Prevention of Bronchopulmonary Dysplasia: A Summary of Evidence-Based Strategies

Erik A. Jensen, MD, MSCE*

**Division of Neonatology and Department of Pediatrics; Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA*

Education Gap

To decrease rates of bronchopulmonary dysplasia among extremely preterm infants, clinicians must implement multiple evidence-based strategies that target disease prevention. Less invasive surfactant administration is an emerging therapy that may help prevent bronchopulmonary dysplasia.

Abstract

Bronchopulmonary dysplasia (BPD) is the most common chronic complication associated with extremely preterm birth. Although BPD is now an uncommon condition in infants born with birthweights higher than 1,500 g, among infants born at or near the current limits of viability, BPD rates have not improved over the past 2 to 3 decades and may be increasing. No single therapeutic intervention is effective at preventing BPD. As such, clinicians must use multiple evidence-based strategies to help reduce BPD rates. This review examines current evidence-based approaches to BPD prevention, primarily focusing on data obtained from randomized controlled trials.

Objectives After completing this article, readers should be able to:

1. Describe current evidence-based therapies shown in randomized controlled trials to reduce bronchopulmonary dysplasia risk among very preterm infants.
2. Become familiar with the data available on the safety and efficacy of corticosteroids for preventing bronchopulmonary dysplasia in extremely preterm infants and explain the current limitations in knowledge about the optimal timing, dosing regimen, and patient selection for treatment.

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ABBREVIATIONS

BPD	bronchopulmonary dysplasia
CI	confidence interval
CP	cerebral palsy
CPAP	continuous positive airway pressure
HFNC	high-flow nasal cannula
HFOV	high-frequency oscillatory ventilation
INSURE	intubation, surfactant administration during brief mechanical ventilation followed by extubation
LISA	less invasive surfactant administration
NEC	necrotizing enterocolitis
NIPPV	nasal intermittent positive pressure ventilation
OR	odds ratio
PDA	patent ductus arteriosus
RCT	randomized controlled trial
RDS	respiratory distress syndrome
RR	relative risk

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is one of the most common complications of preterm birth. It affects approximately half of all infants born with birthweights less than 1,000 g, is associated with increased risk for early childhood mortality, and predisposes survivors to chronic respiratory and cardiovascular impairments,

growth failure, and neurodevelopmental delay. (1)(2)(3)(4)(5)(6)(7) BPD was once a frequent problem among all preterm infants treated with prolonged invasive mechanical ventilation. With increased use of antenatal corticosteroids, surfactant therapy, and gentle ventilation strategies, BPD is now uncommon in preterm infants born with birthweights greater than 1,500 g. (8) However, most of the data available suggest that BPD rates have not improved in recent decades among extremely preterm infants and may be increasing. (7)(8)(9)(10) One hindrance to preventing BPD in this population is the lack of a safe and highly efficacious preventive therapy. As such, clinicians must use multiple evidence-based strategies to reduce BPD risk. This review discusses the evidence supporting currently available therapies for BPD prevention in very preterm infants, primarily focusing on data obtained from randomized controlled trials (RCTs).

RESPIRATORY SUPPORT STRATEGIES

Successful transition to postnatal breathing requires clearance of fetal lung fluid and lung aeration. The high chest wall compliance, weak respiratory muscles, incomplete surfactant production, and underexpression of transepithelial sodium channels in very preterm infants hinder this process. (11)(12)(13)(14) As a result, many very preterm infants require positive airway pressure and supplemental oxygen soon after birth to maintain physiologic stability. Invasive mechanical ventilation can be lifesaving in these instances, but it may also lead to lung injury. Animal data show a clear link between baro- and volutrauma induced by mechanical ventilation and pathologic changes in the lung that mimic BPD. (15)(16) Moreover, observational studies support an association between invasive mechanical ventilation and increased BPD risk. (17)(18) To help minimize lung injury and prevent BPD, investigators have explored several different noninvasive and "gentler" invasive ventilation strategies. Salient results from these efforts are described herein; data from RCTs showing benefit for BPD prevention are summarized in Fig 1.

Noninvasive Positive Airway Pressure

One strategy to prevent ventilator-induced lung injury is to avoid mechanical ventilation altogether. Three large RCTs compared early noninvasive continuous positive airway pressure (CPAP) with immediate intubation and surfactant administration. (19)(20)(21) Although design elements, including gestational ages of the enrolled infants and initial CPAP settings (ranging from 5–8 cm H_2O) varied among the studies, each demonstrated a nonsignificant reduction in the rate of death or BPD at 36 weeks' postmenstural age among the infants initially treated with CPAP. (19)(20)(21) Meta-analyses of the available trial data, some of which also

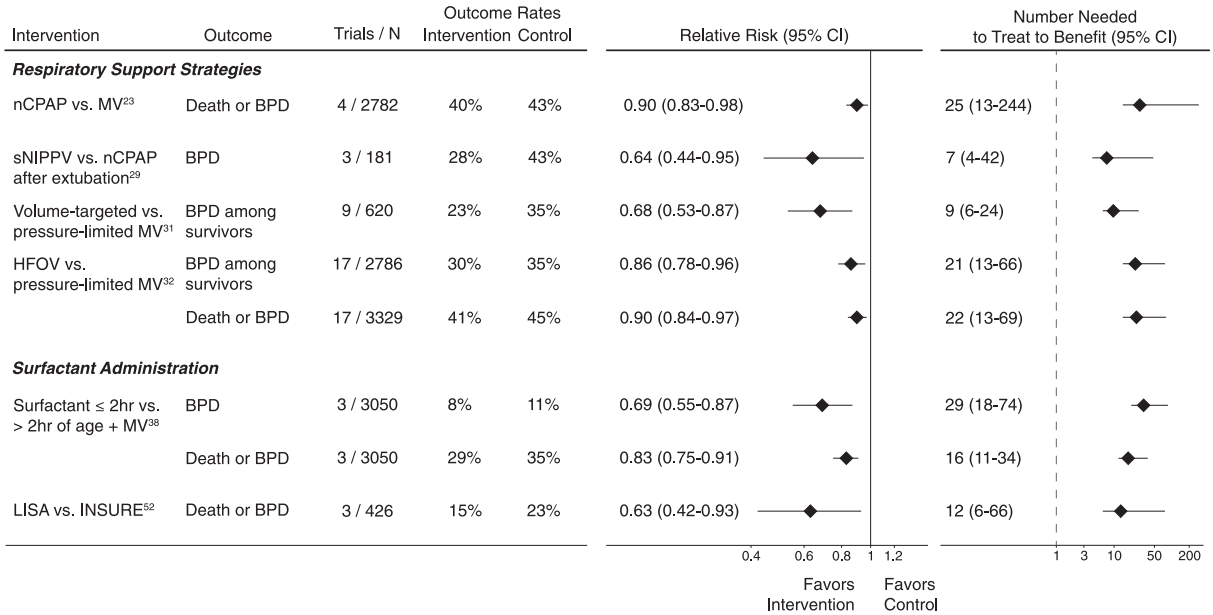

Figure 1. Summary of randomized, controlled trial data on the effects of various respiratory support strategies for preventing death and/or bronchopulmonary dysplasia. Study results are abstracted from the cited publication when available. If not provided in the article, relative risk and number needed to treat to benefit values (inverse of the risk difference) were calculated using original study data in RevMan version 5.3 (the Nordic Cochrane Centre, Copenhagen, Denmark). BPD=bronchopulmonary dysplasia; CI=confidence interval; HFOV=high-frequency oscillatory ventilation; INSURE=*in*tubation, *sur*factant administration during brief mechanical ventilation, followed by *ex*tubation; LISA=less invasive surfactant administration; MV=mechanical ventilation; N=total number of infants evaluated for the outcome; nCPAP=nasal continuous positive airway pressure; sNIPPV=synchronized nasal intermittent positive pressure ventilation.

included smaller RCTs, showed a small but statistically significant reduction in the risk for death or BPD with CPAP therapy (Fig 1). (22)(23)(24) Although one large trial reported higher rates of pneumothorax in CPAP-treated infants, (20) meta-analyses did not show an increased risk for pneumothorax or other adverse events with early CPAP. (22)(23)(24) As a result, the American Academy of Pediatrics Committee on Fetus and Newborn recommends early use of CPAP with subsequent selective surfactant administration in extremely preterm infants as an evidence-based strategy to reduce the risk for death or BPD. (25)

Heated and humidified high-flow nasal cannula (HFNC), typically administered with flow rates higher than 1 to 2 L/min, has gained popularity as an alternative to nasal CPAP. Potential advantages of HFNC include reduced nasal trauma, simpler device setup, and greater facilitation of oral feeding and skin-to-skin care. (26) However, recent trial data indicate that HFNC and nasal CPAP may not be equivalent therapies. Treatment failure is more common among very preterm infants who receive HFNC compared with nasal CPAP as a primary support modality. (26) HFNC may be an acceptable alternative to nasal CPAP for postextubation support among infants born at more than or equal to 28 weeks of gestation, but routine use in less mature infants is not recommended. (27)

Nasal intermittent positive pressure ventilation (NIPPV) augments nasal CPAP by providing brief periods of higher airway pressure, synchronized with an infant's breathing or delivered at set, asynchronous intervals. Use of NIPPV in preterm infants as an initial mode of respiratory support or after extubation from mechanical ventilation, when compared with CPAP, results in improved short-term respiratory outcomes without an increased risk of harm. (28)(29) Despite this benefit, meta-analyses do not show a reduction in BPD with NIPPV. (28)(29) Synchronized NIPPV, particularly when used after extubation, may reduce BPD risk (Fig 1), but further research into the usefulness of this specific form of noninvasive support is needed. (29)

Mode of Invasive Mechanical Ventilation

Not all very preterm infants safely transition to postnatal breathing with noninvasive respiratory support. Data from CPAP trials indicate that up to 65% of spontaneously breathing extremely preterm infants require intubation and mechanical ventilation despite early CPAP therapy. (23) In these instances, or when invasive respiratory support is required soon after birth, clinicians must select a mode of mechanical ventilation. Trauma to the developing lung from excessive volumetric stretch is one proposed contributor to the development of BPD. (30) Owing to rapid changes in lung compliance in the first days and weeks after birth, volume-targeted ventilation in very preterm infants may be optimal. A 2017 Cochrane review found moderate quality of evidence supporting the use of volume-targeted ventilation as opposed to pressure-limited ventilation as a means to reduce the composite outcome of death or BPD, length of mechanical ventilation, and rates of severe intraventricular hemorrhage (Fig 1). (31)

High-frequency oscillatory ventilation (HFOV) is an alternative ventilation strategy that may reduce lung injury. A 2015 Cochrane review evaluating HFOV as a primary mode of invasive respiratory support (ie, not as a rescue therapy after "failed" conventional mechanical ventilation) found a small reduction in the risk for death or BPD and BPD alone among infants treated with HFOV compared with pressure-limited conventional ventilation (Fig 1). (32) Pulmonary air leaks (pneumothorax or pulmonary interstitial emphysema) were more common in HFOV-treated infants. (32) Ultimately, the authors concluded that the "preference for a specific ventilation mode remains a matter of clinical judgment requiring a balance between a relatively small benefit and a possible short-term harm." (32)

SURFACTANT

Endotracheal Surfactant Administration Followed by Mechanical Ventilation

Endogenous pulmonary surfactant is a mixture of lipids and proteins that primarily act to reduce surface tension at the air/liquid interface within the alveoli and improve deflation stability of the lungs. (33) Deficiency of pulmonary surfactant in extremely preterm infants is a key component in the pathophysiology of neonatal respiratory distress syndrome (RDS). (34) Several older RCTs, conducted before the routine use of antenatal corticosteroid and early noninvasive CPAP, showed that administration of exogenous surfactant, compared with mechanical ventilation alone, reduced rates of death or supplemental oxygen use 28 days after delivery (the standard definition of BPD at that time). (35)(36)(37) As described herein, use of noninvasive respiratory support as a primary modality is the preferred approach for most very preterm infants. However, these older trial data support the use of exogenous surfactant in very preterm infants who require intubation and mechanical ventilation within the first 48 to 72 hours of age. In these instances, early treatment with surfactant may be optimal. Rescue surfactant administration to preterm infants receiving mechanical ventilation within the first 2 hours of age, compared with after the second hour of age, reduces the risk for BPD and the composite risk for death or BPD (Fig 1). (38)

There are several commercially available surfactant formulations available for use. The animal-derived preparations (modified or purified from bovine or porcine lungs) provide a small benefit for reductions in rates of mortality and death or BPD compared with first-generation protein free surfactants. (39) Meta-analysis of trials comparing modified bovine-derived surfactant to porcine-based surfactant suggested that bovine products may increase mortality and BPD risk. (40) However, subgroup analyses suggested that these differences were limited to trials using a higher initial dose of porcine-derived surfactant and may not be due to the animal source. (40) Lucinactant, a second-generation synthetic surfactant that contains a peptide analog of surfactant protein B, has similar efficacy as animal-derived products. (41)(42)

Surfactant Administration without Prolonged Mechanical Ventilation

To maximize the potential benefits of early surfactant administration without the harmful effects of prolonged invasive mechanical ventilation, investigators explored alternative means to dosing surfactant. Victorin et al introduced the technique of *in*tubation, *sur*factant administration during brief mechanical ventilation, followed by *e*xtubation (INSURE). (43) Although initial RCTs found that INSURE reduced supplemental oxygen use at 28 days of age, meta-analyses including more recent trials found that compared with CPAP, INSURE does not reduce the risk for death or BPD (relative risk [RR] 0.88, 95% confidence interval [CI] 0.76–1.02). (44)(45)

Several techniques have been developed for less invasive administration of surfactant to avoid standard endotracheal intubation. These include intratracheal instillation of surfactant with a thin catheter (eg, nasogastric tube), aerosolized surfactant, intrapartum pharyngeal instillation, and delivery via a laryngeal mask airway. (46) Of these strategies, surfactant instillation via a thin catheter, typically referred to as less invasive surfactant administration (LISA) or minimally invasive surfactant therapy, is the most studied. Four RCTs conducted in extremely preterm infants compared LISA with endotracheal tube administration of surfactant (3 versus INSURE, 1 versus continued mechanical ventilation after surfactant therapy), (47)(48)(49)(50) and 1 compared LISA with CPAP therapy alone. (51) A meta-analysis combining data from these RCTs showed that LISA versus control therapy reduced the risk for BPD among survivors (RR 0.70, 95% CI 0.50–0.97) and the composite of death or BPD (RR 0.74, 95% CI 0.58–0.94). (52) Compared with INSURE alone, LISA reduced the risk for death or BPD (Fig 1) but not BPD among survivors (RR 0.65, 95% CI 0.35–1.19). (52)

Isayama et al conducted a recent Bayesian network meta-analysis comparing 6 early respiratory strategies (mechanical ventilation, nasal CPAP, noninvasive positive pressure ventilation, INSURE, LISA, and nebulized surfactant administered via laryngeal mask airway). (53) This approach estimated the relative effects of each intervention, even if they were not compared in individual trials. The analysis showed that LISA was associated with the largest reduction in the risk for death or BPD (odds ratio [OR] 0.49, 95% CI 0.30–0.79). (53) However, the authors noted that the findings were limited by the overall low quality of evidence. (53) A large, ongoing trial evaluating LISA in extremely preterm infants will provide important data on this method of surfactant administration. (54)

PHARMACOLOGIC THERAPIES

Despite the strong physiologic and observational data implementing invasive mechanical ventilation in the development of BPD, the beneficial effects of the respiratory support strategies described herein are modest. Longitudinal data also suggest that increased use of noninvasive respiratory support over time has not been accompanied by substantial improvements in BPD rates or childhood lung function among surviving extremely preterm infants. (55) Owing to the limited benefit of gentle ventilation techniques, pharmacologic therapies are an essential component in ongoing efforts to reduce BPD rates. Drug therapies shown in RCTs to reduce BPD are summarized herein and in Fig 2.

Noncorticosteroid Agents

Azithromycin. Azithromycin is a macrolide antibiotic that exhibits both antimicrobial and anti-inflammatory properties. (56)(57) These dual qualities make it a potentially appealing mode of BPD prevention. In very preterm infants, infection with *Ureaplasma* is associated with the development of BPD. (58)(59) Moreover, lung and systemic inflammation contribute to BPD pathophysiology. (60)(61) Three small trials assessed the efficacy of azithromycin in preventing BPD. (62) A meta-analysis of these studies found a reduction in the risk for BPD and death or BPD alone among infants treated with azithromycin (Fig 2), regardless of known *Ureaplasma* colonization or infection. (62) However, none of the individual studies demonstrated benefit, and the quality of evidence was low. (62)(63) Finally, trials evaluating other macrolides have not shown benefit for preventing BPD. (64)(65) Larger trials are needed to establish safety and efficacy of prophylactic azithromycin before recommending this therapy. (63)

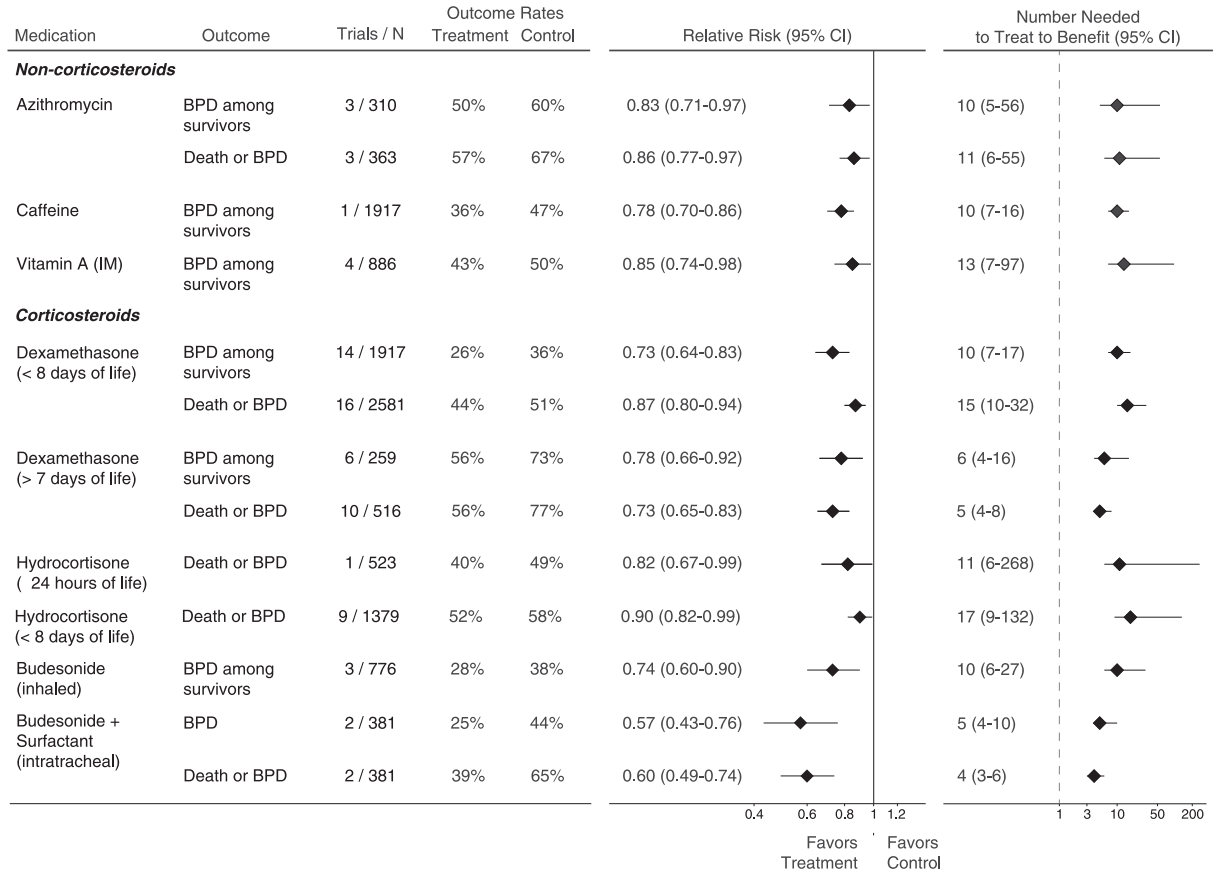

Figure 2. Summary of randomized, controlled trial data on the effects of various medications for preventing death and/or bronchopulmonary dysplasia. Study results are abstracted from the cited publication when available. If not provided in the article, relative risk and number needed to treat to benefit values (inverse of the risk difference) were calculated using original study data in RevMan version 5.3 (the Nordic Cochrane Centre, Copenhagen, Denmark). BPD=bronchopulmonary dysplasia; CI=confidence interval; IM=intramuscular.

Caffeine. Caffeine is approved by the US Food and Drug Administration for the treatment of neonatal apnea among infants born with gestational ages from 28 weeks to less than 33 weeks. The Caffeine for Apnea of Prematurity trial showed that caffeine also reduced BPD risk among infants with birthweights of 500 to 1,250 g and improved neurodevelopmental outcomes at 18 to 21 months' corrected age (Fig 2). (66)(67) Follow-up trial data collected through age 11 years indicated that caffeine resulted in durable, long-term improvement in motor function. (68) Recent neonatal studies showed that beginning caffeine therapy within the first 72 hours of age may result in the greatest reduction in BPD risk. (69)(70)(71)(72)(73) Importantly, it is uncertain whether these findings are indicative of a true benefit of early caffeine or greater illness severity among the infants treated with caffeine beginning at later ages. Although further studies are needed to evaluate the risks and benefits of very early caffeine therapy, particularly among extremely preterm infants receiving invasive mechanical ventilation, use of caffeine soon after birth in most extremely preterm infants is recommended. (63)

Vitamin A. Vitamin A is required for the growth and maturation of epithelial cells lining the respiratory tract. (74)(75) Earlier studies showed that preterm infants who developed BPD, compared with those who did not, had lower plasma vitamin A levels. (76)(77)(78) Subsequently, a large, multicenter trial published in 1999 found that intramuscular injections of vitamin A during the first 4 weeks of age reduced rates of death or BPD and BPD alone among surviving extremely low-birthweight infants. (79) Meta-analysis of all trial data confirmed a small benefit for reducing BPD among survivors (Fig 2) but not for the composite outcome of death or BPD (RR 0.90, 95% CI 0.81–1.01). (80) More recent observational studies call into question the true effectiveness of vitamin A in the current era. One large study showed similar rates of BPD among infants who received vitamin A and untreated controls whereas another found that BPD rates remained stable during a vitamin A shortage in the United States, despite a precipitous drop in use of the supplement. (81)(82) An ongoing RCT investigating enteral vitamin A may help resolve the conflict between the trial and observational data. (83) However, in

the absence of these results, intramuscular vitamin A is recommended, if commercially available, as an evidence-based strategy to prevent BPD in extremely preterm infants.

Corticosteroids

The potent anti-inflammatory properties of corticosteroids make them a logical therapeutic agent for BPD prevention. Unfortunately, the potential for long-term harm with corticosteroids and deficiencies in the available trial data, including variability in study design and frequent open-label steroid use among randomized infants, hinder the ability to determine the true risks and benefits of postnatal corticosteroids in very preterm infants.

Dexamethasone (Systemic). Of all corticosteroids, the use of dexamethasone to prevent BPD has been studied in the largest number of RCTs. Owing to differences in risk profile, meta-analyses incorporating these trials typically group studies evaluating dexamethasone initiated within the first 8 days of age ("early use") separately from those initiating therapy after this time point ("late use"). The most recent Cochrane review on early dexamethasone therapy found that although use within the first 8 days after birth reduced BPD risk (Fig 2), it increased the risks for gastrointestinal perforation, hypertrophic cardiomyopathy, cerebral palsy (CP), and major neurosensory disability. (84) Because of these unacceptable side effects, early dexamethasone for BPD prevention is not recommended.

The risks and benefits of "late" dexamethasone are less well-established. Meta-analysis of the available trial data shows that initiation of dexamethasone after the first week of age reduces BPD risk (Fig 2), but carries the short-term side effects of hyperglycemia, glycosuria, and hypertension. (85) In contrast to early use, a recent meta-analysis did not find clear evidence of increased CP risk among surviving infants treated with late dexamethasone. (85) However, none of the follow-up studies were adequately powered to evaluate long-term outcomes, and the high rates of open-label dexamethasone use in these studies may mask actual treatment effects. (85)(86)

Ultimately, clinicians considering whether to administer "late" dexamethasone to individual infants must balance the medication's beneficial respiratory effects with the potential adverse effects on long-term neurodevelopment. An important component in this calculus is the recognition that BPD is itself a risk factor for poor neurologic outcomes. (87)(88) A meta-regression conducted by Doyle et al provides the best means for clinicians to balance these competing risks. (88) This study showed that when the risk for BPD in the control population (akin to an infant's baseline BPD risk) was less than 33%, corticosteroids significantly increased the risk for death or CP. (88) Alternatively, when the risk for BPD exceeded 60%, corticosteroids reduced death or CP risk. (88) Therefore, in infants at low to moderate risk for BPD, the adverse long-term effects of dexamethasone likely outweigh the benefits. Conversely, among infants at high risk, the balance may favor dexamethasone therapy.

If a clinician decides to administer dexamethasone, he/she must then select a dose and treatment duration. Although general consensus favors the use of low, tapering doses administered for short periods (1–2 weeks at most), robust data to guide these specific choices are limited. (89) The dosing regimen used in the discontinued Dexamethasone: A Randomized Trial (DART) study (0.89 mg/kg administered over 10 days) is one such approach. (90) In this trial of 70 very preterm infants receiving invasive mechanical ventilation, compared with placebo, dexamethasone significantly improved rates of successful extubation (dexamethasone group 60%, placebo group 12%) without evidence of long-term harm. (90)(91) However, the risk for BPD was not significantly reduced in the dexamethasone-treated infants (OR 0.58, 95% CI 0.13–2.66). (90)

Hydrocortisone (Systemic). To date, 9 trials have evaluated the safety and efficacy of systemic hydrocortisone initiated in the first week after birth for prevention of death or BPD. (84) The largest of these studies, the PREMILOC trial, compared a 10-day course of low-dose hydrocortisone initiated within the first 24 hours after birth with placebo in infants born at less than 28 weeks' gestation. (92) Rates of survival without BPD were higher among the hydrocortisone-treated infants (Fig 2). (92) However, a subgroup analysis demonstrated a nearly 2-fold increase in the risk for late-onset sepsis among infants born at 24 to 25 weeks' gestation treated with early hydrocortisone. (92) Hydrocortisone also did not improve 2-year neurodevelopmental outcomes despite a reduction in death or BPD. (93) Meta-analysis of all available trials initiating hydrocortisone in the first week of age showed a reduction in the composite outcome of death or BPD with hydrocortisone therapy (Fig 2) but no benefit for BPD among survivors. (84) Gastrointestinal perforation was more common in the hydrocortisone-treated infants. (84) A recently completed RCT conducted in the US Neonatal Research Network evaluating the safety and efficacy of hydrocortisone administered to preterm infants receiving invasive mechanical ventilation at 14 to 28 days will provide additional safety and efficacy data.

Budesonide (Inhaled). Inhaled corticosteroids offer the potential benefit of reducing inflammation in the lung without the adverse side effects of systemically administered corticosteroids. The efficacy of 4 different inhaled steroids (budesonide, beclamethasone, fluticasone, flunisolide) for preventing BPD has been studied in RCTs. (94)(95)

A meta-analysis of all trial data (inclusive of all 4 steroids) demonstrated a reduced BPD risk among surviving infants (RR 0.76, 95% CI 0.63–0.93) and the composite outcome of death or BPD (RR 0.86, 95% CI 0.75–0.99) among infants treated with inhaled corticosteroids. (94) These beneficial findings are primarily driven by the multicenter NEUROSIS trial, which found that inhaled budesonide decreased rates of BPD among survivors (Fig 2), but at the expense of greater mortality among budesonide-treated infants. (96)(97) Rates of neurodevelopmental impairment at 18 to 22 months' corrected age were similar between the 2 study groups. (97) Although no etiology has been identified for the higher mortality in the budesonide group, this concerning finding outweighs the observed benefit for BPD. (97)

Two RCTs evaluated the usefulness of intratracheal budesonide combined with surfactant relative to surfactant therapy alone among very-low-birthweight infants with severe RDS. (98) The combined therapy reduced the risk for death or BPD (Fig 2). (98) Follow-up performed up to 3 years of age found no difference in motor or cognitive function between the groups. (98) This promising finding awaits confirmation in larger trials before widespread use is recommended.

INEFFECTIVE OR UNPROVEN THERAPIES FOR BPD PREVENTION

Multiple medications and care strategies that are potentially useful for BPD prevention have ultimately been shown in RCTs to not reduce BPD risk. Although review of each of these therapies is outside the scope of this article, a few of the more common strategies warrant discussion.

Antenatal Corticosteroids

Administration of antenatal corticosteroids to pregnant women at 23 to 33 6/7 weeks' gestation who are at increased risk for preterm delivery within the subsequent week is an evidence-based strategy to reduce neonatal morbidity and mortality. Meta-analysis of available trial data indicate that premature infants of women treated with antenatal steroids are at significantly reduced risk for developing neonatal RDS, intraventricular hemorrhage, necrotizing enterocolitis (NEC), and early-onset sepsis. (99) Despite these benefits, antenatal steroids have not been shown to reduce the risk for BPD in RCTs (RR 0.86, 95% CI 0.42–1.79) or large observational studies. (99)(100)

Treatment of a Patent Ductus Arteriosus

Observational data demonstrate a strong association between the presence of a patent ductus arteriosus (PDA) and the development of BPD. (101)(102) Despite this evidence, no medication that targets ductal closure (indomethacin, ibuprofen, acetaminophen) administered prophylactically or after identification of a "hemodynamically significant" PDA has been shown to reduce BPD risk. (103)(104)(105)(106)(107) Surgical ligation effectively achieves closure of the PDA, but may increase the risk for BPD and long-term neurodevelopmental impairment. (108)(109) Although it is possible that some very preterm infants may benefit from medical or interventional closure of the PDA, there are no evidence-based strategies to reliably identify these infants and then select the optimal therapeutic approach.

Fluid Restriction and Diuretics

Excessive fluid intake may result in pulmonary edema and need for greater respiratory support. Observational data indicate that extremely low-birthweight infants who receive higher fluid intake and those with less robust weight loss in the first 1 to 2 weeks of age more commonly develop BPD. (102) However, the limited trial data do not show clear benefit with restrictive versus more liberal fluid administration. (110) Diuretics may reduce pulmonary edema and provide short-term improvement in respiratory mechanics in preterm infants but there are no data indicating reduced BPD risk with regular diuretic use. (111)

Inhaled Nitric Oxide

Inhaled nitric oxide is a potent pulmonary vasodilator and an effective treatment for persistent pulmonary hypertension in near-term and full-term newborns. (112) Despite these benefits, inhaled nitric oxide does not prevent BPD when used as an early routine strategy or as a rescue therapy in very preterm infants. (113)(114) A recent individual patient meta-analysis using data from a subset of trials suggested that inhaled nitric oxide may reduce BPD risk among black preterm infants. (115) This promising finding requires validation in future studies.

Breast Milk

Mother's own milk is the preferred source of enteral nutrition for most very preterm infants. In addition to being associated with reduced risk of developing NEC and late-onset sepsis, observational studies suggest that preterm infants who receive an exclusive diet of the mother's own milk as compared to preterm formula are less likely to develop BPD. (116)(117) Donor human milk is gaining popularity as an alternative to preterm formula when the mother's own milk is not available. Although the current trial data indicate that donor human milk reduces the risk

for NEC, it does not lower BPD risk or improve long-term neurodevelopmental outcomes. (118)

CONCLUSION

BPD remains the most common chronic complication associated with extremely preterm birth. Strategies to minimize lung injury and prevent BPD must begin in the immediate perinatal period and likely continue throughout hospitalization. Initial respiratory care of very preterm infants should begin with nasal CPAP, with endotracheal intubation and surfactant administration reserved for those who fail noninvasive support or do not demonstrate spontaneous respiratory effort after resuscitation. For infants receiving invasive mechanical ventilation, use of a volume-targeted approach rather than pressure-limited ventilation may reduce BPD risk. Caffeine and vitamin A are the only medications with high-quality evidence to support routine use for BPD prevention. Dexamethasone is an effective therapy, but for many infants, the risks for adverse effects with this medication outweigh the benefits. However, for those at high risk of developing BPD, dexamethasone initiated after the first week of age may be appropriate. Hydrocortisone is an alternative option that has been shown in RCTs to reduce rates of death or BPD when initiated in the first week of age. Unfortunately, this benefit may come at the expense of higher rates of sepsis and gastrointestinal perforation without advantages for long-term neurodevelopment. Less invasive surfactant administration is a promising intervention currently under investigation.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Be aware of various preventive strategies for bronchopulmonary dysplasia/chronic lung disease.

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1. Bronchopulmonary dysplasia (BPD) is a common complication of prematurity and is associated with significant long-term morbidities including chronic respiratory and cardiovascular disorders, growth failure, and adverse neurodevelopmental outcomes. Ventilator-induced lung injury is an important factor contributing to the development of BPD and therefore the use of noninvasive respiratory support in very preterm infants has been extensively studied. Which of the following statements regarding the use of noninvasive positive airway pressure to prevent BPD is correct?
    A. Meta-analyses indicate an increased risk of pneumothorax with the use of early continuous positive airway pressure (CPAP) as initial mode of support.
    B. Meta-analyses indicate a small but significant reduction in the risk of death or BPD with early CPAP therapy.
    C. Heated and humidified high-flow nasal cannula has been shown to be equivalent to nasal CPAP for postextubation support.
    D. Nasal intermittent positive pressure ventilation (NIPPV) decreases BPD when used as the initial mode of respiratory support.
    E. Synchronized NIPPV has not been shown to be superior to asynchronous NIPPV with regard to BPD prevention.
2. Although noninvasive respiratory support is the preferred approach for most preterm infants, surfactant administration should be considered in preterm infants requiring intubation and mechanical ventilation. Which of the following statements regarding surfactant administration is correct?
    A. Surfactant administration after 1 hour of age does not reduce the risk for BPD.
    B. Lucinactant, a synthetic surfactant containing a peptide analog of protein B, has a lower efficacy than animal-derived surfactants.
    C. The INSURE (*in*tubation, *sur*factant administration during brief mechanical ventilation, followed by *e*xtubation) technique has been shown to decrease the risk for BPD compared with CPAP alone.
    D. Less invasive surfactant administration techniques reduce BPD risk among survivors compared with control therapies.
    E. In a recent Bayesian network meta-analysis, nebulized surfactant administered via laryngeal mask airway was associated with the largest reduction in the risk for death or BPD.
3. BPD is multifactorial and strategies for prevention must include multiple evidence-based practices. Which of the following statements regarding pharmacologic measures to prevent BPD in preterm infants is FALSE?
    A. Azithromycin reduces the risk for death or BPD in preterm infants colonized or infected with *Ureaplasma*.
    B. Caffeine decreases the risk for BPD in preterm infants with birthweights of 500 to 1,250 g.
    C. Intramuscular injections of vitamin A for 4 weeks after birth has been shown to decrease BPD in extremely low-birthweight infant survivors.
    D. In the PREMILOC trial, hydrocortisone within the first 24 hours after birth was associated with an increased risk of late-onset sepsis in infants born at 24 to 25 weeks.
    E. In the multicenter NEUROSIS trial, inhaled budesonide reduced the risk for BPD in survivors but was associated with increased mortality.

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4. Corticosteroids are attractive therapeutic agents for BPD prevention because of their potent anti-inflammatory properties. Among corticosteroid agents, dexamethasone has been the most studied. Which of the following statements regarding the use of dexamethasone to decrease BPD is correct?
    A. Early dexamethasone is defined as treatment initiation within 14 days of birth.
    B. Early dexamethasone treatment is associated with increased risk of gastrointestinal perforation and hypertrophic cardiomyopathy, but not cerebral palsy.
    C. In a meta-analysis of late dexamethasone use, the risk for cerebral palsy was found to be significantly increased in dexamethasone-treated infants.
    D. Based on a meta-regression study by Doyle et al, late dexamethasone should be considered in infants in whom the risk for BPD exceeds 80%.
    E. In the Dexamethasone: A Randomized Trial (DART) study, low-dose dexamethasone did not result in lower BPD risk.
5. In very preterm infants in the NICU, BPD has remained a challenging morbidity to prevent and treat. Which of the following interventions or practices in neonatal care has been associated with lower BPD risk either in controlled trials or consistently in observational studies?
    A. Donor human milk.
    B. Inhaled nitric oxide in early preventive strategies, but only for non-black patients.
    C. Higher fluid intake during the first week after birth.
    D. Indomethacin prophylaxis or treatment for patent ductus arteriosus within the first week after birth.
    E. Low-dose hydrocortisone initiated soon after birth for a 10-day course.

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