Published in final edited form as:

Semin Perinatol. 2016 October ; 40(6): 348–355. doi:10.1053/j.semperi.2016.05.010.

Prevention and management of bronchopulmonary dysplasia: Lessons learned from the neonatal research network

Kathleen A. Kennedy, MD, MPH^{a,*}, C. Michael Cotten, MD, MHS^b, Kristi L. Watterberg, MD^c, and Waldemar A. Carlo, MD^d

^aDepartment of Pediatrics, University of Texas Medical School at Houston, Houston, TX

^bDepartment of Pediatrics, Duke University, Durham, NC

^cUniversity of New Mexico Health Sciences Center, Albuquerque, NM

^dDivision of Neonatology, University of Alabama at Birmingham, Birmingham, AL

Abstract

Despite remarkable improvements in survival of extremely premature infants, the burden of BPD among survivors remains a frustrating problem for parents and caregivers. Advances, such as antenatal steroids and surfactant replacement, which have dramatically improved survival, have not reduced BPD among survivors. Other advances that have significantly improved the combined outcome of death or BPD, such as vitamin A and avoidance of mechanical ventilation, have had smaller magnitude effects on the outcome of BPD alone. Postnatal steroids have a clear beneficial effect on BPD, but the optimal preparation, dose, and timing for maximizing benefit and minimizing harm have yet to be determined. This persistent burden of BPD among the most immature survivors remains a challenge for the NRN and other researchers in neonatal medicine.

Keywords

Bronchopulmonary dysplasia; Corticosteroids; Ventilation

Introduction

Survival has significantly improved for extremely low gestational age infants over the past 2–3 decades. Unfortunately this improvement in survival has not led to reduced morbidity for the most immature survivors, those born at <25 weeks gestation.¹ In fact, the prevalence of BPD (expressed as BPD diagnosed at 36 weeks adjusted age) has increased as survival has increased among infants <28 weeks gestation.¹ There are several potential explanations for these findings. The most effective interventions adopted for these infants in the past 3 decades are antenatal steroids and surfactant replacement. While these strategies have dramatically improved survival, their effect on BPD among survivors has been less impressive.^{2,3} An increase in the proportion of infants who survive without BPD is clearly valuable from the parents' perspective, but the trade-off has been the ongoing burden of

*Corresponding author: Kathleen.A.Kennedy@uth.tmc.edu (K.A. Kennedy).

survivors with BPD. Reducing this burden has proven to be a difficult challenge for researchers in neonatal medicine. The purpose of this review is to highlight the work that the NRN has done since 1986 to improve respiratory outcomes for infants at risk for BPD and to put this work in the context of related studies underway at the same time.

Prediction

Accurate prediction of the risk of BPD is important for several reasons. In addition to its importance for counseling families, prediction of risk for individual infants and groups of infants is critical for the design of prevention trials. A number of prediction formulas have been proposed since BPD was first described in 1967.⁴⁻⁷ Two of these methods^{4,6} defined BPD at 28 days (no longer the preferred definition)⁸ and the others defined BPD as the “use” rather than the “need” for supplemental oxygen at 36 weeks postmenstrual age. Two NRN studies have refined and updated our ability to predict BPD. In 2004, the NRN reported that a standardized “physiologic definition” of BPD (the need for supplemental oxygen to maintain O₂ saturation ≥90%), as compared to clinician-driven use of supplemental oxygen at 36 weeks postmenstrual age, reduced the reported prevalence of BPD and also reduced among-center differences in the prevalence of BPD.⁹ In 2011, the NRN published a validated strategy for prediction of BPD, categorized as none, mild, moderate, or severe using the physiologic definition; prediction was based on demographic variables and respiratory support at days 1, 3, 7, 14, 21, and 28.¹⁰ This model is available online (<https://neonatal.rti.org>) and has since been used for establishing eligibility, enrollment stratification, and sample size calculations in NRN trials.

Existing predictive models for BPD have been based on readily available demographic and clinical characteristics of infants and use of interventions such as high-frequency ventilation at certain postnatal time points. Genetic information offers the promise of more precise prediction. Collins¹¹ summarized the goals of personalized medicine as “the ability to utilize this information in the real world to influence health behaviors and achieve better outcomes.” These -omics approaches, including genomics, proteomics, metabolomics, provide data about individuals in almost unfathomable detail, including thousands of variants in gene expression for compounds involved with organ development and response to the environment, including response to injuries and interventions. These investigations are challenged to distinguish not only which genetic variant is independently associated with disease, but whether it actually contributes to pathophysiology, or is a downstream effect of true causative variants. A causative role must be established before the genetic variant can be considered a target for interventions. We have just begun in neonatology to explore the inclusion of -omics approaches to understand disease pathophysiology, hopefully leading us to better strategies for disease prevention and treatment based on individual characteristics.

The NRN has taken small steps toward personalized medicine for BPD. The NRN’s cytokines study enrolled 1067 extremely low birth weight infants from 17 NRN centers, collected a blood sample within 4 h after birth and on days 3, 7, 14, and 21, and measured levels of 25 cytokines from each time point. The study’s primary hypothesis was that cytokine levels would be associated with neurodevelopmental impairment and/or cerebral palsy¹²; however, the NRN also tested cytokines for associations with BPD and has

completed a genome-wide association study of BPD using DNA extracted from the cytokines study sample set.^{13,14}

Prior to the NRN report on the associations between cytokine levels and BPD, several studies had reported associations between BPD and cytokines, but these small studies assessed a restricted number of cytokines.^{15–18} In the NRN study of 1062 infants, 606 infants developed BPD or died. The composite outcome of BPD or death was associated with higher concentrations of interleukins 1, 6, 8, and 10 and interferon γ and with lower concentrations of interleukin 17, RANTES (*regulated on activation, normal T cell expressed and secreted*—a cytokine that leads to activation of T lymphocytes), and tumor necrosis factor β . These cytokine patterns suggested an increased neutrophil influx, a decrease in circulating effector T cells, and lower IL-17 levels, which could be associated with impaired angiogenesis. The addition of cytokine data to models that included clinical and demographic data improved predictive ability by a statistically significant but clinically modest magnitude. In the multivariable models that included peak cytokine levels, average cytokine levels over time, early cytokines levels, and late cytokine levels, the clinical variables that remained consistently associated with BPD or death were male gender, mechanical ventilation, and the NRN center where the baby was treated.¹³

Supportive rationale for the NRN genomics study of BPD was provided by twin studies suggesting that a considerable portion of BPD risk is inherited.¹⁹ In complex diseases with an environmental contribution (as suggested by the association between “NRN center” and BPD), a search based on a composite of genes linked in biological pathways is warranted.²⁰ The NRN partnered with National Human Genome Research Institute to conduct a genome-wide association study (GWAS) on 1.2 million genotyped single nucleotide polymorphisms (SNPs) and an additional 7 million imputed SNPs from 751 infants whose samples were included in the NRN’s DNA bank derived from the cytokines study. Individual variants and composite variants in pathways were compared for infants who died or had BPD versus those who survived without BPD, with BPD defined according to the NICHD Workshop classification.⁸ Not surprisingly, none of the single variants was associated with genome-wide significance with BPD (or severe BPD or composite outcomes with death). Three pathways (out of over 7500) were significant with false discovery rates <0.1 for all three outcomes: BPD/death, severe BPD/death, and severe BPD in survivors. These three pathways are involved in lung development and repair. While only three pathways were consistently shared across mild, moderate, and severe BPD, 105 pathways were shared among severe BPD and BPD/death. This suggests that different pathophysiologic mechanisms, perhaps beginning at the genetic level, could be contributing to the development of severe versus mild to moderate BPD. We also found that different pathways were associated with severe BPD among infants of different genetically defined ancestry. The NRN analysis was strengthened by evaluating gene expression from the identified pathways in BPD lung tissue autopsy samples from a separate cohort.¹⁴

The BPD cytokines study and the BPD GWAS study have provided small incremental insights into this complex disease but must be considered more hypothesis-generating than hypothesis-proving regarding the pathogenesis of BPD. The cytokine levels added only slightly to the predictive strength of the clinical model. Center was a strong predictor

variable, suggesting that there is still much to learn about how our management contributes to an individual infant's genetic risk of BPD.²¹ The GWAS study provided evidence supporting, but far from proving, the hypothesis that the pathophysiologic mechanisms leading to severe BPD could be different from the mechanisms that lead to mild or moderate BPD. Data from the NRN GWAS have been incorporated into the publicly available Database for Genotypes and Phenotypes (dbGaP: <http://www.ncbi.nlm.nih.gov/gap>) and the cytokines and genomic data have been included as validation sets with other investigators' cohorts.²² While the cytokines study has provided valuable hypothesis generation regarding the complex diseases associated with extreme prematurity, we must acknowledge that the NRN's genomic and cytokine data are derived from a cohort enrolled between 1999 and 2001. Examining the -omics profiles of extremely preterm infants to identify pathways involved in survival and morbidity among infants born before 25 completed weeks gestation may require recruitment of new cohorts.¹ Additionally, most genetic variants are not represented by the SNPs tested in GWAS studies that occur in >1% of the population. More specific disease causing variants may be findable only with whole genome or whole exome sequencing among patients with well-defined phenotypes.²³

Surfactant studies for prevention of BPD

In part because of the need for FDA approval of a new agent, surfactant replacement is one of the best studied interventions in neonatal medicine.^{3,24} That said, most of the early studies addressed the question of whether exogenous surfactant replacement versus no surfactant was beneficial for infants who had been intubated for respiratory distress syndrome (RDS). These studies left clinicians with unanswered questions regarding the optimal preparation and optimal criteria for treatment.

In 1993, the NRN published the first large randomized trial comparing the effectiveness of the animal-derived and synthetic surfactants that were commercially available at the time.²⁵ A meta-analysis of this trial, along with nine others published from 1993 to 2000, reported fewer pneumothoraces and lower mortality with animal-derived surfactant as compared to protein-free synthetic surfactant for the treatment of RDS.²⁶ As a result of this work, protein-free synthetic surfactant is no longer used in the US; other more recent trials have not established a clear benefit/risk advantage among the currently available bovine and porcine surfactants and a peptide-containing synthetic surfactant.²⁷

In the early trials of surfactant versus no surfactant, one of two strategies was used: a prophylactic approach with treatment given shortly after birth based on gestational age criteria or a rescue approach with treatment for ventilated infants with specified severity criteria for RDS. Each strategy was shown to be beneficial with respect to mortality and survival without BPD.^{3,28} Later studies compared these two approaches. When combined in a meta-analysis, these studies showed a clear survival benefit for the prophylactic approach,²⁹ although the optimal gestational age criteria for prophylactic surfactant were not well-defined. Based on these findings, prophylactic or very early use of surfactant became accepted as a "potentially better practice" for quality improvement in neonatal care in the 1990s.^{30,31} During this time, observational studies led some clinicians to believe that a more conservative approach to intubation (rather than intubation for prophylactic surfactant) with

more liberal use of CPAP would result in better outcomes.³² The observational studies were significantly limited by the opportunity for confounding and lack of follow-up after hospital discharge.

This controversy persisted until 2008–2011 when four separate multicenter trials compared a strategy of delivery room CPAP with later intubation as needed to delivery room intubation for prophylactic surfactant among 24–29 weeks gestational age infants.^{33–36} The largest of these was the SUPPORT Trial conducted by the NRN. None of the individual trials reported a statistically significant difference in BPD or in survival without BPD, but the combined outcome of death or BPD was significantly lower (RR = 0.90, 95% CI: 0.83–0.98) in the CPAP group when a meta-analysis combined the results from all four trials.³⁷ The NRN SUPPORT trial has evaluated neurodevelopmental and pulmonary outcomes at 18–22 months adjusted age for infants enrolled in the NRN trial.^{38,39} There was no significant difference between groups in the combined outcome of death or neurodevelopmental impairment at 18–22 months, and the point estimate for death before 18–22 months favored the CPAP group (18.4% in the CPAP group versus 21.9% in the Surfactant group). There were no significant differences in most of the respiratory outcomes assessed at 6-month intervals after discharge, but the CPAP group had significantly fewer episodes of wheezing and emergency visits for breathing problems. Although it remains unclear whether the use of early CPAP or the high prevalence of antenatal steroid administration explains the lack of benefit for prophylactic surfactant in the more recent trials, together these studies have provided reassuring evidence to support the practice of routine CPAP in the delivery room with intubation and surfactant as needed for respiratory distress/failure. Extremely preterm infants can frequently be stabilized right after birth with CPAP and other less invasive approaches such as the technique of intubation, surfactant, and extubation (INSURE).⁴⁰ Although two-thirds of the infants in the SUPPORT Study CPAP group ultimately received surfactant and mechanical ventilation, there were no adverse effects of the more selective approach. In more mature preterm infants (birthweight $\geq$ 1250 g) with mild to moderate RDS, intubation and early surfactant also did not improve outcomes.⁴¹

This new evidence has prompted a major practice change in the approach to the respiratory support of very premature infants in the minutes to hours after birth. The Respiratory Support in Preterm Infants report from the American Academy of Pediatrics states that CPAP started at birth (without prophylactic surfactant) results in rates of BPD or death comparable to prophylactic surfactant; in addition, infants treated with early CPAP are not at increased risk of adverse outcomes from delaying or eliminating surfactant administration.⁴² Following the documentation of lower morbidity with the CPAP approach in these trials, there has been increased adoption of this practice. An observational study in the NRN reported changes in practice, including a decrease in delivery room intubations, after the SUPPORT trial.⁴³

Ventilation strategies for prevention of BPD

Mechanical ventilation became established as routine practice in the 1960s–1970s without any rigorous trials to define optimal criteria for intubation or maintenance of ventilation. Mechanical ventilation in general, and barotrauma or volutrauma in particular, have long

been suspected as contributing to the pathogenesis of BPD.⁴⁴ Strategies to minimize volutrauma have included two general approaches: avoiding initiation of mechanical ventilation or using more liberal criteria for adjusting and discontinuing mechanical ventilation. The NRN has contributed to the literature in both of these areas.

Several randomized clinical trials (RCTs) have tested CPAP as the initial mode of respiratory support in preterm infants. In the SUPPORT trial described above,³⁴ CPAP was initiated in the delivery room at a recommended pressure of 5 cm of water in infants 24–27 weeks gestation. Infants in the CPAP arm were given surfactant only if they required intubation for resuscitation or respiratory failure. CPAP could be increased up to 8 cm of water if clinically indicated. Infants were intubated and given surfactant if they met any of the following criteria: fraction of inspired oxygen (FiO_2) > 0.50 , arterial carbon dioxide (PaCO_2) > 65 mmHg, or hemodynamic instability. Attempted extubation was required for infants who met all of the following: $\text{PaCO}_2 < 65$ mmHg with a $\text{pH} > 7.20$, $\text{FiO}_2 < 0.5$, a mean airway pressure less than 10 cm of water, a ventilator rate of < 20 breaths per minute, an amplitude of less than twice the mean airway pressure if high-frequency ventilation was being used, hemodynamic stability, and the absence of clinically significant patent ductus arteriosus. Criteria for re-intubation were the same as those for initial intubation. The occurrence of death or BPD in the CPAP group was 48% compared to 51% in the surfactant group (RR = 0.91, 95% CI: 0.83–1.01, $P = 0.07$). Among infants 24 and 25 weeks, death was lower in the CPAP group than in the surfactant group (20% vs. 29%, RR = 0.68, 95% CI: 0.5–0.92, $P = 0.01$). Follow-up at 18–22 months corrected age reported that death or neurodevelopmental impairment occurred in 28% of the infants in the CPAP group compared with 30% of the surfactant/ventilation group (RR = 0.93, 95% CI: 0.78–1.10, $P = 0.38$).³⁸

In two other large RCTs, the Continuous Positive Airway Pressure or Intubation at Birth (COIN) and Vermont Oxford Network Delivery Room Management (VON DRM) trials, similar approaches were investigated.^{33,36} The COIN trial used initial CPAP of 8 cm of water and the VON DRM trial used initial CPAP of 5 cm of water. In the COIN trial, there was a higher occurrence of pneumothorax in the CPAP group, a finding that did not occur in either the VON DRM or SUPPORT trial. In the COIN trial, infants in the CPAP group were intubated if the pH was < 7.25 with a PaCO_2 of > 60 mmHg or if the FiO_2 increased to > 0.60 . In the VON DRM trial, infants in the CPAP group were intubated if the PaCO_2 was > 65 mmHg or the FiO_2 was > 0.40 (discretionary criterion) or > 0.60 (mandatory criterion). Neither the COIN nor the VON DRM trial had specific criteria for extubation. As detailed in the previous section, the meta-analysis of these trials reported that death or BPD was significantly lower in the CPAP groups (RR = 0.90, 95% CI: 0.83–0.98). Together these trials provide the best contemporary evidence to support a conservative approach to initiation and an aggressive approach to discontinuation of mechanical ventilation in extremely premature infants.³⁷

The strategy of “permissive hypercapnia” aims to modify blood gas targets to accept a higher-than-normal PaCO_2 so that patients may avoid invasive ventilation and ventilated patients can be supported with lower tidal volumes. Permissive hypercapnia is usually achieved by decreasing ventilatory support, especially tidal volume and/or inspiratory

pressures, in an effort to reduce lung injury. Experimental and clinical evidence suggests an overall benefit of permissive hypercapnia in neonates with respiratory failure. Most animal research suggests that CO₂ can have both direct and indirect beneficial effects on the neonatal lung. Several observational studies in human infants suggest that permissive hypercapnia may reduce adverse pulmonary outcomes. However, it is difficult to make firm conclusions regarding causation from these observational studies.

In a small feasibility trial of intubated preterm infants with RDS and birth weight <1250 g, more of the infants treated with permissive hypercapnia (PaCO₂: 45–55 mmHg) were extubated during the first 4 days compared to the infants in the normocapnia group (PaCO₂: 35–45 mmHg).⁴⁵ In the multicenter NRN trial of 220 extremely low birth weight infants, permissive hypercapnia (PaCO₂ target >52 mmHg compared to routine ventilation with a PaCO₂ target <48 mmHg) reduced the use of mechanical ventilation at 36 weeks from 16% to 1%.⁴⁶ A subsequent single center small trial reported no difference in the occurrence of BPD or death for infants treated with permissive hypercapnia.⁴⁷ A recently published multicenter randomized trial of more severe permissive hypercapnia (up to 75 mmHg compared to up to 55 mmHg) in ventilated infants during the first 2 weeks after birth reported no benefits of more severe hypercapnia.⁴⁸ All of these trials enrolled infants who were already intubated; therefore permissive hypercapnia was evaluated for maintenance rather than initiation of mechanical ventilation. Only two of these trials reported follow-up outcomes. Although the smaller trial by Thome et al.⁴⁷ raised some concerns about a higher occurrence of MDI <70 or death in the hypercapnia group, the larger NRN trial reported no differences at 2-year follow-up.⁴⁶

In the NRN SUPPORT trial described previously, early permissive hypercapnia (PaCO₂ <65 mmHg compared to <50 mmHg) was evaluated as a criterion for initiation and discontinuation of ventilation in 1316 infants of 24–27 weeks' gestation. The permissive hypercapnia strategy was continued for 14 days. In the similarly designed VON DRM and COIN trials,^{36,33} relatively conservative (65 and 60 mmHg, respectively) PaCO₂ criteria for intubation were also used. Meta-analyses have reported a reduced occurrence of the combined outcome of BPD or death using early nasal CPAP with permissive hypercapnia, compared to elective mechanical ventilation for prophylactic surfactant [OR = 0.91 (95% CI: 0.84–0.99)].³⁷ In a more inclusive meta-analysis of seven trials, strategies including permissive hypercapnia to avoid endotracheal mechanical ventilation decreased BPD/death [OR = 0.83 (95% CI: 0.71–0.96)].⁴⁹ It is possible that mild to moderate permissive hypercapnia during the first weeks is effective in reducing BPD, but the benefit seems most apparent when the strategy is included in the criteria for initiation of mechanical ventilation as well as maintenance and discontinuation. An observational study in 173 European neonatal intensive care units suggests that permissive hypercapnia has become a widespread strategy in ventilated neonates.⁵⁰

Postnatal steroids for prevention, moderation, or treatment

The history of glucocorticoid therapy to prevent or treat bronchopulmonary dysplasia in preterm infants is an instructive cautionary tale that highlights the importance of monitoring long-term outcomes when adopting novel neonatal therapies. The dexamethasone experience

has helped change the way that interventional studies in newborns are constructed, with researchers and clinicians calling for the inclusion of longer term evaluation of all new therapies. As such, the story itself and the NRN contributions to it are worth recounting.

Based on small studies in the 1980s that showed short-term respiratory improvements with dexamethasone treatment, the therapy was widely adopted by clinicians, with a typical starting dose of 0.5 mg/kg/d and a therapeutic regimen often extending up to 42 days.^{51–54} In this climate, the NRN performed two important RCTs. The first trial, conducted from 1992 to 1995, compared the benefits and hazards of starting a 14-day course of dexamethasone at 2 postnatal weeks versus 4 postnatal weeks.⁵⁵ This trial enrolled 371 ventilator-dependent VLBW infants (<1500 g birth weight) who received either 2 weeks of dexamethasone treatment (0.5 mg/kg/d tapering course) followed by 2 weeks of placebo or vice versa. There was no difference between groups in the primary endpoint, the number of days from randomization to successful extubation, or in the incidence of BPD at 36 weeks. In addition, the group receiving earlier dexamethasone had a higher incidence of infection and hyperglycemia, and both groups showed a significant reduction in weight gain and head circumference growth during dexamethasone treatment. Thus, earlier treatment did not confer benefit.

During the 1990s, studies continued to test high doses of dexamethasone (0.5–0.6 mg/kg/d) starting as early as <48 h postnatal age^{56,57} and documented additional short-term adverse effects. In response, the NRN undertook a new RCT of dexamethasone in 1998, testing a lower dose of dexamethasone, 0.15 mg/kg/d, in ELBW infants (<1000 g birth weight), begun within 24 hours of birth and tapered over 10 days.⁵⁸ This trial was stopped after enrollment of 220 babies because of a high rate of unanticipated adverse events, specifically spontaneous gastrointestinal perforations, among the dexamethasone-treated infants. As more reports were published, the list of short- and long-term adverse effects of dexamethasone accumulated^{59,60} and included adverse effects on growth and development that persisted until school age.⁶¹ The cumulative effect of these publications was a decrease in clinical use⁵⁴ and an almost complete halt to studies of glucocorticoids for BPD.

In the ensuing years, the decrease in dexamethasone use was accompanied by an increase in the incidence of BPD, with no apparent improvement in neurodevelopmental outcomes.^{62,63} During this time, 2-year outcomes were published for both the NRN study of early lower-dose dexamethasone and another multicenter trial of later, lower-dose dexamethasone (the DART trial).^{64,65} Both of these RCTs used a starting dose of 0.15 mg/kg/d. Although both studies reported no significant reduction in BPD at 36 weeks postmenstrual age, they also found no difference between treatment and placebo groups for the combined outcome of death or neurodevelopmental impairment (NDI) (NRN: 144/164 survivors evaluated, 65% versus 66% death/NDI; DART: 58/59 survivors evaluated, 46% versus 43% death/NDI). Publication of these follow-up results, together with a growing realization that neurodevelopmental outcomes had not improved after decreasing dexamethasone use, resulted in an increased willingness to consider new trials of glucocorticoids for BPD.

In an effort to take advantage of the anti-inflammatory properties of glucocorticoids while avoiding the adverse effects of dexamethasone, the NRN designed a study of hydrocortisone

to prevent BPD, starting between 2 and 4 weeks postnatal age at a dose of 4 mg/kg/d tapered over 10 days (clinicaltrials.gov NCT01353313). This study, currently enrolling patients, was based in part on the information that dexamethasone and hydrocortisone behave differently in the brain: hydrocortisone, identical to native cortisol, binds to both mineralocorticoid receptors and glucocorticoid receptors; dexamethasone binds only to glucocorticoid receptors and suppresses native cortisol production, which promotes apoptosis and results in adverse outcomes in animal models.^{66,67} These data, combined with the continuing high prevalence of BPD in extremely preterm infants and the apparent lack of adverse effects of hydrocortisone on long-term outcomes, motivated the NRN to undertake this RCT.^{68–70} The primary outcome of this RCT incorporates both the incidence of BPD at 36 weeks and the incidence of survival without NDI at 2 years adjusted age. With this trial, the NRN continues its long history of rigorous investigation of glucocorticoid therapy for the seemingly intractable burden of BPD in the extremely preterm infant.

Other strategies

Besides postnatal steroids, the only systemic pharmacologic intervention that has been proven in rigorous clinical trials to reduce BPD is vitamin A. The NRN conducted the largest randomized trial of vitamin A for BPD prevention to date⁷¹ and contributed the majority of participants to the Cochrane review of vitamin A supplementation for prevention of BPD.⁷² Unlike the use of postnatal steroids, vitamin A supplementation had no identified adverse effects in these studies.

Inhaled nitric oxide (iNO) was once considered to be a promising intervention to prevent progression of RDS to BPD. There have now been 14 randomized trials to investigate the use of iNO in infants at risk for BPD⁷³; one of these was conducted by the NRN.⁷⁴ Among the trials, study participants varied in age at enrollment and severity of lung disease. In the systematic review, none of the strategy subgroups (early rescue, early routine use, or later treatment) had a significant benefit from iNO. The NRN study was the largest of the early rescue trials and raised the concern that severe intracranial hemorrhage could be increased with the early use of iNO in preterm infants with severe respiratory failure. This finding was an important consideration in the NICHD Consensus Development Conference Statement and the American Academy of Pediatrics Clinical Report recommending against the routine use of iNO in preterm infants.^{75,76}

Center variation and benchmarking

Striking differences among centers in the prevalence of BPD first garnered attention with the publication of a landmark multicenter observational study in 1987.⁷⁷ Since that time, neonatologists have struggled to explain these differences and to capitalize on them by attempting to emulate the practices in the best performing centers. The NRN has reported smaller but still clinically important differences in the prevalence of BPD among participating centers.^{21,78}

In 2007, the NRN published a cluster-randomized “benchmarking” trial in which 14 centers were randomized to participate or not in a benchmarking quality improvement effort

fashioned after the practices in the best-performing NRN centers.⁷⁹ Overall survival without BPD (averaged across centers) did not improve over the study interval in either the intervention or control centers (although there were changes over time in individual centers in each group). These findings were in contrast to a similar, albeit not randomized, study conducted in the Vermont Oxford Network (VON).³⁰ The contrast between these two studies has interesting implications for other quality improvement (QI) studies. These two studies chose similar clinical interventions (prophylactic surfactant, permissive hypercapnia/limiting tidal volume, fluid restriction, liberal use of CPAP versus ventilation) for implementation in intervention centers; the main difference between the two studies was that intervention centers were randomly selected in the NRN trial and self-selected in the VON study. A likely explanation for the different outcomes in these two similar studies is that center self-selection in the VON study resulted in intervention sites that improved because they had an unusually unfavorable year at the beginning of the study or because the clinicians were particularly motivated to improve care rather than any intrinsic benefit from the implementation of specific changes in practice.

The Fig. is a heat map that illustrates the ranks among continuously participating centers for risk-adjusted survival without BPD for each year from 2002 to 2015. As shown, some of the centers had consistently high (Center F) or consistently low (Centers I and K) ranks over time, but others had considerable variation in rank over the 14-year interval. For centers with variation in outcome over time, QI studies that are initiated in a poor-outcome year are likely to show improvement over time even if the chosen intervention has no causal effect on outcome. The contrast between the findings of these two similar QI studies highlights the need to test interventions that are identified as “potentially better practices” in rigorous randomized trials.

Future directions

Despite the advances detailed above, much remains to be learned about the prevention and management of BPD. The NRN has developed clinical trials to investigate: conservative versus aggressive management of patent ductus arteriosus, volume-targeted versus pressure-limited ventilation, and a factorial trial of liberal versus conservative use of thiazide diuretics and sodium supplementation. These trials are ready for implementation when competing studies are completed and funding becomes available. Other questions that could be addressed in future studies include caffeine for prevention of BPD, the use of sildenafil for pulmonary hypertension with BPD, optimal PaCO₂ targets, and criteria for intubation and extubation.

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Center	Center Rank for Rate of Survival without BPD*										
	(Higher rank number denotes lower survival without BPD)										
	A	B	C	D	E	F	G	H	I	J	K
2002	9	3	8	4	6	10	5	11	2	7	1
2003	3	5	10	6	7	9	4	11	2	8	1
2004	3	5	11	7	6	10	4	8	1	9	2
2005	3	7	9	4	6	10	5	8	1	11	2
2006	3	4	9	6	5	10	8	7	1	11	2
2007	6	7	10	8	5	11	3	4	1	9	2
2008	4	9	10	6	7	11	1	5	3	8	2
2009	5	5	10	6	9	11	2	3	1	7	4
2010	6	11	9	3	8	10	7	5	4	2	1
2011	7	2	8	4	10	11	6	9	5	3	1
2012	8	6	9	10	5	11	3	1	2	7	4
2013	11	7	5	1	8	10	9	3	2	6	4
2014	8	5	7	3	10	11	9	2	1	5	4
2015	8	7	2	4	10	11	9	5	1	3	6

*traditional definition of BPD for 2002-2005, physiologic definition for 2006-2015

Fig.

Heat map of ranks among NRN centers for risk-adjusted survival without BPD for each year from 2002 to 2015 (higher rank number denotes lower survival without BPD).