Davis PG. Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants. Cochrane Database Syst Rev 2016:CD001243. online pub.
[59] Wheeler KI, Klingenberg C, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation for preterm infants: a systematic review and meta-analysis.

Neonatology 2011;100:219–27.
[60] Cools F, Askie LM, Offringa M, Asselin JM, Calvert SA, Courtney SE, et al. Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. Lancet 2010;375:2082–91.
[61] Kassim Z, Greenough A, Rafferty GF. Effect of caffeine on respiratory muscle strength and lung function in prematurely born, ventilated infants. Eur J Pediatr 2009;168:1491–5.
[62] Julien CA, Joseph V, Bairam A. Caffeine reduces apnea frequency and enhances ventilatory long-term facilitation in rat pups raised in chronic intermittent hypoxia. Pediatr Res 2010;68:105–11.
[63] Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med 2007;357:1893–902.
[64] Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Caffeine therapy for apnea of prematurity. N Engl J Med 2006;354:2112–21.
[65] Dobson NR, Patel RM, Smith PB, Kuehn DR, Clark J, Vyas-Read S, et al. Trends in caffeine use and association between clinical outcomes and timing of therapy in very low birth weight infants. J Pediatr 2014;164:992–8. [e3].
[66] Demauro SB, Dysart K, Kirpalani H. Stopping the swinging pendulum of postnatal corticosteroid use. J Pediatr 2014;164:9–11.
[67] Doyle LW, Ehrenkranz RA, Halliday HL. Late (> 7 days) postnatal corticosteroids for chronic lung disease in preterm infants. Cochrane Database Syst Rev 2014:CD001145.
[68] Doyle LW, Halliday HL, Ehrenkranz RA, Davis PG, Sinclair JC. An update on the impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk of bronchopulmonary dysplasia. J Pediatr 2014;165:1258–60.
[69] Uberos J, Lardon-Fernandez M, Machado-Casas I, Molina-Oya M, Narbona-Lopez E. Nutrition in extremely low birth weight infants: impact on bronchopulmonary dysplasia. Minerva Pediatr 2016;68:419–26.
[70] Eriksson L, Haglund B, Odlind V, Altman M, Ewald U, Kieler H. Perinatal conditions related to growth restriction and inflammation are associated with an increased risk of bronchopulmonary dysplasia. Acta Paediatr 2015;104:259–63.
[71] Massaro GD, Massaro D. Postnatal treatment with retinoic acid increases the number of pulmonary alveoli in rats. Am J Physiol 1996;270:L305–10.
[72] Tyson JE, Wright LL, Oh W, Kennedy KA, Mele L, Ehrenkranz RA, et al. Vitamin a supplementation for extremely-low-birth-weight infants. National Institute of Child Health and Human Development neonatal research network. N Engl J Med 1999;340:1962–8.