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Epidemiology of Bronchopulmonary Dysplasia

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Abstract

Bronchopulmonary dysplasia (BPD) is among the most common and serious sequelae of preterm birth. BPD affects at least one-quarter of infants born with birth weights less than 1500g. The incidence of BPD increases with decreasing gestational age and birth weight. Additional important risk factors include intrauterine growth restriction, sepsis, and prolonged exposure to mechanical ventilation and supplemental oxygen. The diagnosis of BPD predicts multiple adverse outcomes including chronic respiratory impairment and neurodevelopmental delay. This review summarizes the diagnostic criteria, incidence, risk factors, and long-term outcomes of BPD.

Keywords

bronchopulmonary dysplasia; chronic lung disease; epidemiology; mechanical ventilation; very low birth weight

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most prevalent and one of the prognostically most important sequelae of preterm birth. In the US, it impacts 10,000–15,000 infants annually, including approximately 50% of infants with birth weight less than 1000g (Stoll, 2010; Martin, 2013). BPD predisposes infants to prolonged initial hospitalization and increased rates of mortality and childhood morbidity (Cotten, 2005; Ehrenkranz, 2005). Chronic respiratory and cardiovascular impairments, growth failure, and neurodevelopmental delay are more common in preterm infants with than without BPD (Ehrenkranz, 2005; Bott, 2006; Doyle, 2006; Berkelhamer, 2013; Carraro, 2013; Cristea, 2013).

In 1964, Shepard et al. described pulmonary fibrosis in a series of mechanically ventilated preterm infants. Three years later, Northway et al. (1967) coined the term *bronchopulmonary dysplasia* in a seminal description of the clinical, pathologic, and radiographic characteristics

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of lung disease observed in 32 moderately to late preterm infants (mean gestational age of 34 weeks and mean birth weight of 2200g) following prolonged exposure to supplemental oxygen and mechanical ventilation. In 1978, a National Heart, Lung, and Blood Institute (NHLBI) sponsored workshop defined BPD as 28 days of oxygen exposure with characteristic radiographic changes (Report of Workshop on Bronchopulmonary Dysplasia, 1979). Ten years later, Shennan et al. (1988) reported that oxygen requirement at 36 weeks postmenstrual age (PMA) better predicted adverse pulmonary outcomes in infants with birth weights less than 1500g.

The introduction of gentler ventilation strategies, antenatal corticosteroids, and surfactant therapy in subsequent decades changed the pathophysiology of lung disease associated with prematurity. BPD is now an infrequent finding in infants born with birth weights greater than 1500g and exceeding 32 weeks gestation (Bancalari, 2003). In 1998, Hussain et al. compared the lung histology of surfactant exposed and unexposed preterm infants with BPD. Surfactant-treated infants displayed a consistent pattern of more diffuse disease. The number of alveoli and capillaries was reduced, but with fewer areas of alternating hyperinflation and focal collapse that are common in surfactant-unexposed infants. Evidence of airway injury, inflammation, and parenchymal fibrosis was also less prominent in surfactant-treated infants (Hussain, 1998). These histologic differences as well as the shift in BPD prevalence to smaller, more premature infants following the introduction of surfactant led to the distinction between “old” and “new” BPD (Jobe, 1999).

DIAGNOSTIC CRITERIA

In 2000, a workshop sponsored by the National Institute of Child Health and Human Development (NICHD), NHLBI, and Office of Rare Diseases (ORD) proposed the current (NIH consensus) definition of BPD (Jobe and Bancalari, 2001). This definition assesses for BPD at 36 weeks postmenstrual age (PMA) in infants born less than 32 weeks gestation who required supplemental oxygen for at least 28 days. For the first time, this definition also stratified BPD severity into three groups (mild, moderate, or severe) based on the amount of supplemental oxygen and mode of respiratory support at 36 weeks PMA. The presence of abnormal radiograph findings was no longer required. The current definition includes a few features worth noting. First, a day of treatment with supplemental oxygen is defined as 12 hours or more of oxygen exposure. Second, infants must require supplemental oxygen for a cumulative of 28 days or more prior to assessment at 36 weeks PMA. Finally, respiratory support at the time of assessment should reflect the infant’s usual therapy in the days surrounding assessment and not an “acute” event. Studies that rely on a simple “snapshot” of respiratory support at 28 days or 36 weeks PMA may therefore incompletely assess BPD rates based on these criteria (Bancalari, 2003).

Ehrenkranz et al. (2005) attempted to evaluate the NIH consensus definition in a cohort of extremely low birth weight (ELBW; birth weight < 1000g) infants followed in the NICHD Neonatal Research Network’s very low birth weight registry. However, not all data required to apply the consensus definition were available in the Network database. Respiratory support was only assessed on day 28 of life and at 36 weeks PMA or discharge. The data needed to assess the cumulative days of oxygen exposure prior to 36 weeks PMA and

whether oxygen exposure was greater or less than 12 hours per day were not recorded. Based on the available data, increasing severity of BPD was associated with increasing incidence of neurodevelopmental impairment, re-hospitalization for pulmonary causes, and use of respiratory medications at 18 to 22 months (Ehrenkranz, 2005).

Despite association with long-term outcomes, use of supplemental oxygen as a diagnostic criterion for BPD has limitations. First, appropriate oxygen saturation limits for preterm infants remain controversial. As a result, oxygen administration varies across centers (Ellsbury, 2002; Vermont Oxford Network, 2012). Second, to meet the criterion of oxygen therapy at 36 weeks PMA, infants born extremely preterm require a longer postnatal duration of oxygen exposure compared to more mature preterm infants. Third, supplemental oxygen requirement is influenced by factors other than the severity of lung disease. Mode of oxygen delivery, altitude, upper airway obstruction, and certain medications (e.g. diuretics, corticosteroids, pulmonary vasodilators) can all affect gas exchange (Kao, 1994; Bancalari, 2003; Lee, 2013).

To decrease variability in BPD diagnosis, Walsh et al. (2003) proposed to standardize the threshold saturation on which a diagnosis of oxygen dependency is based. The “physiologic” definition requires an oxygen reduction test to determine oxygen dependency at 36 weeks PMA in infants receiving ≤ 30% of supplemental oxygen. To conduct the test, the fraction of administered oxygen is reduced in a stepwise manner over a defined timed interval. Infants who are unable to maintain saturations ≥ 90% during that time are diagnosed with BPD. Application of the physiologic definition decreased rates of BPD on average by 10% (35% vs. 25%, p=<0.0001) at NICHD Neonatal Research Network centers (Walsh, 2004). A smaller, but significant decrease in between-center variation in BPD rates was also observed (Walsh, 2004). Natarajan et al. (2012) evaluated neurodevelopmental outcome in 1189 ELBW infants who were classified using the physiologic definition of BPD. While rates of impairment overall were higher in infants with than without BPD, only 109 of the evaluated infants met criteria to undergo an oxygen reduction test. Among those 109 infants, there was no difference in the rates of impairment between the 60 infants who failed the oxygen reduction test and the 49 infants who passed it (Natarajan, 2012).

INCIDENCE OF BPD

The Israeli Neonatal Network recently reported outcomes for all very low birth weight infants (VLBW; birth weight < 1500g) infants born in Israel between 2000–2010 who survived to 36 weeks PMA (n=12,139) (Klinger, 2013). Based on need for supplemental oxygen at 36 weeks PMA, 13.7% of VLBW and 31% of ELBW infants met diagnostic criteria (Klinger, 2013). In the Canadian and Japanese Neonatal Networks, rates of BPD between 2006 and 2008 were 12.3% and 14.6% respectively for surviving VLBW infants (Isayama, 2012). In the Vermont Oxford Network (VON), yearly rates of BPD for VLBW infants ranged from 26.2% to 30.4% between 2000–2009 (n=305,770) (Horbar, 2012). The NICHD Neonatal Research Network compared rates of BPD in extremely preterm infants (22–28 weeks gestation) using three different definitions (Stoll, 2010). Rates based on the NIH consensus definition were highest (68%), owing to inclusion of infants who received supplemental oxygen for ≥28 days but were on room air by 36 weeks PMA. Forty-two

percent were diagnosed with BPD based on supplemental oxygen use at 36 weeks PMA and 40% by the physiologic definition (Stoll, 2010).

Inter-center variability adds additional difficulty in determining true BPD rates. At 17 NICHD Neonatal Research Network centers, rates of BPD based on the physiologic definition ranged from <10% to >50% in infants with birth weights less than 1250g (Walsh, 2007). Similar variability is seen across VON centers and internationally (Payne, 2006a, b; Zeitlin, 2008; Choi, 2012; Rojas, 2012). In 10 European regions, rates of BPD ranged between 10.5% and 21.5% for infants born less than 32 weeks gestation in 2003 (Zeitlin, 2008). Across all South Korean neonatal intensive care units, rates of BPD in VLBW infants varied from 5 to 50% (Choi, 2012).

While some reports indicate BPD rates are beginning to decline, the majority of studies suggest that rates remained stable or even increased during the past two to three decades, possibly due to increased survival of the highest risk infants (Parker, 1992; Smith, 2005; Fanaroff, 2007; Stoll, 2010; Stroustrup, 2010; Botet, 2012; Horbar, 2012). Results from two epochs of the EPICure study indicated no change in rates of BPD between 1995 and 2006 for infants born between 22 and 26 weeks gestation (Costeloe, 2012). The NICHD Neonatal Research Network reported similar rates of BPD between 1995–1996, 1997–2002, and 2003–2007 (Fanaroff, 2007; Stoll, 2010). Between 2000–2009 annual BPD rates reported by VON in infants born 501–1500g varied from 26.2% to 30.4% without clinically relevant decline during that period (Horbar, 2012).

RISK FACTORS FOR BPD

Many potential risk factors for BPD have been identified. True risk factors, however, are often difficult to isolate, particularly from observational data, due to interrelation of many perinatal and neonatal factors. We discuss below several of the best-described or most controversial risk factors. Others, including low Apgar scores (Oh, 2005), perinatal asphyxia (Hakulinen, 1988; Darlow, 1992), greater weight-adjusted fluid intake in the first days of life (Van Marter, 1990; Palta, 1991; Marshall, 1999; Oh, 2005), additional surfactant doses (Ambalavanan, 2008), severe intraventricular hemorrhage (Oh, 2005), necrotizing enterocolitis (Oh, 2005), white race (Avery, 1987; Palta, 1991), maternal smoking (Antonucci, 2004), family history of asthma (Nickerson, 1980), and genetic factors (Lavoie, 2010; Somaschini, 2012) have also been associated with BPD.

Prenatal Risk Factors

Intrauterine Growth Restriction: Fetal growth restriction and birth small for gestational age increase the risk of BPD. Klinger et al. (2013) reported risk-adjusted odds for BPD of 2.65 (95% CI 2.24–3.12) in VLBW infants with birth weight less than the 10% for gestational age. Infants born at the lowest gestation had the highest risk. The Extremely Low Gestational Age Newborn (ELGAN) study found a strong association between fetal growth restriction and BPD in infants born less than 29 weeks gestation (Bose, 2009). Odds of BPD in that cohort were over three-fold higher for infants with birth weight more than one standard deviation below the mean (Bose, 2009).

Lack of Antenatal Corticosteroids: Antenatal corticosteroids accelerate lung and other organ maturation and are now the mainstay of prophylactic treatment for threatened preterm birth (ACOG Committee Opinion No. 475, 2011). Despite lower rates of neonatal death, respiratory distress syndrome, intraventricular hemorrhage, and other neonatal morbidities following exposure to antenatal corticosteroids, BPD rates are not improved (Van Marter, 2001; Roberts, 2006; Carlo, 2011). It is uncertain whether this finding is due to a true lack of beneficial effect of antenatal corticosteroids on BPD or insufficient statistical power for this particular outcome. A recent Cochrane review found reduced need for respiratory support, mechanical ventilation or continuous positive airway pressure, time requiring mechanical ventilation, and time requiring supplemental oxygen with antenatal corticosteroid use (Roberts, 2006). Rates of BPD, however, were not significantly reduced (RR 0.86, 95% CI 0.61–1.22). In an observational study, Carlo et al. (2011) found no significant decrease in rates of BPD or the composite outcome of death or BPD in 7,808 ELBW infants born to mothers who received antenatal corticosteroids at 23 NICHD Neonatal Research Network centers between 1993 and 2009.

Chorioamnionitis: Whether maternal chorioamnionitis increases BPD risk remains controversial. The unreliability of both clinical and histologic diagnoses of chorioamnionitis make the interpretation of available data difficult (Redline, 2003; Jobe, 2012). A recent meta-analysis of studies involving 13,583 infants found that histologically but not clinically diagnosed chorioamnionitis was associated with higher odds of BPD (Hartling, 2011). After accounting for likely publication bias due to non-publication of studies demonstrating a lack of association as well as potential confounding by gestational age and birth weight, the association was no longer significant (Hartling, 2011). The ELGAN study reported that while 51% of placental cultures obtained from 1,119 extremely preterm deliveries yielded positive results, no association with BPD was observed (Bose, 2009). In the Alabama Preterm Birth Study, no relationship between placental signs of cellular inflammation and BPD were observed, although umbilical cord blood cultures that were positive for *Ureaplasma urealyticum* or *Mycoplasma hominis* increased the risk of BPD over two-fold (26.8% vs. 10.1%, p=0.0001) (Andrews, 2006; Goldenberg, 2008). In the multivariable analysis, however, this association was less strong (OR 1.99, 95% CI 0.91–4.37) (Goldenberg, 2008).

Risk Factors at Birth

Gestational Age and Birth Weight: Prematurity and low birth weight are the strongest predictors of BPD, with incidence and severity inversely proportional to both. The Canadian Neonatal Network reported that 28.1% of surviving infants born less than 25 weeks gestation developed BPD (defined as oxygen use at 36 weeks PMA following oxygen use on the 28th day after birth) compared to only 4% of infants born at 29–32 weeks gestation (Isayama, 2012). In an Israeli national cohort, 50.1% of surviving infants born at 24–25 weeks gestation developed BPD diagnosed by oxygen requirement at 36 weeks PMA compared to only 4.1% born between 30–32 weeks (Klinger, 2013). In the same cohort, 29.3% of infants who were born with birth weights between 1000g and 1500g and over 70% of infants with birth weights less than 1000g developed BPD. In the NICHD Neonatal Research Network, the incidence of BPD in infants born at 23 weeks gestation was 73%,

56% of whom developed severe disease (Stoll, 2010). At 28 weeks gestation, 23% develop BPD, with severe disease found in only 8% (Stoll, 2010).

Gender: Male infants are at increased risk of BPD compared to females of similar gestational age and birth weight (Palta, 1991; Rojas, 1995; Ambalavanan, 2008; Costeloe, 2012). Surviving males in the EPICure studies were over twice as likely to develop BPD than similar females (Costeloe, 2012). Among VLBW infants enrolled in the NICHD trial of inhaled nitric oxide, the adjusted odds of BPD or death were nearly 5 times greater for males than females (Ambalavanan, 2008).

Birth Hospital Level of Neonatal Intensive Care: Mortality rates are lower for preterm infants born in hospitals with higher-level specialty care nurseries (Phibbs, 2007; Lasswell, 2010). The impact of birth hospital on BPD risk, however, is less well established. Several reports demonstrate higher BPD rates in outborn preterm infants who are subsequently transferred to high level centers compared to antenatally transferred infants (Shlossman, 1997; Chan, 2001; Hohlagschwandtner, 2001). These reports failed to risk adjust for important potential confounders, including gestational age or birth weight (Shlossman, 1997; Chan, 2001), intrauterine growth restriction (Shlossman, 1997; Chan, 2001; Hohlagschwandtner, 2001), and maternal morbidities (Shlossman, 1997; Chan, 2001; Hohlagschwandtner, 2001). As maternal and neonatal factors differ among prenatally transferred compared to antenatally transferred infants, failure to do so may bias the results (Delaney-Black, 1989). A secondary analysis of the NEOPAIN trial found no difference in rates of BPD in inborn versus outborn infants after adjusting for differences in gestational age (Palmer, 2004). Warner et al. (2004), however, reported higher risk-adjusted odds of death or BPD for infants born at non-subspecialty perinatal centers in the greater Cincinnati region. In a three state population based cohort, Lorch et al. (2012) reported differing results between states. The adjusted risk of BPD was lower for VLBW infants born in high level units in Missouri (RR 0.29 95% CI 0.12–0.52), higher in California (RR 1.33 95% CI 1.03–1.81), and no different in Pennsylvania (Lorch, 2012).

Postnatal Risk Factors

Mechanical ventilation and supplemental oxygen: Mechanical ventilation and supplemental oxygen are often life saving in premature and critically ill neonates. There is concern, however, that these therapies may cause injurious sequelae. Experimental evidence shows a clear link between barotrauma and volutrauma induced by mechanical ventilation and pathologic structural and inflammatory changes in animal lung that mimic human BPD (Bjorklund, 1997; Dreyfuss, 1998; Mokres, 2010). Supplemental oxygen can cause oxygen toxicity leading to adverse effects in the developing lung and other organs (Bonikos, 1976; Delacourt, 1996; Saugstad, 1998). Numerous observational studies support an association between these exposures and development of BPD (Kraybill, 1989; Van Marter, 2000; Oh, 2005; Ambalavanan, 2008). Epidemiologic evidence of a causal link is less robust. In particular, whether supplemental oxygen is responsible for lung injury in preterm infants or simply reflects lung immaturity and disease severity is difficult to discern from available data.

Several studies of delivery room resuscitation and early respiratory management evaluated whether interventions aimed at reducing mechanical ventilation and supplemental oxygen exposure result in improved respiratory outcomes. In a small randomized controlled trial (RCT) in infants born 24–28 weeks gestation, Vento et al. (2009) found a lower incidence of BPD in infants resuscitated in the delivery room with 30% compared to 90% supplemental oxygen (15.4% vs. 31.7%; $p<0.05$). Kapadia et al. (2013) compared rates of BPD in infants with gestational age of 24–34 weeks randomized to two different delivery room resuscitation strategies. In one arm (n = 44), resuscitation was initiated with room air and supplemental oxygen was titrated to achieve the Neonatal Resuscitation Program (Kattwinkel 2010) recommended saturation levels. The alternate arm (n = 44) titrated from 100% supplemental oxygen to achieve a saturation of 85–94%. BPD rates were lower in the infants initially resuscitated without supplemental oxygen (7% vs. 25%; p=0.04) (Kapadia 2013). The Room Air versus Oxygen Administration During Resuscitation of Preterm Infants (ROAR) study, however, found no difference in BPD rates between preterm infants treated with room air (n=34), titrated oxygen (n=34), or 100% supplemental oxygen (n=38) (Rabi, 2011). Laughon et al. (2009) found that early oxygen requirements varied in infants born 23–27 weeks completed gestation who subsequently developed BPD. While BPD was most frequent in infants with early severe disease, over 50% with mild and nearly 20% with minimal early lung disease also developed BPD (Laughon, 2009).

Whether differential oxygen saturation targeting beyond the initial resuscitation influences BPD rates has also been prospectively evaluated. The Benefits of Oxygen Saturation Targeting (BOOST-I) trial evaluated outcomes following randomization to high (95%−98%) and low (92%−94%) oxygen saturation thresholds in infants born less than 30 weeks gestation (Askie, 2003). Infants in the high saturation group were more likely to receive supplemental oxygen at 36 weeks PMA (OR 1.40; 95% CI 1.15–1.70), however an oxygen reduction test was not conducted (Askie, 2013). Several subsequent large RCTs compared saturation targets of 85%−89% and 91%−95% in extremely preterm infants and found no difference in rates of severe BPD (Schmidt, 2013) or BPD diagnosed by physiologic definition (SUPPORT, 2010; The BOOST II Collaborative Groups, 2013).

Early use of non-invasive ventilation has been investigated as a means to prevent BPD. In a secondary analysis from the Caffeine for Apnea of Prematurity (CAP) trial, DeMauro et al. (2011) found higher rates of BPD in infants who were intubated at birth compared to those who were stabilized with non-invasive continuous positive airway pressure (CPAP). A recent meta-analysis of 4 RCTs with a total of 2,782 very preterm infants compared early use of CPAP to intubation and mechanical ventilation (Morley, 2008; Finer, 2010; Sandri, 2010; Dunn, 2011; Schmolzer, 2013). BPD rates were only modestly reduced with early CPAP (32.4% vs. 34.0%), and the results failed to meet statistical significance (RR 0.91; 95% CI 0.82–1.01) (Schmolzer, 2013). However, a significant benefit with early CPAP was observed for the combined outcome of BPD, death, or both at 36 weeks PMA (RR 0.91; 95%CI 0.84–0.99) (Schmolzer, 2013). The two largest RCTs showed a significant reduction in duration of mechanical ventilation and a non-significant trend towards shorter duration of oxygen exposure with early CPAP (Morley, 2008; Finer, 2010).

Early, non-invasive sustained lung inflation has shown promise in preliminary studies. In single center RCT, te Pas and Walther (2007) reported lower rates of intubation, duration of respiratory support, and BPD in very preterm infants who received sustained inflation with CPAP delivered through a nasal pharyngeal tube compared to bag-mask resuscitation in the delivery room. Further randomized trials are needed to confirm these findings.

Patent Ductus Arteriosus: The role of a patent ductus arteriosus (PDA) in the development of BPD is much-debated. There is strong evidence to support an association but not a causal relationship between persistent PDA and BPD (Palta, 1991; Rojas, 1995; Benitz, 2010; Trzaski, 2011; Benitz, 2012). With the exception of a trial conducted over 30 years ago, no RCT has compared management strategies for prolonged exposure to PDA in premature infants requiring mechanical ventilation (Cotton, 1978). Studies of prophylactic closure of PDA showed no benefit for prevention of BPD and some suggest that treatment may increase BPD risk (Cooke, 2003; Fowlie, 2010; Ohlsson, 2013). In the Trial of Indomethacin Prophylaxis in Preterms (TIPP), Schmidt et al. (2001) found no reduction in BPD rates (45% vs. 43%; $p=0.41$) despite reduction of PDA incidence by more than 50% (21% vs. 49%; $p<0.05$). In a subsequent analysis, the authors raised concern that indomethacin may have had an untoward impact on BPD development that offset any potential benefit of early duct closure (Schmidt, 2006). BPD rates were considerably lower (30% vs. 43%) in infants in whom PDAs closed spontaneously without indomethacin compared to those with closure following indomethacin (Schmidt, 2006).

In an updated analysis of a small RCT of prophylactic surgical closure of PDA (Cassady, 1989), Clyman et al. (2009) found an increased incidence of BPD (oxygen requirement at 36 weeks PMA) and need for mechanical ventilation at 36 weeks PMA in ELBW infants who underwent ligation within the first 24 hours of life. Moreover, development of BPD in the control group was limited to those who subsequently underwent ligation after the first day of life (Clyman, 2009). A recent Cochrane Review found no difference in the incidence of BPD following medical versus surgical closure of PDA in preterm infants, although the analysis contained only a single small RCT (Malviya, 2013). In a systematic review of all RCTs evaluating both surgical and pharmacologic methods of PDA closure, Benitz (2010) found no reduction in BPD or the combined outcome of death or BPD with any therapy.

Sepsis and Systemic Inflammatory Response: Multiple observational studies implicate postnatal sepsis as an independent risk factor for BPD (Marshall, 1999; Oh, 2005; Lahra, 2009; Klinger, 2010; Schlapbach, 2011). Van Marter et al. (2002) reported decreased rates of BPD in VLBW infants exposed to chorioamnionitis, except in those who subsequently developed sepsis. Odds of BPD in those cases were nearly three-fold higher (OR 2.9; 95% CI 1.1–7.4). Lahra et al. (2009) reported a similar decrease in BPD with histologic chorioamnionitis alone but an increase when postnatal sepsis was also present. These findings suggest that postnatal infection may be a more important predictor of BPD than antenatal inflammation.

Although the direct role infection plays is unknown, growing evidence suggests systemic inflammation coupled with changes in vascular permeability lead to immediate alveolar injury and possibly long-term disruption of alveolarization (Bose, 2008; Cornell, 2010;

Wynn, 2010). Regardless of the precise pathophysiology, postnatal corticosteroids and vitamin A, potent anti-inflammatory and anti-oxidant agents, reduce rates of BPD in preterm infants (Tyson, 1999; Halliday, 2003a, b, c; Halliday, 2010; Onland, 2012).

Gastroesophageal Reflux: Whether gastroesophageal reflux (GER) and microaspiration contribute to the development of BPD is unclear. The high prevalence of GER in infants and inability of diagnostic tests to differentiate pathologic from benign GER confound investigation (Bauer, 1999; Lopez-Alonso, 2006; Salvatore, 2007). Moreover, the majority of studies evaluated infants for GER only after BPD was established, not prior to BPD development (Fuloria, 2000; Akinola, 2004; Jadcherla, 2011). In an analysis of 249 tracheal aspirates collected during the first 28 days of life in 59 preterm infants, Farhath et al. (2008) detected higher concentrations of pepsin, a marker of gastric contents, in those who developed BPD compared to healthy controls. Pepsin levels were also higher in infants who developed severe compared to moderate BPD (Farhath, 2008).

LONG-TERM OUTCOME

BPD is a strong predictor of several adverse health outcomes including chronic cardiopulmonary impairments (Bhat, 2012; Bolton, 2012; Berkelhamer, 2013; Carraro, 2013), growth failure (Korhonen, 2004; Bott, 2006; Natarajan, 2013), hearing and vision deficits (Ehrenkranz, 2005), neurodevelopmental delay (Schmidt, 2003; Ehrenkranz, 2005; Walsh, 2005; Schlapbach, 2012), and post neonatal mortality (Werthammer, 1982; Walsh, 2005; Cristea, 2013). While most long-term follow-up data were obtained in patients from the pre-surfactant era, emerging data indicate the “new” BPD predisposes survivors to chronic morbidities that persist into adulthood as well.

Respiratory

Re-hospitalization: Half or more of infants with BPD will require hospital readmission during early childhood. In a study of 238 infants who were born at less than 33 weeks gestation, 49% of infants with BPD required readmission during the first year of life compared to 23% of non-BPD infants (Smith, 2004). Mean number of readmissions and length of stay were also greater for infants with BPD (Smith, 2004). Chye and Gray (1995) reported re-hospitalization in 58% in infants with BPD compared to 35% in matched controls during the first year of life. During the first two years, Greenough et al. (2001) reported that 57% of infants with BPD required re-hospitalization for respiratory reasons alone. Respiratory syncytial virus (RSV) infection in particular is associated with higher readmission rates (Greenough, 2001; Drysdale, 2011). In the NICHD Neonatal Research Network, rates of re-hospitalization and pulmonary medication use at 18–22 months increased with increasing severity of BPD (Ehrenkranz, 2005). During the second and third year of life, re-hospitalization rates decline, although BPD survivors may remain at increased risk for respiratory related hospitalizations well into adulthood (Greenough, 2002; Greenough, 2006; Walter, 2009).

Respiratory Symptoms: Persistent respiratory symptoms and lung function abnormalities are common in former preterm infants and are particularly prevalent in those

with BPD. In a cohort of 308 extremely preterm infants followed through 6 years of life, wheezing, coughing, and use of inhaled medications were significantly more common in those with than without BPD (Hennessy, 2008). At 11-year follow-up of infants from the same cohort, 28% with a history of BPD were diagnosed with asthma, 24% suffered exercise induced wheezing, and 22% experienced nocturnal cough (Fawke, 2010). Cough, wheeze, and dyspnea are also common in young adult survivors with BPD (Gough, 2012). In a survey of 690 former VLBW adults with BPD, female survivors reported higher rates of wheezing without a cold, asthma, and shortness of breath with exercise compared to preterm controls (Vrijlandt, 2005). These findings were not observed in males with BPD, which the authors hypothesize may reflect differences in chest growth during puberty (Vrijlandt, 2005).

Pulmonary Function: Although improvements in lung function during childhood are noted in some former preterm infants with BPD, several longitudinal studies following survivors though adolescence and into adulthood demonstrate persistently reduced lung function (Blayney, 1991; Doyle, 2006; Filippone, 2009; Filbrun, 2011; Bolton, 2012; Hacking, 2012). Doyle et al. (2006) performed pulmonary function tests on 147 former VLBW infants who were born prior to the surfactant era at a mean age of 18.9 years. All tests reflecting airflow limitation were substantially diminished in those with a history BPD, even after adjustment for confounding variables. Lung function also declined in BPD survivors between the ages of 8 and 18 years (Doyle, 2006). A recent systematic review of adults born during the pre-surfactant era found higher rates of pulmonary function abnormalities and radiographic evidence of persistent structural changes in the lungs of those with a history of BPD (Gough, 2012).

Long-term respiratory morbidity is not limited to BPD survivors born prior to routine surfactant use. At 11 years of age, BPD survivors from the EPICure cohort, 89% of whom received surfactant, suffered significantly decreased lung function compared to extremely preterm and term controls without BPD (Fawke, 2010). Vollsætter et al. (2013) compared lung function at 18 years of age in two cohorts of ELBW infants, one born before and the other after availability of surfactant. Significant airway obstruction was found in preterm survivors from both cohorts with airflow limitations most pronounced in those with a history of BPD (Vollsæter, 2013).

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) frequently complicates the clinical course of infants with BPD (Berkelhamer, 2013). While the true incidence of PAH in infants with BPD is unknown, several small retrospective reports estimate rates at 25% to 37% (An, 2010; Slaughter, 2011; Kim, 2012; Check, 2013). PAH was diagnosed by echocardiogram in these studies, which may not be sufficiently reliable to detect PAH, particularly in infants and children with BPD (Mourani, 2008). Bhat et al. (2012) reported a single center prospective evaluation in which all ELBW infants underwent routine echocardiography at 4 weeks of age and again later if clinically indicated. Forty-five percent of infants who required supplemental oxygen at 36 weeks PMA were diagnosed with PAH. The incidence of PAH increased with increasing BPD severity. Only 2% of infants with mild BPD had evidence of

PAH compared to 36% with moderate and 50% with severe BPD (Bhat, 2012). In a series of 42 VLBW infants with BPD and PAH, mortality was 38% during a median follow-up period of 10.9 months and only 25% with severe PAH and BPD survived to 2–3 years of age (Khemani, 2007). Among all survivors with BPD and PAH, however, 89% demonstrated improvement in PAH during the follow-up period (Khemani, 2007).

Neurodevelopment

BPD significantly increases the risk of neurodevelopmental impairment (NDI) in preterm infants. BPD is associated with low mental and psychomotor developmental index scores on the Bayley Scales of Infant Development (BSID) II (Singer, 1997; Ehrenkranz, 2005; Wood, 2005), low composite language and cognitive scores on the BSID III (Natarajan, 2012), neurologic abnormalities (Hack, 2000), vision and hearing impairments (Ehrenkranz, 2005), and higher rates of cerebral palsy (Skidmore, 1990; Palta, 2000; Ehrenkranz, 2005; Natarajan, 2012). In a Swiss national cohort of ELBW infants, a history of BPD increased the risk-adjusted odds of death or severe NDI at 2 years of life nearly three-fold (OR 2.81; 95% CI 1.59–4.96) (Schlapbach, 2012). In the NICHD Neonatal Research Network, rates of NDI increased with increasing severity of BPD, from 28.1% in ELBW infants without BPD to 61.9% in infants with severe BPD (Ehrenkranz, 2005). All evaluated adverse neurodevelopmental outcomes including cerebral palsy, mental and psychomotor impairments, and vision and hearing deficits were higher in infants with BPD than those without (Ehrenkranz, 2005). In a secondary analysis of data from the TIPP trial, Schmidt et al. (2003) reported death or NDI at 18-month follow-up in 47% of ELBW infants on supplemental oxygen at 36 weeks PMA compared to 26% on room air (OR 2.5; 95% CI 1.9–3.4). When combined with two other adverse outcomes, BPD contributed additional risk for death or NDI. In infants with evidence of brain injury on cranial ultrasound or severe retinopathy of prematurity (ROP), rates of death or NDI impairment doubled in that same cohort. When all three complications were present, 88% of infants died or survived with NDI (Schmidt, 2003). Walsh et al. (2005) reported that protracted mechanical ventilation at 60, 90, and 120 days of life was associated with stepwise increases in both NDI and death in ELBW infants. Cognitive, motor, and behavioral deficits are also more common in school age children with a history of BPD compared to similar preterm controls (Vohr, 1991; Majnemer, 2000; Short, 2003).

SUMMARY

Since the first descriptions over 40 years ago, the epidemiology and pathophysiology of BPD has evolved. The “new” BPD primarily affects infants born less than 1500g and 32 weeks gestation. Although several individual risk factors have been identified, BPD likely results from a complex interaction between developmentally immature lungs and multiple perinatal and postnatal exposures. Trials of interventions intended to reduce individual exposures have often failed to decrease BPD rates, further suggesting a multifactorial etiology. Survivors with BPD are at risk for chronic sequelae, including high rates of re-hospitalization, prolonged deficits in pulmonary function, neurodevelopmental impairment, and post-neonatal mortality. Emerging evidence indicates that many of these sequelae persist well into adulthood even for infants who were born in the post-surfactant era.

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REFERENCES

ACOG Committee Opinion No. 475. 2011. Antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol 117:422–424. [PubMed: 21252775]

Akinola E, Rosenkrantz TS, Pappagallo M, Mckay K, Hussain N. 2004. Gastroesophageal reflux in infants < 32 weeks gestational age at birth: lack of relationship to chronic lung disease. Am J Perinatol 21:57–62. [PubMed: 15017467]

Ambalavanan N, Van Meurs KP, Perritt R, Carlo WA, Ehrenkranz RA, Stevenson DK, Lemons JA, Poole WK, Higgins RD. 2008. Predictors of death or bronchopulmonary dysplasia in preterm infants with respiratory failure. J Perinatol 28:420–426. [PubMed: 18337740]

An HS, Bae EJ, Kim GB, Kwon BS, Beak JS, Kim EK, Kim HS, Choi JH, Noh C, Yun YS. 2010. Pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. Korean Circ J 40:131–136. [PubMed: 20339498]

Andrews WW, Goldenberg RL, Faye-Petersen O, Cliver S, Goepfert AR, Hauth JC. 2006. The Alabama Preterm Birth study: polymorphonuclear and mononuclear cell placental infiltrations, other markers of inflammation, and outcomes in 23- to 32-week preterm newborn infants. Am J Obstet Gynecol 195:803–808. [PubMed: 16949415]

Antonucci R, Contu P, Porcella A, Atzeni C, Chiappe S. 2004. Intrauterine smoke exposure: a new risk factor for bronchopulmonary dysplasia? J Perinat Med 32:272–277. [PubMed: 15188804]

Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. 2003. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 349:959–967. [PubMed: 12954744]

Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB, Epstein MF, Fitzhardinge PM, Hansen CB, Hansen TN. 1987. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 79:26–30. [PubMed: 3797169]

Bancalari E, Claure N, Sosenko IRS. 2003. Bronchopulmonary dysplasia: changes in pathogenesis, epidemiology and definition. Semin Neonatol 8:63–71. [PubMed: 12667831]

Bauer ML, Lyrene RK. 1999. Chronic aspiration in children: evaluation of the lipid-laden macrophage index. Pediatr Pulmonol 28:94–100. [PubMed: 10423308]

Benitz WE. 2010. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol 30:241–252. [PubMed: 20182439]

Benitz WE. 2012. Patent ductus arteriosus: to treat or not to treat? Arch Dis Child Fetal Neonatal Ed 97:F80–82. [PubMed: 22174019]

Berkelhamer SK, Mestan KK, Steinhorn RH. 2013. Pulmonary hypertension in bronchopulmonary dysplasia. Semin Perinatol 37:124–131. [PubMed: 23582967]

Bhat R, Salas AA, Foster C, Carlo WA, Ambalavanan N. 2012. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. Pediatrics 129:e682–689. [PubMed: 22311993]

Bjorklund LJ, Ingimarsson J, Curstedt T. 1997. Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lungs. Pediatr Res 42:348–355. [PubMed: 9284276]

Blayney M, Kerem E, Whyte H, O'Brodovich H. 1991. Bronchopulmonary dysplasia: improvement in lung function between 7 and 10 years of age. J Pediatr 118:201–206. [PubMed: 1993945]

Bolton CE, Stocks J, Hennessy E, Cockcroft JR, Fawke J, Lum S, McEniery CM, Wilkinson IB, Marlow N. 2012. The EPICure Study: Association between hemodynamics and lung function at 11 years after extremely preterm birth. J Pediatr 161:595–601. [PubMed: 22575246]

Bonikos DS, Benson KG, Northway WHJ. 1976. Oxygen toxicity in the newborn. The effect of chronic continuous 100 percent oxygen exposure on the lung of newborn mice. Am J Pathol 85:623–650. [PubMed: 998734]

Bose CL, Dammann CEL, Laughon MM. 2008. Bronchopulmonary dysplasia and inflammatory biomarkers in the premature neonate. Arch Dis Child Fetal Neonatal Ed 93:F455–461. [PubMed: 18676410]

Bose C, Van Marter LJ, Laughon M, O'Shea TM, Allred EN, Karna P, Ehrenkranz RA, Boggess K, Leviton A. 2009. Fetal growth restriction and chronic lung disease among infants born before the 28th week of gestation. Pediatrics 124:e450–458. [PubMed: 19706590]

Botet F, Figueras-Aloy J, Miracle-Echegoyen X, lez JMRg-M, Salvia-Roiges MD, Carbonell-Estrany X. 2012. Trends in survival among extremely-low-birth-weight infants (less than 1000g) without significant bronchopulmonary dysplasia. BMC Pediatrics 12:63–70. [PubMed: 22682000]

Bott L, Béghin L, Devos P, Pierrat V, Matran R, Gottrand F. 2006. Nutritional status at 2 years in former infants with bronchopulmonary dysplasia influences nutrition and pulmonary outcomes during childhood. Pediatr Res 60:340–344. [PubMed: 16857773]

Carlo WA, McDonald SA, Fanaroff AA, Vohr BR, Stoll BJ, Ehrenkranz RA, Andrews WW, Wallace D, Das A, Bell EF, Walsh MC, Laptook AR, Shankaran S, Poindexter BB, Hale EC, Newman NS, Davis AS, Schibler K, Kennedy KA, Sánchez PJ, Van Meurs KP, Goldberg RN, Watterberg KL, Faix RG, Frantz ID, Higgins RD, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. 2011. Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. JAMA 306:2348–2358. [PubMed: 22147379]

Carraro S, Filippone M, Da Dalt L, Ferraro V, Maretti M, Bressan S, El Mazloum D, Baraldi E. 2013. Bronchopulmonary dysplasia: The earliest and perhaps the longest lasting obstructive lung disease in humans. Early Hum Dev 89:S3–5.

Cassady G, Crouse DT, Kirklin JW, Strange MJ, Joiner CH, Godoy G, Odrezin GT, Cutter GR, Kirklin JK, Pacifico AD. 1989. A randomized, controlled trial of very early prophylactic ligation of the ductus arteriosus in babies who weighed 1000 g or less at birth. N Engl J Med 320:1511–1516. [PubMed: 2498657]

Chan K, Ohlsson A, Synnes A, Lee DSC, Chien L-Y, Lee SK. 2001. Survival, morbidity, and resource use of infants of 25 weeks' gestational age or less. Am J Obstet Gynecol 185:220–226. [PubMed: 11483932]

Check J, Gotteiner N, Liu X, Su E, Porta N, Steinhorn R, Mestan KK. 2013. Fetal growth restriction and pulmonary hypertension in premature infants with bronchopulmonary dysplasia. J Perinatol 33:553–557. [PubMed: 23328924]

Choi CW, Kim BI, Kim E-K, Song ES, Lee J-J. 2012. Incidence of bronchopulmonary dysplasia in Korea. J Korean Med Sci 27:914. [PubMed: 22876059]

Chye JK, Gray PH. 1995. Rehospitalization and growth of infants with bronchopulmonary dysplasia: a matched control study. J Paediatr Child Health 31:105–111. [PubMed: 7794609]

Clyman R, Cassady G, Kirklin JK, Collins M, Philips JB. 2009. The role of patent ductus arteriosus ligation in bronchopulmonary dysplasia: reexamining a randomized controlled trial. J Pediatr 154:873–876. [PubMed: 19324366]

Cooke L, Steer P, Woodgate P. 2003. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev Issue 1. Art. No.:CD003745.

Cornell TT, Wynn J, Shanley TP, Wheeler DS, Wong HR. 2010. Mechanisms and regulation of the gene-expression response to sepsis. Pediatrics 125:1248–1258. [PubMed: 20478944]

Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. 2012. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ 345:e7976. [PubMed: 23212881]

Cotten MC, Oh W, McDonald S, Carlo W, Fanaroff AA, Duara S, Stoll B, Laptook A, Poole K, Wright LL, Goldberg RN. 2005. Prolonged hospital stay for extremely premature infants: risk factors, center differences, and the impact of mortality on selecting a best-performing center. J Perinatol 25:650–655. [PubMed: 16079906]

Cotton RB, Stahlman MT, Bender HW, Graham TP, Catterton WZ, Kovar I. 1978. Randomized trial of early closure of symptomatic patent ductus arteriosus in small preterm infants. J Pediatr 93:647–651. [PubMed: 702245]

Cristea AI, Carroll AE, Davis SD, Swigonski NL, Ackerman VL. 2013. Outcomes of children with severe bronchopulmonary dysplasia who were ventilator dependent at home. Pediatrics 132:e727–734. [PubMed: 23918888]

Darlow BA, Horwood LJ. 1992. Chronic lung disease in very low birth weight infants: a prospective population-based study. J Paediatr Child Health 28:301–305. [PubMed: 1497957]

Delacourt C, d'Ortho MP, Macquin-Mavier I, Pezet S, Housset B, Lafuma C, Harf A. 1996. Oxidant-antioxidant balance in alveolar macrophages from newborn rats. Eur Resp J 9:2517–2524.

Delaney-Black V, Lubchenco L, Butterfield L, Goldson E, Koops B, Lazotte D. 1989. Outcome of very-low-birth-weight infants: are populations of neonates inherently different after antenatal versus neonatal referral? Am J Obstet Gynecol 160:545–552. [PubMed: 2929672]

DeMauro SB, Roberts RS, Davis P, Alvaro R, Bairam A, Schmidt B, and Caffeine for Apnea of Prematurity Trial Investigators. 2011. Impact of delivery room resuscitation on outcomes up to 18 months in very low birth weight infants. J Pediatr 159:546–550. [PubMed: 21592510]

Doyle LW, Faber B, Callanan C, Freezer N, Ford GW, Davis NM. 2006. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. Pediatrics 118:108–113. [PubMed: 16818555]

Dreyfuss D, Saumon G. 1998. Ventilator-induced lung injury: lessons from experimental studies.. Am J Respir Crit Care Med 157:294–323. [PubMed: 9445314]

Drysdale SB, Wilson T, Alcazar M, Broughton S, Zuckerman M, Smith M, Rafferty GF, Johnston SL, Greenough A. 2011. Lung function prior to viral lower respiratory tract infections in prematurely born infants. Thorax 66:468–473. [PubMed: 21447496]

Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, Howard D, Ferrelli K, O'Conor J, Soll RF, and for the Vermont Oxford Network DRM Study Group. 2011. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics 128:e1069–1076. [PubMed: 22025591]

Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, Wrage LA, Poole K. 2005. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics 116:1353–1360. [PubMed: 16322158]

Ellsbury DL, Acarregui MJ, McGuinness GA, Klein JM. 2002. Variability in the use of supplemental oxygen for bronchopulmonary dysplasia. J Pediatr 140:247–249. [PubMed: 11865280]

Fanaroff A, Stoll B, Wright L, Carlo W, Ehrenkranz R, Stark A, Bauer C, Donovan E, Korones S, Laptook A. 2007. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol 196:147.e141–147. [PubMed: 17306659]

Farhath S, He Z, Nakhla T, Saslow J, Soundar S, Camacho J, Stahl G, Shaffer S, Mehta DI, Aghai ZH. 2008. Pepsin, a marker of gastric contents, is increased in tracheal aspirates from preterm infants who develop bronchopulmonary dysplasia. Pediatrics 121:e253–259. [PubMed: 18245400]

Fawke J, Lum S, Kirkby J, Hennessy E, Marlow N, Rowell V, Thomas S, Stocks J. 2010. Lung function and respiratory symptoms at 11 years in children born extremely preterm. Am J Resp Crit Care Med 182:237–245. [PubMed: 20378729]

Filbrun AG, Popova AP, Linn MJ, McIntosh NA, Hershenson MB. 2011. Longitudinal measures of lung function in infants with bronchopulmonary dysplasia. Pediatr Pulmonol 46:369–375. [PubMed: 21438170]

Filippone M, Bonetto G, Cherubin E, Carraro S, Baraldi E. 2009. Childhood course of lung function in survivors of bronchopulmonary dysplasia. JAMA 302:1418–1420. [PubMed: 19809022]

Finer N, Carlo W, Walsh M, Rich W, Gantz M, Laptook A, Faix R, Das A, Poole W, Donovan E, Newman N, Ambalavanan N, Frantz I, Buchter S, Sánchez P. 2010. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 362:1970–1979. [PubMed: 20472939]

Fowlie PW, Davis PG, McGuire W. 2010. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev Issue 7. Art. No.:CD000174.

Fuloria M, Hiatt D, Dillard RG, O'Shea TM. 2000. Gastroesophageal reflux in very low birth weight infants: association with chronic lung disease and outcomes through 1 year of age. J Perinatol 20:235–239. [PubMed: 10879336]

Goldenberg RL, Andrews WW, Goepfert AR, Faye-Petersen O, Cliver SP, Carlo WA, Hauth JC. 2008. The Alabama preterm birth study: umbilical cord blood Ureaplasma urealyticum and Mycoplasma hominis cultures in very preterm newborn infants. Am J Obstet Gynecol 198:43.e41–43. [PubMed: 18166302]

Gough A, Spence D, Linden M, Halliday HL, McGarvey LPA. 2012. General and respiratory health outcomes in adult survivors of bronchopulmonary dysplasia. Chest 141:1554–1567. [PubMed: 22116801]

Greenough A, Cox S, Alexander J, Lenney W, Turnbull F, Burgess S, Chetcuti PA, Shaw NJ, Woods A, Boorman J, Coles S, Turner J. 2001. Health care utilisation of infants with chronic lung disease, related to hospitalisation for RSV infection. Arch Dis Child 85:463–468. [PubMed: 11719328]

Greenough A, Alexander J, Burgess S, Chetcuti PAJ, Cox S, Lenney W, Turnbull F, Shaw NJ, Woods A, Boorman J, Coles S, Turner J. 2002. Home oxygen status and rehospitalisation and primary care requirements of infants with chronic lung disease. Arch Dis Child 86:40–43. [PubMed: 11806882]

Greenough A, Alexander J, Burgess S, Bytham J, Chetcuti P, Hagan J, Lenney W, Melville S. 2006. Preschool healthcare utilisation related to home oxygen status. Arch Dis Child Fetal Neonatal Ed 91:F337–341. [PubMed: 16705008]

Hack M, Wilson-Costello D, Friedman H, Taylor GH, Schluchter M, Fanaroff AA. 2000. Neurodevelopment and predictors of outcomes of children with birth weights of less than 1000 g: 1992–1995. Arch Pediatr Adolesc Med 154:725–731. [PubMed: 10891026]

Hacking DF, Gibson A-M, Robertson C, Doyle LW, (VICS) ftVICSG. 2012. Respiratory function at age 8–9 after extremely low birthweight or preterm birth in Victoria in 1997. Pediatr Pulmonol 48:449–455. [PubMed: 22826206]

Hakulinen A, Heinonen K, Jokela V, Kiekara O. 1988. Occurrence, predictive factors and associated morbidity of bronchopulmonary dysplasia in a preterm birth cohort. J Perinat Med 16:437–446. [PubMed: 3241290]

Halliday HL, Ehrenkranz RA, Doyle LW. 2003a. Early postnatal (< 96 hours) corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database Syst Rev Issue 1. Art. No.: CD001146.

Halliday HL, Ehrenkranz RA, Doyle LW. 2003b. Moderately early (7–14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database Syst Rev Issue 1. Art. No.:CD001144

Halliday HL, Ehrenkranz RA, Doyle LW. 2003c. Delayed (> 3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants. Cochrane Database Syst Rev Issue 1. Art. No.: CD001145.

Halliday H, Ehrenkranz R, Doyle L. 2010. Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database Syst Rev Issue 1. Art. No.: CD001146.

Hartling L, Liang Y, Lacaze-Masmonteil T. 2011. Chorioamnionitis as a risk factor for bronchopulmonary dysplasia: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 97:F8–17. [PubMed: 21697236]

Hennessy EM, Bracewell MA, Wood N, Wolke D, Costeloe K, Gibson A, Marlow N, for the EPICure Study Group. 2008. Respiratory health in pre-school and school age children following extremely preterm birth. Arch Dis Child 93:1037–1043. [PubMed: 18562451]

Hohlagschwandtner M, Husslein P, Klebermass K, Weninger M, Nardi A, Langer M. 2001. Perinatal mortality and morbidity. Comparison between maternal transport, neonatal transport and inpatient antenatal treatment. Arch Gynecol Obstet 265:113–118. [PubMed: 11561737]

Horbar JD, Carpenter JH, Badger GJ, Kenny MJ, Soll RF, Morrow KA, Buzas JS. 2012. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. Pediatrics 129:1019–1026. [PubMed: 22614775]

Hughes CA, A OGL, Shyr Y, Schork MA, Bozynski ME, McCormick MC. 1999. Cognitive performance at school age of very low birth weight infants with bronchopulmonary dysplasia. J Dev Behav Pediatr 20:1–8. [PubMed: 10071939]

Hussain AN, Siddiqui NHStocker JT. 1998. Pathology of arrested acinar development in postsurfactant bronchopulmonary dysplasia. Hum Pathol 29:710–717. [PubMed: 9670828]

Isayama T, Lee SK, Mori R, Kusuda S, Fujimura M, Ye XY, Shah PS, and the Canadian Neonatal Network and the Neonatal Research Network of Japan. 2012. Comparison of mortality and morbidity of very low birth weight infants between Canada and Japan. Pediatrics 130:e957–965. [PubMed: 22966031]

Jadcherla SR, Peng J, Chan CY, Moore R, Wei L, Fernandez S, Di Lorenzo C. 2011. Significance of gastroesophageal fefluxate in relation to physical, chemical, and spatiotemporal characteristics in symptomatic intensive care unit neonates. Pediatr Res 70:192–198. [PubMed: 21730816]

Jobe AJ. 1999. The New BPD: an arrest of lung development. Pediatr Res 46:641–643. [PubMed: 10590017]

Jobe AH, Bancalari E. 2001. Bronchopulmonary dysplasia. Am J Resp Crit Care Med 163:1723–1729. [PubMed: 11401896]

Jobe AH. 2012. Effects of chorioamnionitis on the fetal lung. Clin Perinatol 39:441–457. [PubMed: 22954262]

Kao LC, Durand DJ, McCrea RC, Birch M, Powers RJ, Nickerson BG. 1994. Randomized trial of long-term diuretic therapy for infants with oxygen-dependent bronchopulmonary dysplasia. J Pediatr 124:772–781. [PubMed: 8176568]

Kapadia VS, Chalak LF, Sparks JE, Allen JR, Savani RC, Wyckoff MH. 2013. Resuscitation of preterm neonates with limited versus high oxygen strategy. Pediatrics 132:e1488–1496. [PubMed: 24218465]

Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, Hazinski MF, Halamek LP, Kumar P, Little G, McGowan JE, Nightengale B, Ramirez MM, Ringer S, Simon WM, Weiner GM, Wyckoff M, Zaichkin J. 2010. Neonatal resuscitation: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatrics 126:e1400–1413 [PubMed: 20956432]

Khemani E, McElhinney DB, Rhein L, Andrade O, Lacro RV, Thomas KC, Mullen MP. 2007. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics 120:1260–1269. [PubMed: 18055675]

Kim D-H, Kim H-S, Choi CW, Kim E-K, Kim BI, Choi J-H. 2012. Risk factors for pulmonary artery hypertension in preterm infants with moderate or severe bronchopulmonary dysplasia. Neonatology 101:40–46. [PubMed: 21791938]

Klinger G, Levy I, Sirota L, Boyko V, Lerner-Geva L, Reichman B, and in collaboration with the Israel Neonatal Network. 2010. Outcome of early-onset sepsis in a national cohort of very low birth weight infants. Pediatrics 125:e736–740. [PubMed: 20231184]

Klinger G, Sokolover N, Boyko V, Sirota L, Lerner-Geva L, Reichman B, in collaboration with the Israel Neonatal Network. 2013. Perinatal risk factors for bronchopulmonary dysplasia in a national cohort of very-low-birthweight infants. Am J Obstet Gynecol 208:115.e111–115. [PubMed: 23178245]

Korhonen P Hyodynmaa E, Lenko H-L, Tammela O. 2004. Growth and adrenal androgen status at 7 years in very low birth weight survivors with and without bronchopulmonary dysplasia. Arch Dis Child 89:320–324. [PubMed: 15033838]

Kraybill EN, Runyan DK, Bose CL. 1989. Risk factors for chronic lung disease in infants with birth weights of 751 to 1000 grams. J Pediatr 115:115–120. [PubMed: 2500509]

Lahra MM, Beeby PJ, Jeffery HE. 2009. Intrauterine inflammation, neonatal sepsis, and chronic lung disease: a 13-year hospital cohort study. Pediatrics 123:1314–1319. [PubMed: 19403497]

Lasswell SM, Barfield WD, Rochat RW, Blackmon L. 2010. Perinatal regionalization for very low-birth-weight and very preterm infants. JAMA 304:992–1000. [PubMed: 20810377]

Laughon M, Allred EN, Bose C, O'Shea TM, Van Marter LJ, Ehrenkranz RA, Leviton A, for the ELGAN Study Investigators. 2009. Patterns of respiratory disease during the first 2 postnatal weeks in extremely premature infants. Pediatrics 123:1124–1131. [PubMed: 19336371]

Lavoie PM, Pham C, Jang KL. 2010. Genetics of bronchopulmonary dysplasia in the age of genomics. Curr Opin Pediatr 22(2):479–485.

Lee S, Ye X, Singhal N, De La Rue S, Lodha A, Shah P, for the Canadian Neonatal Network. 2013. Higher altitude and risk of bronchopulmonary ysplasia among preterm infants. Am J Perinatol 30:601–606. [PubMed: 23147080]

Lopez-Alonso M, Moya MJ, Cabo JA, Ribas J, del Carmen Macias M, Silny J, Sifrim D. 2006. Twenty-four-hour esophageal impedance-pH monitoring in healthy preterm neonates: rate and characteristics of acid, weakly acidic, and weakly alkaline gastroesophageal reflux. Pediatrics 118:e299–308. [PubMed: 16831894]

Lorch SA, Baiocchi M, Ahlberg CE, Small DS. 2012. The differential impact of delivery hospital on the outcomes of premature infants. Pediatrics 130:270–278. [PubMed: 22778301]

Majnemer A, Riley P, Shevell M, Birnbaum R, Greenstone H, Coates AL. 2000. Severe bronchopulmonary dysplasia increases risk for later neurological and motor sequelae in preterm survivors. Dev Med Child Neurol 42:53–60. [PubMed: 10665976]

Malviya MN, Ohlsson A, Shah SS. 2013. Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev Art. Issue 3. No.:CD003951.

Marshall DD, Kotelchuck M, Young TE, Bose CL, Kruyer L, O'Shea TM, and the North Carolina Neonatologists Association. 1999. Risk factors for chronic lung disease in the surfactant era: A North Carolina population-based Study of very low birth weight Infants. Pediatrics 104:1345–1350. [PubMed: 10585987]

Martin JA, Hamilton BE, Ventura SJ, Osterman MJK, Mathews TJ. 2013. Births: final data for 2011. Natl Vital Stat Rep 62:1–69.

Mokres LM, Parai K, Hilgenforff A. 2010. Prolonged mechanical ventilation with air induces apoptosis and causes failure of alveolar septation and angiogenesis in lungs of newborn mice. Am J Physiol 298:L23–35.

Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet J-M, Carlin JB. 2008. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 358:700–708. [PubMed: 18272893]

Mourani PM, Sontag MK, Younoszai A, Ivy DD, Abman SH. 2008. Clinical utility of echocardiography for the diagnosis and management of pulmonary vascular disease in young children with chronic lung disease. Pediatrics 121:317–325. [PubMed: 18245423]

Natarajan G, Pappas A, Shankaran S, Kendrick DE, Das A, Higgins RD, Laptook AR, Bell EF, Stoll BJ, Newman N, Hale EC, Bara R, Walsh MC. 2012. Outcomes of extremely low birth weight infants with bronchopulmonary dysplasia: impact of the physiologic definition. Early Hum Dev 88:509–515. [PubMed: 22236557]

Natarajan G, Johnson Y, Brozanski B, Farrow K, Zaniletti I, Padula M, Asselin J, Durand D, Short B, Pallotto E, Dykes F, Reber K, Evans J, Murthy K, and for the Children's Hospital Neonatal Consortium Executive Board and Study Group. 2013. Postnatal weight gain in preterm infants with severe bronchopulmonary dysplasia. Am J Perinatol. [Epub ahead of print].

Nickerson BG, Taussig LM. 1980. Family history of asthma in infants with bronchopulmonary dysplasia. Pediatrics 65:1140–1144. [PubMed: 7375238]

Northway W, Rosan R, Porter D. 1967. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med 276:357–368. [PubMed: 5334613]

Oh W, Poindexter BB, Perritt R, Lemons JA, Bauer CR, Ehrenkranz RA, Stoll BJ, Poole K, Wright LL. 2005. Association between fluid intake and weight loss during the first ten days of life and risk of bronchopulmonary dysplasia in extremely low birth weight infants. J Pediatr 147:786–790. [PubMed: 16356432]

Ohlsson A, Walia R, Shah SS. 2013. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev Issue 4. Art. No.CD003481.

Onland W, Offringa M, van Kaam A. 2012. Late (≥ 7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Issue 4. Rev Art. No.:CD002311.

Palmer KG, Kronsberg SS, Barton BA, Hobbs CA, Hall RW, Anand KJS. 2004. Effect of inborn versus outborn delivery on clinical outcomes in ventilated preterm neonates: secondary results from the NEOPAIN trial. J Perinatol 25:270–275.

Palta M, Gabbert D, Weinstein MR, Peters ME. 1991. Multivariate assessment of traditional risk factors for chronic lung disease in very low birth weight neonates. The Newborn Lung Project. J Pediatr 119:285–292. [PubMed: 1861218]

Palta M, Sadek-Badawi M, Evans M, Weinstein MR, McGuiness G, Peters ME, for the Newborn Lung Project. 2000. Functional assessment of a multicenter very low-birth-weight cohort at age 5 years. Arch Pediatr Adolesc Med 154:23–30. [PubMed: 10632246]

Parker RA, Lindstrom DP, Cotton RB. 1992. Improved survival accounts for most, but not all, of the increase in bronchopulmonary dysplasia. Pediatrics 90:663–668. [PubMed: 1408535]

Payne NR, LaCorte M, Karna P, Chen S, Finkelstein M, Goldsmith JP, Carpenter JH, on behalf of the Breathsavers Group. 2006a. Reduction of bronchopulmonary dysplasia after participation in the breathsavers group of the Vermont Oxford Network neonatal intensive care quality improvement collaborative. Pediatrics 118:S73–S77. [PubMed: 17079626]

Payne NR, LaCorte M, Sun S, Karna P, Lewis-Hunstiger M, Goldsmith JP, on behalf of the Breathsaver Group. 2006b. Evaluation and development of potentially better practices to reduce bronchopulmonary dysplasia in very low birth weight infants. Pediatrics 118:S65–S72. [PubMed: 17079625]

Phibbs CS, Baker LC, Caughey AB, Danielsen B, Schmitt SK, Phibbs RH. 2007. Level and volume of neonatal intensive care and mortality in very-low-birth-weight infants. N Engl J Med 356:2165–2175. [PubMed: 17522400]

Rabi Y, Singhal N, Nettel-Aguirre A. 2011. Room-air versus oxygen administration for resuscitation of preterm infants: the ROAR study. Pediatrics 128:e374–381. [PubMed: 21746729]

Redline RW, Faye-Petersen O, Heller D, Qureshi F, Savell V, Vogler C. 2003. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 6:435–448. [PubMed: 14708737]

Report of Workshop on Bronchopulmonary Dysplasia; 1979. NIH Publication No. 80–1660 Wasthington, DC: National Institutes of Health.

Roberts D, Dalziel S. 2006. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Issue 3. Rev Art. No.:CD004454.

Rojas MA, Gonzalez A, Bancalari E, Claure N, Poole C, Silva-Neto G. 1995. Changing trends in the epidemiology and pathogenesis of neonatal chronic lung disease. J Pediatr 126:605–610. [PubMed: 7699543]

Rojas MX, Rojas MA, Lozano JM, Rondón MA, Charry LP. 2012. Regional variation on rates of bronchopulmonary dysplasia and associated risk factors. ISRN Pediatr 2012:1–9.

Salvatore S, Hauser B, Vandenplas Y. 2007. The natural course of gastro-oesophageal reflux. Acta Paediatrica 93:1063–1069.

Sandri F, Plavka R, Ancora G, Simeoni U, Stranak Z, Martinelli S, Mosca F, Nona J, Thomson M, Verder H, Fabbri L, Halliday H, for the CURPAP Study Group. 2010. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Pediatrics 125:e1402–1409. [PubMed: 20439601]

Saugstad OD. 1998. Chronic lung disease: the role of oxidative stress. Biol Neonate 74:21–28. [PubMed: 9730588]

Schlapbach LJ, Adams M, Proietti E, Aebischer M, Grunt S, Borradori-Tolsa C, Bickle-Graz M, Bucher HU, Latal B, Natalucci G. 2012. Outcome at two years of age in a Swiss national cohort of extremely preterm infants born between 2000 and 2008. BMC Pediatr12:198–210. [PubMed: 23272671]

Schlapbach LJ, Aebischer M, Adams M, Natalucci G, Bonhoeffer J, Latzin P, Nelle M, Bucher HU, Latal B, and the Swiss Neonatal Network and Follow-Up Group. 2011. Impact of sepsis on neurodevelopmental outcome in a Swiss national cohort of extremely premature infants. Pediatrics 128:e348–357. [PubMed: 21768312]

Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, Solimano A, Vincer M, Wright LL, for the Trial of Indomethacin Prophylaxis in Preterms Investigators. 2001. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 344:1966–1972. [PubMed: 11430325]

Schmidt B, Asztalos EV, Roberts RS, Robertson CMT, Sauve RS, Whitfield MF. 2003. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months. JAMA 289:1124–1129. [PubMed: 12622582]

Schmidt B, Roberts RS, Fanaroff A, Davis P, Kirpalani HM, Nwaesei C, Vincer M. 2006. Indomethacin prophylaxis, patent ductus arteriosus, and the risk of bronchopulmonary dysplasia: Further analyses from the Trial of Indomethacin Prophylaxis in Preterms (TIPP). J Pediatr 148:730–734. [PubMed: 16769377]

Schmidt B, Whyte RK, Asztalos EV, Moddemann D, Poets C, Rabi Y, Solimano A, Roberts RS, for the Canadian Oxygen Trial (COT) Group. 2013. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants a randomized clinical trial. JAMA 309:2111–2120. [PubMed: 23644995]

Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. 2013. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ 347:f5980. [PubMed: 24136633]

Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. 1988. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 82:527–532. [PubMed: 3174313]

Shepard F, Gray J, Stahlman MT. 1964. Occurrence of pulmonary fibrosis in children who had idiopathic RDS. J Pediatr 65:1078.

Shlossman PA, Manley JS, Sciscione AC, Colmorgen GH. 1997. An analysis of neonatal morbidity and mortality in maternal (in utero) and neonatal transports at 24–34 weeks' gestation. Am J Perinatol 14:449–456. [PubMed: 9376004]

Short EJ, Klein NK, Lewis BA, Fulton S, Eisengart S, Kercsmar C, Baley J, Singer LT. 2003. Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. Pediatrics 112:e359–359. [PubMed: 14595077]

Singer L, Yamashita T, Lilien L, Collin M, Baley J. 1997. A longitudinal study of developmental outcome of infants with bronchopulmonary dysplasia and very low birth weight. Pediatrics 100:987–993. [PubMed: 9374570]

Skidmore MD, Rivers A, Hack M. 1990. Increased risk of cerebral palsy among very low-birthweight infants with chronic lung disease. Dev Med Child Neurol 32:325–332. [PubMed: 2332123]

Slaughter JL, Pakrashi T, Jones DE, South AP, Shah TA. 2011. Echocardiographic detection of pulmonary hypertension in extremely low birth weight infants with bronchopulmonary dysplasia requiring prolonged positive pressure ventilation. J Perinatol 31:635–640. [PubMed: 21311503]

Smith VC, Zupancic JAF, McCormick MC, Croen LA, Greene J, Escobar GJ, Richardson DK. 2004. Rehospitalization in the first year of life among infants with bronchopulmonary dysplasia. J Pediatr 144:799–803. [PubMed: 15192629]

Smith VC, Zupancic JAF, McCormick MC, Croen LA, Greene J, Escobar GJ, Richardson DK. 2005. Trends in severe bronchopulmonary dysplasia rates between 1994 and 2002. J Pediatr 146:469–473. [PubMed: 15812448]

Somaschini M, Castiglioni E, Volonteri C, Cursi M, Ferrari M, Carrera P. 2012. Genetic predisposing factors to bronchopulmonary dysplasia: preliminary data from a multicentre study. J Matern Fetal Neonatal Med 25:119–122. [PubMed: 22348528]

Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Schibler K, Carlo WA, Kennedy KA, Poindexter BB, Finer NN, Ehrenkranz RA, Duara S, Sanchez PJ, O'Shea TM, Goldberg RN, Van Meurs KP, Faix RG, Phelps DL, Frantz ID, Watterberg KL, Saha S, Das A, Higgins RD, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. 2010. Neonatal outcomes of extremely preterm infants from the NICHD neonatal research network. Pediatrics 126:443–456. [PubMed: 20732945]

Stroustrup A, Trasande L. 2010. Epidemiological characteristics and resource use in neonates with bronchopulmonary dysplasia: 1993–2006. Pediatrics 126:291–297. [PubMed: 20643728]

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. 2010. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med 362:1959–1969. [PubMed: 20472937]

te Pas AB, Walther FJ. 2007. A randomized, controlled trial of delivery-room respiratory management in very preterm infants. Pediatrics 120:322–329. [PubMed: 17671058]

The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups. 2013. Oxygen Saturation and Outcomes in Preterm Infants. N Engl J Med 368:2094–2104. [PubMed: 23642047]

Trzaski J, Hagadorn J, Hussain N, Schwenn J, Wittenzellner C. 2011. Predictors of successful discontinuation of supplemental oxygen in very low-birth-weight infants with bronchopulmonary dysplasia approaching neonatal intensive care unit discharge. Am J Perinatol 29:79–86. [PubMed: 22131045]

Tyson JE, Wright LL, Oh W, Kennedy KA, Mele L, Ehrenkranz RA, Stoll BJ, Lemons JA, Stevenson DK, Bauer CR. 1999. Vitamin A supplementation for extremely-low-birth-weight infants. N Engl J Med 340:1962–1968. [PubMed: 10379020]

Van Marter LJ, Leviton A, Allred EN, Pagano M, Kuban KC. 1990. Hydration during the first days of life and the risk of bronchopulmonary dysplasia in low birth weight infants. J Pediatr 116:942–949. [PubMed: 2189976]

Van Marter LJ, Allred EN, Pagano M, Sanocka U, Parad R, Moore M, Susser M, Paneth N, Leviton A, 2000. Do Clinical Markers of Barotrauma and Oxygen Toxicity Explain Interhospital Variation in Rates of Chronic Lung Disease? Pediatrics 105:1194–1201 [PubMed: 10835057]

Van Marter LJ, Allred EN, Leviton A, Pagano M, Parad R, Moore M, Th TNCf. 2001. Antenatal glucocorticoid treatment does not reduce chronic lung disease among surviving preterm infants. J Pediatr 138:198–204. [PubMed: 11233077]

Van Marter LJ, Dammann O, Allred EN, Leviton A, Pagano M, Moore M, Martin C. 2002. Chorioamnionitis, mechanical ventilation, and postnatal sepsis as modulators of chronic lung disease in preterm infants. J Pediatr 140:171–176. [PubMed: 11865267]

Vento M, Moro M, Escrig R, Arruza L, Villar G, Izquierdo I, Roberts LJ, Arduini A, Escobar JJ, Sastre J, Asensi MA. 2009. Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. Pediatrics 124:e439–449. [PubMed: 19661049]

Vermont Oxford Network. 2012. VON days pulse oximetry audit summary. http://www.vtoxford.org/quality/vondays/PO/POResultsSummary.pdf. Accessed 2013 Dec. 17.

Vohr B, Garcia Coll C, Lobato D, Yunis KA, O'Dea C, Oh W. 1991. Neuro- developmental and medical status of low-birthweight survivors of bronchopulmonary dysplasia at 10 to 12 years of age. Dev Med Child Neurol 33:690–697. [PubMed: 1717327]

Vollsæter M, Roksund OD, Eide GE, Markestad T, Halvorsen T. 2013. Lung function after preterm birth: development from mid-childhood to adulthood. Thorax 68:767–776. [PubMed: 23749815]

Vrijlandt EJ, Gerritsen J, Boezen HM, Duiverman EJ. 2005. Gender differences in respiratory symptoms in 19-year-old adults born preterm. Respir Res 6:117. [PubMed: 16223446]

Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaroff A. 2003. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. J Perinatol 23:451–456. [PubMed: 13679930]

Walsh MC, Yao Q, Gettner P, Hale E, Collins M, Hensman A, Everette R. 2004. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics 114:1305–1311. [PubMed: 15520112]

Walsh MC, Morris BH, Wrage LA, Vohr BR, Poole WK, Tyson JE, Wright LL, Ehrenkranz RA, Stoll BJ, Fanaroff AA. 2005. Extremely Low Birthweight Neonates with Protracted Ventilation: Mortality and 18-Month Neurodevelopmental Outcomes. J Pediatr 146:798–804. [PubMed: 15973322]

Walsh M, Laptook A, Kazzi SN, Engle WA, Yao Q, Rasmussen M, Buchter S, Heldt G, Rhine W, Higgins R, Poole K, for the National Institute of Child Health and Human Development Neonatal Research Network. 2007. A cluster-randomized trial of benchmarking and multimodal quality improvement to improve rates of survival free of bronchopulmonary dysplasia for infants with birth weights of less than 1250 grams. Pediatrics 119:876–890. [PubMed: 17473087]

Walter EC, Ehlenbach WJ, Hotchkin DL, Chien JW, Koepsell TD. 2009. Low birth weight and respiratory disease in adulthood. Am J Resp Crit Care Med 180:176–180. [PubMed: 19372251]

Warner B, Musial MJ, Chenier T, Donovan E. 2004. The effect of birth hospital type on the outcome of very low birth weight infants. Pediatrics 113:35–41. [PubMed: 14702444]

Werthammer J, Brown ER, Neff RK, Taeusch HW Jr. Sudden infant death syndrome in infants with bronchopulmonary dysplasia. Pediatrics 69:301–304. [PubMed: 7199705]

Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR, for the Epicure Study Group. 2005. The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. Arch Dis Child Fetal Neonatal Ed 90:F134–140. [PubMed: 15724037]

Wynn J, Cornell TT, Wong HR, Shanley TP, Wheeler DS. 2010. The host response to sepsis and developmental impact. Pediatrics 125:1031–1041. [PubMed: 20421258]

Zeitlin J, Draper ES, Kollee L, Milligan D, Boerch K, Agostino R, Gortner L, Van Reempts P, Chabernaud JL, Gadzinowski J, Breart G, Papiernik E, MOSIAC Research Group. 2008. Differences in rates and short-term outcome of live births before 32 weeks of gestation in Europe in 2003: results from the MOSAIC Cohort. Pediatrics 121:e936–944. [PubMed: 18378548]