Quality Improvement in Respiratory Care: Decreasing Bronchopulmonary Dysplasia

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KEYWORDS

• Chronic lung disease • Quality improvement
• Respiratory care • Bronchopulmonary dysplasia

NOMENCLATURE AND DEFINITION

Chronic lung disease (CLD) is 1 of the most common long-term complications in very preterm infants. Bronchopulmonary dysplasia (BPD), initially characterized by Northway and colleagues[1] in 1967, is the most common cause of CLD occurring in infancy. BPD was originally defined as the presence of clinical symptoms, the need for supplemental oxygen to treat hypoxemia, and an abnormal chest radiograph at 28 days of age, later revised to 36 weeks postmenstrual age (PMA).[2,3] In 2001, the National Institutes of Health developed a consensus definition of BPD to help compare the incidence of the disease among institutions and evaluate potential preventive strategies and treatments. This definition was based on gestational age at birth, time of assessment, and severity of disease (**Table 1**).[4] More recently, a new physiologic description by Walsh and colleagues[2] has been proposed: the inability to maintain an oxygen saturation of 90% or greater in room air. This definition is particularly useful for centers implementing quality improvement (QI) methods to improve pulmonary outcomes because of its objectivity. However, none of these definitions uses P_{CO_2} levels in defining the severity of the disease, and this value at 36 weeks PMA may be the best predictor of future respiratory morbidity.

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Table 1
Diagnostic criteria for BPD

Gestational Age	<32 wk	≥32 wk
Time of assessment	36 wk PMA or discharge to home, whichever comes first	>28 d but <56 d postnatal age or discharge to home, whichever comes first
Mild BPD	Oxygen>21% for at least 28 d plus: breathing room air at 36 wk PMA or discharge, whichever comes first	Breathing room air by 56 d postnatal age or discharge, whichever comes first
Moderate BPD	Need for <30% oxygen at 36 wk PMA or discharge, whichever comes first	Need for <30% oxygen at 56 d postnatal age or discharge, whichever comes first
Severe BPD	Need for ≥30% oxygen or positive pressure,(PPV or NCPAP) at 36 wk PMA or discharge, whichever comes first	Need for ≥30% oxygen or positive pressure (PPV or NCPAP) at 56 d postnatal age or discharge, whichever comes first

Abbreviations: NCPAP, nasal continuous positive airway pressure; PMA, postmenstrual age; PPV, positive pressure ventilation.

Data from Jobe AH, Bancalari E. NICHD/NHLBI/ORD workshop summary: bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723–9.

BPD was originally described as a complication of respiratory distress syndrome (RDS) and included the influence of 3 key factors: lung immaturity, acute lung injury, and disordered repair of the original lung injury. This classic BPD was noted during an era when mechanical ventilation was just beginning to be used to treat preterm infants with respiratory distress and was characterized by airway injury, smooth muscle hypertrophy, and areas of lung parenchymal fibrosis alternating with areas with emphysematous changes. Improvements in prenatal care, such as the use of antenatal steroids, combined with improvements in respiratory management, such as the use of pulmonary surfactants, have resulted in the successful treatment of increasingly smaller infants with less resulting BPD as it was originally described. However, in lieu of the classic BPD, modern neonatal respiratory care has witnessed the emergence of a new BPD. This new BPD may occur with little acute lung injury, or after resolution of lung injury, and is believed to be affected by other factors such as inflammation (secondary to sepsis or chorioamnionitis) and the presence of a patent ductus arteriosus (PDA).[3,5,6] Compared with classic BPD, preterm infants who have new BPD have decreased fibrosis and emphysema but also have a marked decrease in alveolar septation and microvascular development (**Table 2**).

CLD encompasses both the classic and the new BPD but also recognizes that lung injury can occur not only in preterm infants but in term infants who need aggressive ventilatory support for severe lung disease and develop lung injury as a result. In addition, the term CLD is used to reflect that, although the primary pathology is related to the lungs, CLD is a multisystem disease. Extremely-low-birth-weight (ELBW) infants with CLD suffer not only more pulmonary morbidity but also more neurodevelopmental problems, nutritional deficiencies, and prolonged lengths of hospital stay compared with infants without CLD.[7–9]

CLINICAL PRESENTATION AND PATHOPHYSIOLOGY

On physical examination, infants with CLD have certain characteristic features. Tachypnea with shallow breathing, retractions, and a paradoxic breathing pattern is

Table 2
Classic versus new BPD

Classic BPD	New BPD
Premature and term infants before steroids, surfactants	Very-low-birth-weight and extremely-low-birth-weight infants
Short periods of high ventilatory support: baro- and volutrauma	Modest ventilatory support over months
Hyperventilation with normal or low P_{CO_2}	Permissive hypercapnia but inability to wean off assisted ventilation
Associated with pulmonary air leaks, meconium aspiration syndrome, and pneumonia	Associated with chorioamnionitis, sepsis, PDA; poor nutrition (vitamin deficiencies)
Inflammation, fibrosis prominent; areas of atelectasis alternating with areas of emphysema	Less prominent inflammation, fibrosis; dilated alveolar ducts
Injury/repair sequence	Maldevelopment sequence: ↓ alveolar septation, ↓ alveolar surface area, ↓ microvascular development

Data from Jobe AH, Ikegami M. Mechanisms initiating lung injury in the preterm. Early Hum Dev 1998;53(1):81–94.

common. On auscultation, nonspecific, but atypical, breath sounds that include rhonchi, rales, and wheezes may all be heard. The heterogeneous damage to airways and lungs results in variable time constants and increasing ventilation-perfusion mismatch. Dynamic lung compliance is often diminished secondary to fibrosis and edema.[10] Increased airway resistance of small and larger airways has been reported.[11] Tracheomalacia is often present and may be exacerbated by bronchodilator therapy.[12] As the course of CLD progresses, initial low lung volumes secondary to atelectasis are often at least partially replaced by hyperinflation and gas trapping.

CLD is marked by distortion and dysfunction of the pulmonary circulation in parallel to pulmonary parenchymal injury. Epithelial lesions, fibroblast proliferation, and smooth muscle hyperplasia have been observed. These structural changes result in a pulmonary vascular bed that is markedly reduced compared with normal. Abnormally marked vasoconstriction in response to hypoxia often accompanies these structural abnormalities, further increasing pulmonary vascular resistance.[13] The structural and functional changes contribute to the rapid development of progressive and often severe pulmonary hypertension. This finding, in turn, may lead to poor right ventricular function, diminished cardiac output, and impaired oxygen delivery, and is a predictor of mortality in affected infants.[14] A pathognomonic sign of this end stage of the disease is a thickened protruding tongue, sometimes called ''clubbing'' of the tongue, which is probably caused by the reduced ability of venous blood to return to the thorax (**Fig. 1**). Other cardiovascular abnormalities associated with CLD include systemic hypertension, left ventricular hypertrophy, and development of systemic-pulmonary collateral vessels.[15]

Factors that Affect Pathogenesis of BPD

CLD has a multifactorial cause. Northway and colleagues[1] originally documented the presence of cytotoxic oxygen free radicals and postulated that oxygen toxicity was a major cause of CLD. Mechanical ventilators, although an important tool for management of critically ill newborns, are universally implicated in the development of

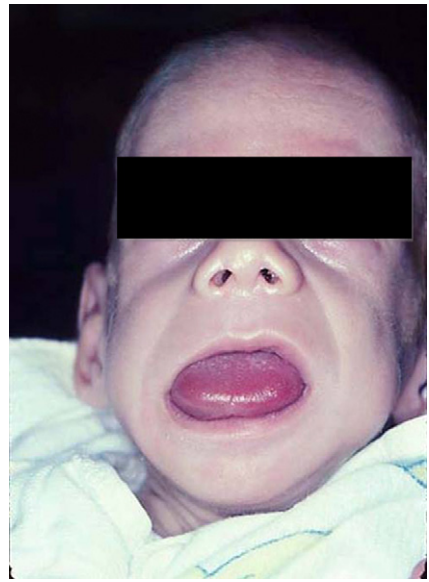

Fig. 1. Clubbing of the tongue seen in end-stage BPD.

CLD.[16,17] Barotrauma and volutrauma from mechanical ventilation combined with oxygen toxicity contribute to inflammatory reactions that contribute to the development of CLD and persist past the immediate neonatal period.[18–21] Inflammation contributing to the development of CLD may also occur after chorioamnionitis, fetal infection, sepsis, and ventilator-associated or nosocomial pneumonia.[22–28] Infection may also exacerbate evolving CLD and result in increased lung injury secondary to release of proteolytic enzymes. The link between fluid overload and the presence of a symptomatic PDA with CLD can potentially be explained by an increased need for mechanical ventilation in these infants.[5] CLD occurs in about one-fifth of ventilated newborns, with risk inversely proportional to birth weight and gestational age. Although most infants developing CLD are premature, about 75% of affected infants have birth weight less than 1000 g and only 5% of those affected have birth weight greater than 1500 g.[29] Genetic factors have been implicated in the severity of acute respiratory disease and the development of CLD.[22,23]

Antenatal factors have also been implicated in the pathogenesis of CLD. Antenatal steroids are believed to be protective from CLD through the amelioration of RDS (although epidemiologic studies do not support this association).[24–26] Inadequate nutrition is believed to lead to decreased alveolar development, impaired surfactant production, and a catabolic state that inhibits growth and repair of the premature lung.

WHY QI TO REDUCE CLD?

Despite the many interventions that have been shown to be efficacious in reducing CLD, the incidence of CLD has remained stable during the past 2 decades.[27,28] The Vermont Oxford Network (VON) 2008 Database Summary reports a 25.5% incidence of BPD at discharge on infants whose birth weight was less than 1500 g. This observation represents a decrease of almost 3% from the previous 3 years in this large cohort of approximately 50,000 infants from 700 centers. Despite this slow but

encouraging drop in the incidence of BPD, many of the reported best practice interventions have not been effectively translated into practice in many neonatal intensive care units (NICUs) in the United States. CLD rates in individual institutions vary from a 5% to 65% incidence within the VON. Risk adjustment for confounders such as birth weight, gestational age, race, antenatal steroid administration frequency, and RDS severity reduce the variation between centers but do not eliminate it. Shrunken estimates that adjust for NICU volume and random variation similarly do not account for all of the wide variation noted. This variation also exists when correcting for the risk of chance. Given that neither case mix (disease severity) nor chance explains the variation that exists between centers, treatment practices must be a large contributing reason behind the variation in outcomes.

Recognition of wide variability in the rates of CLD among centers has existed since the 1980s and persisted into the present decade.[30,31] Van Marter and colleagues's[31] comparison of 2 Boston hospitals with Columbia Babies' Hospital shows the stark differences in approaches to use of mechanical ventilation, surfactant, and nasal continuous positive airway pressure (NCPAP) and the resultant wide variation in BPD rates; however, survival in the comparison institutions was not statistically different (**Fig. 2**). This wide variation in outcomes, even among highly respected centers, which cannot be explained by other factors, is the justification for the use of QI methods as an ideal method for CLD reduction. Because there remains a gap between what is known and what is done, QI programs are increasingly being used as a method for incorporating evidence into practice.

Specific Prevention/Treatment Practices and Their Evidence

When neonatal centers decide to use QI methods in an effort to decrease CLD, they have a myriad of practice options from which to choose. Because many factors contribute to the pathogenesis of CLD, QI efforts typically use a bundle of interventions together; each practice used has varying levels of supporting evidence. Although it might seem intuitive that clinicians would embrace practices supported by the highest level of evidence (LOE), this is not uniformly the case.[32] Any practice to be implemented should be carefully researched and the underpinning evidence should be

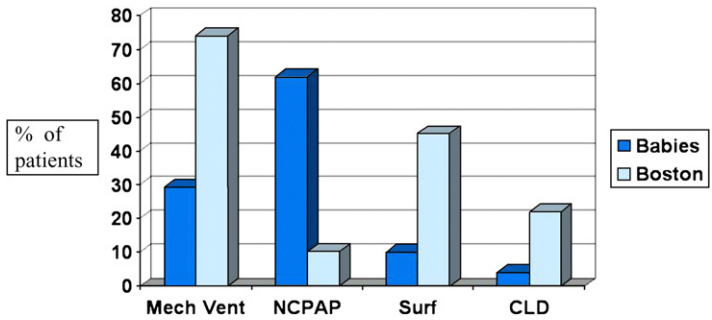

Fig. 2. Variation in practice and outcomes for VLBW infants: Columbia Babies' Hospital (New York) versus 2 Boston hospitals. *Abbreviations:* Mech vent, mechanical ventilation; NCPAP, nasal continuous positive airway pressure; Surf, surfactant use; CLD, chronic lung disease. (*From* Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? The Neonatology Committee for the Developmental Network. Pediatrics 2000;105(6):1194–201; with permission.)

assessed. Because very few practices in neonatology are supported by the highest LOE, these practices are sometimes called potentially better practices (PBPs).

There are several systems for grading the LOE for a practice.[33,34] High LOEs are more likely to yield a true estimate of the effects of an intervention, and lower levels less likely to do so. In such hierarchies, expert opinion, which was historically considered to be the best source of evidence, is relegated to the lowest level. The pinnacle of the hierarchy is now occupied by large, well-designed and conducted, randomized, controlled trials (RCTs), or systematic reviews of multiple RCTs (meta-analysis). However, when attempting to decrease the incidence of a complication such as CLD, which is known to have a multifactorial cause, the effect of 1 or more changes in practice may have no effect on the desired goal even though the practices chosen have a high LOE for a particular outcome. For example, use of prophylactic exogenous surfactant to decrease the severity of RDS and shorten days on mechanical ventilatory support has an LOE of 1 for these outcomes. Intuitively, this effect would seem to also reduce the incidence of BPD, but this intervention alone has not been shown to alter the incidence of this disease.

Many organizations have attempted to categorize LOEs for the systematic evaluation of published scientific manuscripts. The system used by the American Heart Association, modeled on the original Oxford system, is widely used and is seen in **Box 1**.[35]

PREVENTATIVE MEASURES TO LOWER THE INCIDENCE OF CLD: PBPS

This section briefly reviews some of the more common PBPs, which include preventative measures and treatment interventions for CLD. LOEs are noted in parentheses.

Vitamin A (LOE 1)

BPD has multiple causes and influencing factors, including factors inhibiting normal epithelial healing. Vitamin A is an important nutrient during recovery from epithelial lung injury; however, preterm infants have low vitamin A levels at birth.[36] This vitamin A–deficient state may contribute to an increased risk of developing BPD. A Cochrane systematic review examined the effect of vitamin A supplementation in infants with birth weight of 1500 g or less and reported clinical outcomes (death, BPD, long-term neurodevelopmental status).[37] The meta-analysis suggested that supplementation of very preterm infants with vitamin A is beneficial in reducing death or oxygen requirement at 1 month of age (typical risk ratio [RR] 0.93, 95% confidence interval [CI] 0.88, 0.99; risk difference [RD] −0.05, 95% CI −0.10, −0.01; number need to treat [NNT] 20 [10, 100]) and oxygen requirement at 36 weeks PMA (typical RR 0.87, 95% CI

Box 1
American Heart Association: LOEs for therapeutic interventions

LOE 1: RCTs or meta-analyses of RCTs

LOE 2: Studies using concurrent controls without true randomization (eg, pseudorandomization or meta-analysis of such studies)

LOE 3: Studies using retrospective controls

LOE 4: Studies without a control group (eg, case series)

LOE 5: Studies not directly related to the specific patient/population (eg, different patient/population, animal models, mechanical models, and so forth.

0.77, 0.98; RD −0.08, 95% CI −0.14, −0.01; NNT 13 [7, 100]). The results of the meta-analysis are heavily influenced by one multi-institutional study by Tyson and colleagues[38] that is the largest randomized study of vitamin A supplementation reported, having a sample size more than twice that of all other studies combined. This trial included infants with birth weight of 401 to 1000 g. Another trial, by Ambalavanan and colleagues,[39] which compared different intramuscular dosing regimes, suggests that, at least for infants with birth weight between 401 and 1000 g, the optimal dose seems to be 5000 IU 3× weekly for 4 weeks.

Prophylactic or Early Surfactant Treatment (LOE 1–2)

Evidence supports the provision of pulmonary surfactant by prophylactic or early treatment strategies to prevent acute lung injury and to reduce mortality.[40,41] How this translates into improvements in terms of reductions in rates of CLD is less clear. Prophylactic strategies that provide exogenous pulmonary surfactant in the initial 20 minutes of life to infants deemed at risk for developing RDS have shown efficacy at limiting RDS severity, but this gain has not been shown to translate into decreases in rates of CLD (RR = 0.96, 95% CI 0.82, 1.12).[40] Given the clear improvement in initial respiratory status, a reduction in CLD would seem plausible. However, this failure to reduce CLD is, at least in part, a result of the development of CLD among extremely small, ill-surviving infants who might otherwise have died. Although CLD is not reduced, prophylactic surfactant has been shown to be beneficial in increasing survival without CLD (RR = 0.85, 95% CI 0.76, 0.95). Compared with delayed treatment, surfactant administration strategies that deliver surfactant in the first 2 hours of life to patients with established RDS have been efficacious in limiting CLD (RR = 0.70, 95% CI 0.55, 0.88).[41] Because of this finding and the increasing usefulness of CPAP, one viable approach is to attempt to stabilize infants initially on NCPAP and provide early surfactant only if the infants deteriorate.

Antenatal Steroids (LOE 3)

Antenatal steroids have been shown to be remarkably effective at reducing mortality and decreasing RDS; however, these gains have not translated into meaningful decreases in rates of CLD.[24–26] At least 2 mechanisms exist to explain this phenomenon. Antenatal steroids, like pulmonary surfactant administration, may be keeping patients alive who would have otherwise died, but at the cost of developing CLD. A second possible explanation for this lack of effect is that antenatal steroids improve lung function initially, but impair alveolar development.[42] Given that the survival and early fetal lung maturation benefits of maternally administered corticosteroids are well documented, centers should consider perinatal programs aimed at increasing the rates of administration of antenatal steroids to mothers threatening to deliver before 34 weeks' gestation. When administered, betamethasone is preferred, rather than dexamethasone.[43,44]

Optimal Nutrition (LOE 3)

Preterm infants with CLD have nutritional deficits that may contribute to short- and long-term morbidity and mortality. Although no studies exist that examine the effects of increased energy intake, early parental protein, early introduction of lipids, or provision of breast milk for preterm infants with (or developing) CLD, most experts believe that optimal nutritional support is important for premature lung maturation and repair.

Optimal Oxygen Therapy (LOE 2–3)

The optimal target range for blood oxygen tension (Pa_{O_2}) or oxygen saturation (Sp_{O_2}) in premature infants has not been determined, although it is generally accepted that

extremes are injurious.[45] Premature lungs have decreased defense mechanisms against oxygen toxicity. In addition, alveolar macrophages and surfactant-producing type II pneumocytes are adversely affected by hyperoxia. Even low levels of inspired oxygen and arterial Pa_{O_2} levels of 50 to 80 mm Hg are higher than levels in the fetus and potentially toxic. For example, Askie and colleagues[45] compared the effects of standard targeted oxygen saturations (91%–94%) with high saturations (95%–98%) amongst infants born after less than 30 weeks' gestation. The high-saturation group had higher rates of BPD and higher rates of home-based oxygen therapy. In the STOP-ROP trial of higher (96%–99%) versus conventional (89%–94%) pulse oximetry targets, the group receiving higher inspired oxygen had higher rates of BPD, diuretic use, and longer hospital stays.[46]

Both studies evaluated infants who were not in the immediate postnatal period. Early in the course of RDS, expert opinion is not unified as to the optimal oxygen saturation range; however, it is probably appropriate to maintain the oxygen saturation at less than 95% and the arterial oxygen tension at less than 90 mm Hg. If BPD is already established, higher targets may be prudent to avoid the development of cor pulmonale.[47] Compliance with intended pulse oximetry targets is typically poor, with most noncompliance greater than the intended range. Success with maintaining the intended pulse oximeter saturation range has been shown to vary markedly among centers, among patients within centers, and for individual patients over time.[48] Regardless of the intended range of targeted oxygen saturations, it is of vital importance to achieve buy-in and a culture motivated toward compliance among staff at the local grassroots level to achieve the desired target ranges with any degree of consistency.[49]

Conventional Mechanical Ventilation Strategies

All types of mechanical ventilation are injurious to the premature lung. Ventilator-induced lung injury (VILI) is associated with alveolar structural damage, pulmonary edema, inflammation, and fibrosis. Causes of this injury include high airway pressure (barotrauma),[50] excessive gas volumes (volutrauma),[51–53] alveolar collapse and re-expansion (atelectotrauma),[54] and increased inflammation (biotrauma).[55] When using conventional ventilation, a strategy for minimizing lung injury is to limit the duration of mechanical ventilation and provide optimal lung volumes using gentle ventilation techniques, as reflected by moderate permissive hypercapnia. In practice, this entails optimal positive expiratory end pressure (PEEP)[51] for lung recruitment and ventilation with low lung tidal volumes (4–6 mL/kg). Hypocapnia is clearly to be avoided as it has been shown to be associated with increased rates of BPD, intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL).[56–58] A small study by Mariani and colleagues[59] suggested that ventilation strategies amongst very-low-birth-weight (VLBW) infants who had received surfactant and were maintained mildly hypercapnic ($Paco_2$ 45–55 mm Hg) were safe (ie, no increased rates of IVH or PVL) and reduced the duration of mechanical ventilation. A larger, multicenter, randomized trial reported that $Paco_2$ targeted at 52 mm Hg resulted in a reduction in mechanical ventilation at 36 weeks PMA but did not decrease death or BPD.[60]

In the early phase of RDS, it is appropriate to maintain a $Paco_2$ of 45 to 55 mm Hg with a pH greater than 7.20 to 7.25. By postnatal day 3 to 4, metabolic compensation gradually develops, which permits a higher $Paco_2$ for the same pH. Volume-targeted ventilation allows for the peak inflating pressure (PIP) to respond to changes in lung compliance and patient respiratory effort and may deliver desired tidal volumes more consistently at lower pressures.[61] Although targeted tidal volume ventilation may be useful in avoiding injurious over-distention and reduction of hypocapnea, there are no long-term data to support its routine use.[62] Patient-triggered ventilation, when

used in the recovery phase of RDS, significantly shortens the weaning from mechanical ventilation.[63]

Some of the strongest evidence for an effective prevention strategy to decrease BPD includes limiting the duration of mechanical ventilation.[6,31,64] Very premature infants who have been intubated and provided surfactant may often be successfully extubated to NCPAP quickly.[65] A Cochrane systematic review reported that NCPAP reduces extubation failure and BPD.[66] Nasal intermittent positive pressure ventilation (NIPPV) has been shown to increase the effectiveness of CPAP in extubated infants, leading to a decrease in reintubation rates and a trend toward decreased BPD.[67] Administration of methylxanthines, such as caffeine citrate, to very preterm infants for treatment of apnea of prematurity, reduces the need for mechanical ventilation and has recently been shown to significantly reduce need for reintubation and the rate of BPD.[68,69]

High-frequency Oscillation (LOE 3)

The results of RCTs and even meta-analyses of studies of high-frequency ventilation as a primary mode of respiratory support have been inconsistent. The 2 largest neonatal studies that both enrolled infants who received antenatal steroids and surfactant, and that used an alveolar recruitment strategy, had different results.[70,71] Meta-analytical techniques have been similarly conflicting: 1 showed a modest reduction in BPD,[72] whereas another showed no benefit.[73]

NCPAP (LOE 2–3)

CPAP applied at birth reduces lung injury and improves lung volumes after birth.[64] Several observational studies suggest that preterm infants treated with early CPAP have a reduced need for intubation, mechanical ventilation, and incidence of BPD without increasing morbidity.[30,74–79] The COIN trial, which compared outcomes of 25- to 28-week gestation infants receiving NCPAP at birth with those receiving intubation, surfactant administration, and ventilation, showed that not all preterm infants in this gestational age range need to be intubated at birth. Infants receiving CPAP without intubation had a decreased incidence of death or oxygen need at 28 days, although they had similar rates of these outcomes by 36 weeks' gestation.[80] However, infants treated initially with CPAP who failed and required intubation, had a higher incidence of pulmonary air leaks. Ammari and colleagues[74] reported that larger preterm infants (751–1250 g) were more successful (76% did not require intubation) when stabilized on CPAP than smaller ones. Fifty percent of the smaller infants in that study (<751 g) ultimately required intubation. Evidence also suggests that infants treated with early CPAP who also have higher oxygen requirements (F_{IO_2}>45%) have reduced complications if transiently intubated and treated with surfactant.[81] Technique and experience applying the NCPAP prongs with a snug fit and using a chin strap to minimize air leak influence success. The VON Delivery Room Management study (DRM) was designed to compare the effects of 3 distinct methods of postdelivery stabilization and subsequent respiratory care on BPD and survival in premature infants at high risk of RDS. The 3 approaches to postdelivery care include (1) intubation, prophylactic surfactant administration shortly after delivery, and subsequent stabilization on ventilator support; (2) early stabilization on CPAP with selective intubation and surfactant administration for clinical indications; and (3) intubation, prophylactic surfactant administration shortly after delivery, and rapid extubation to CPAP. Until the results of this and other trials are completed, a strategy of applying NCPAP selectively to spontaneously breathing VLBW infants with characteristics suggesting sufficient surfactant pools and success on CPAP should be considered. The selection of these

patients is crucial, because omitting intubation and surfactant administration may allow the development of atelectasis and a higher risk of pneumothorax if intubation is required. Patient selection for CPAP alone should consider gestational age, weight, completion of antenatal steroids, presence of infection (chorioamnionitis), and signs of asphyxia, all factors that affect the production of endogenous surfactant.

T-Piece Resuscitator (LOE 3)

In the delivery room, clinicians are prone to contributing to volutrauma secondary to vigorous ventilation of infants transitioning poorly. Uncontrolled excessively large or small tidal volumes are injurious to the developing lung. Measuring and controlling tidal volumes in the delivery room, including the use of a T-piece resuscitator, may be desirable but are unproven in terms of prevention of CLD.[17,82,83]

Treatment of Symptomatic PDA (LOE 3)

The presence of a symptomatic PDA in VLBW infants has been shown to be predictive of the need for supplemental oxygen and prolonged ventilation.[84] Treatment of a symptomatic PDA has been shown to prevent the decrease in alveolar septation and microvascular development that characterizes the new BPD but has not been shown to reduce the risk of developing BPD.[85] Surgical closure of a symptomatic PDA increases the risk of BPD and is associated with adverse neurodevelopmental outcomes.[86] However, this finding may be because of the adverse selection of infants who require surgical, as opposed to pharmacologic or medical, treatment alone.

Fluid Restriction (LOE 3)

Excessive intravenous fluid administration, colloid administration, and early sodium supplementation increase the risk of CLD.[87,88] In addition, infants who lose less weight and receive more intravenous fluids immediately after birth have an increased risk for development of CLD.[89,90] However, it is not clear that fluid restriction reduces the incidence of BPD.[91] Given these data, careful restriction of water intake so that physiologic needs are met without allowing significant dehydration seems prudent.

Prevention from Infection (LOE 2–3)

Nosocomial bacteremia increases the risk of developing CLD.[92,93] Nosocomial pneumonia contributes to increased lung injury and BPD secondary to polymorphonuclear leukocyte infiltration and release of protelolytic enzymes.[94] Prevention of sepsis or pneumonia will result in decreased inflammation and decreased time on mechanical ventilation and should be a goal of every center. Programs to reduce ventilator associated pneumonia (VAP) have been advocated and commercial bundles are marketed; however, no data have shown that these programs reduce the incidence of CLD.

Methylxanthines (LOE 1)

Traditional pharmacologic intervention for apnea of prematurity has included methylxanthine medications, such as caffeine citrate. These medications decrease the frequency of apnea events and decrease the need for reintubation and mechanical ventilation.[68] Recently, it has been shown that these short-term gains also translate into long-term benefits. In a well-conducted study of 2006 infants, Schmidt and colleagues[69] reported the effect of caffeine citrate, administered to infants born weighing between 500 and 1250 g, for any of the following purposes: to prevent apnea, to treat apnea, and to facilitate extubation. This study reported decreased time on ventilatory support, decreased oxygen use, decreased corticosteroid administration, and decreased need for transfusions. Most importantly, a significant

reduction in the rate of development of BPD (adjusted odds ratio [OR] 0.64, 95% CI 0.52–0.78) was noted in the treatment group.[69]

Postnatal Corticosteroids

Few interventions for CLD have received as much attention and controversy as the administration of corticosteroids to premature infants. Studies have reported that inhaled and systemic steroids improve lung mechanics and gas exchange and reduce inflammation.[95,96] Systemic corticosteroids have been used early ($\leq$7 days) to prevent the development of CLD and late (>7 days) to treat established lung disease. Early and late corticosteroids significantly reduce the incidence of CLD.[97,98] However, there are important concerns regarding adverse events associated with systemic steroids. Although immediate pulmonary benefit is realized, increased alveolar simplification is reported.[99] Other adverse events include systemic hypertension, hypertrophic cardiomyopathy, infection, hyperglycemia, gastrointestinal bleeding, and perforation.[97,98,100] In addition, long-term follow-up studies of infants who received early steroids report an increased risk of abnormal neurologic examination and cerebral palsy.[97] However, major neurosensory disability, and the combined rate of death or major neurosensory disability, were not significantly different between steroid and control groups in infants randomized to receive late steroids.[98] The adverse events associated with steroids are generally based on data from studies that used high doses of dexamethasone for long periods of time and questions remain over the potential safety of other steroids and for smaller doses given for shorter periods of time.[15,101] Because of concerns regarding these adverse events, the American Academy of Pediatrics and the Canadian Pediatric Society recommended against the routine use of systemic steroids to treat or prevent CLD.[102] The clinician must weigh the potential risks of short-term late or rescue use of steroids versus the potential benefits of potentiating extubation in those infants who are still ventilator dependent or on high concentrations of inspired oxygen after several weeks of therapy.

To avoid the adverse effects of systemic steroids, inhaled steroids have been tested and found to have no significant advantage with respect to prevention or treatment of CLD compared with systemic steroids.[103,104] No long-term neurodevelopmental outcome data are available regarding inhaled steroids. One trial reported a decrease in the perceived need for systemic steroids after inhaled steroid administration.[105]

Other Potential Better Practices to Reduce BPD

Several other practices have been proposed to reduce the incidence of BPD in an individual hospital. These include practices which are difficult to test and for which there are few data. Some of these practices include Golden Hour care, during which the resuscitation team for a VLBW infant has a scripted protocol for resuscitation and the team is graded in some standard way after the first hour of life; standard protocols for ventilatory management; standard extubation criteria; avoidance of unplanned extubation; standard nutritional protocols; and others. Each of these has some scientific rationale, but none has been shown to individually reduce the incidence or severity of BPD. However, the involvement of the entire NICU team in QI protocols establishes a unit rapport, identifies problem outcomes, and heightens the awareness of members of the care team to new techniques and methods of care. Here the Hawthorne effect may be advantageous even if the individual PBP is not.

QI: METHODS FOR IMPLEMENTATION AND SUCCESS

The Institute for Health Care Improvement (IHI) first adopted and described many of the QI methods widely used. These landmark methods, called the Breakthrough Series, showed how collaborative improvement models bring health care professionals together to focus on the gap between evidence-based practices and implementation of these practices, and to accelerate the pace of improvement in their organizations.[106] Key to any QI movement is multidisciplinary grassroots involvement and effective leadership. Successful QI efforts require conscious emphasis on 4 key habits as described by Plsek.[107] The first of these is to view the clinical process at hand as a system that involves many factors and many participants. Understanding that any improvement strategy is a complex process or system that involves multiple disciplines and influences is vital to making meaningful change. The second habit, fostering teamwork from a variety of disciplines to improve collaborative learning, has been shown to hasten implementation and success of QI efforts.[108] Meetings, conference calls, Internet meeting rooms, and list serves are all integral to the success of any QI movement. A fun and social atmosphere can be important in energizing the process. The third habit involves the need for adoption and adherence to evidence-based practice. Understanding the importance and the limits of the literature behind any potential change in practice is compelling. The habit for change should be embraced. Significant resistance to change will uniformly exist in almost all cultures. Centers that embrace change will be more successful in terms of initiating change. Because the QI process is a progressive, repetitive process, Plan-Do-Study-Act (PDSA; see the article by Ellsbury and Ursprung elsewhere in this issue) cycles are frequently used.[109] These cycles are frequently embraced by QI teams and emphasize continuous improvement through change, analysis of this change, and feedback.

QI requires consistent accurate data on performance and outcomes. Data from an individual hospital's NICU are essential in identification of individual practices and outcomes that need improvement. Comparisons of outcomes and processes with those of high-performing centers (benchmarking) and with large databases are important to the improvement process. The comparison databases to which centers may have access include those available from the California Perinatal Quality Care Collaborative (CPQCC), the National Association of Children's Hospitals and Related Institutions (NACHRI), the National Institute for Child Health and Development (NICHD), the Pediatrix Medical Group Data Warehouse, and the VON.

The VON NIC/Q Experience

The VON has participated and led several successive QI collaborative efforts framed around the IHI method, called NIC/Q. These collaboratives have often focused on improvement of respiratory care practices to reduce CLD. The initial VON NIC/Q collaborative represented the initial use of QI in neonates.[110] Participating hospitals received instruction in QI, reviewed performance data, identified common improvement goals, and implemented PBPs developed through analysis of the processes of care, literature review, and site visits. The term PBP was chosen to indicate that, although the interventions had supporting evidence and internal validity, they needed to be proven effective via implementation and local customization.

The initial NIC/Q experience identified 9 PBPs adopted by 4 participating centers and showed a 12% decrease in CLD, although significant heterogeneity of outcome was noted. The 2000 NIC/Q Collaborative that focused on reduction in CLD was successful in identifying and implementing 9 PBPs but did not document improvement in the rates of CLD.[106,111,112] The 2002 NIC/Q group, also referred to as the

Breathsavers Group, identified and implemented 13 PBPs. They noted improvements in process outcomes including time on mechanical ventilation, steroid use, time to initial surfactant administration, and increased use of NCPAP. These changes were responsible for a decrease in the rates of CLD in 14 of 18 participating centers and a 27% overall reduction in the incidence of CLD between 2001 and 2003 in a cohort of approximately 1800 infants per year.[113,114] Among the NIC/Q collaboratives aimed at reducing CLD, individual centers had markedly varying results. Some participating NICUs witnessed paradoxic increases in CLD rates; however, these centers were often among the hospitals with the lowest rates of CLD at the outset, reflecting a regression toward the mean phenomenon. The question of why the NIC/Q 2002 collaborative was successful may potentially be explained by several factors. The PBPs identified were different from those selected by the NIC/Q 2000 group and had critically appraised evidence. In addition, the NIC/Q 2002 group members benefited from previous experience in the VON QI process. Many of the participant hospitals had participated in the initial NIC/Q effort and NIC/Q 2000.

Other Groups

Other groups have documented and published their attempts to reduce CLD using similar QI methods. One recent study by Birenbaum and colleagues[115] described the experience of one center that compared cohorts before and after changes in clinical management implemented in their hospital by using QI methods. Although this center did not participate in the VON Breathsavers Group, their focused interventions were similar to those adopted by many centers in the VON Group: lower, tighter pulse oximeter limits; a selective intubation and prophylactic surfactant policy; delivery room stabilization using CPAP via T-piece resuscitator; and initial treatment in the NICU with NCPAP. The group was successful in terms of improvement in process outcomes: more use of the T-piece resuscitator in the delivery room, more use of NCPAP delivered in the delivery room, and less time on the ventilator. These changes may have contributed to a reduction in the incidence of CLD in the center from 46.5% in 2002 to 20.5% in 2005, representing an overall relative risk reduction of 55.8%. Limitations of the study are that it is an unblinded retrospective cohort review from a single center. In addition, because it was a before-and-after study, the possibility exists that other unrecognized changes were taking place concurrently with the study.

A second recent attempt to use QI methods to decrease CLD has been documented by Nowadzky and colleagues.[116] This group focused on implementation of a single intervention, use of nasal bubble CPAP to facilitate a reduction in mechanical ventilation and ultimately a reduction in CLD. This group was successful in implementing the planned intervention: more infants received bubble NCPAP during the study period. This clinical change did translate into a reduction in the use of conventional ventilation but did not yield an improvement in the incidence of CLD. However, an increase in the rates of ROP was observed. This study is similarly limited by its designs as an unblended retrospective cohort review from a single center. It should be noted that the study occurred in a center at high altitude (Denver, CO, USA), where the incidence of BPD defined by the need for oxygen at 36 weeks PMA is much higher than at sea level.

There is inherent difficulty in limiting the exposure to bias that comes with retrospective studies. Many different factors may inject bias into a model. In addition, it is often difficult for a center to concurrently provide 2 varying methods of caring for an infant. Because of these limitations, several prospective cluster-RCTs, which use single NICU centers instead of individual patients as the unit of randomization, have been performed. The earliest attempt of cluster trial techniques to test QI methods in reducing CLD was performed by the VON. They conducted a cluster-RCT that tested

whether centers that were exposed to a multifaceted collaborative QI intervention could be successful in earlier surfactant administration and thereby reduce CLD.[117] One-hundred and fourteen member hospitals (which treated 6039 infants of 23–29 weeks' gestation) within the VON participated in the trial. The intervention consisted of audit and feedback regarding surfactant administration practices, evidence-based workshops with didactic sessions and QI exercises, and collaboration with participating centers via conference calls and an e-mail discussion list. Compared with infants from control hospitals, infants in the intervention hospitals received their first dose of surfactant sooner after birth (median time of 21 minutes vs 78 minutes, $P<.0010$).[117] The intervention did not create a statistically significant change in the rate of CLD or mortality, but was successful at changing the behavior of neonatologists toward more evidence-based practice.

The National Institute of Child Health and Human Development Neonatal Research Network published the findings of a cluster-randomized trial of benchmarking and QI techniques for high-risk infants in 2007.[118] This study contained 17 centers within the network and enrolled 4093 infants with birth weight less than 1250 g. Three of the 17 centers were identified as best performers based on their high rates of survival without CLD. These centers were used as benchmarks; their respiratory practices were examined and emulated at 7 centers (the intervention group) using QI methods. Seven other centers did not initiate a respiratory QI program (control centers). Intervention centers were successful in implementing PBPs that were similar to the benchmark centers, including reduced oxygen saturation targets and reduced exposure to mechanical ventilation. Changes in rates of survival free of CLD between the 7 intervention centers and 7 control centers were not observed in the 3-year study period.

A third cluster trial to reduce CLD was published in 2009 that tested QI methods emphasizing the role of evidence in QI.[119] Twelve NICUs in the Canadian Neonatal Network participated in the study; 6 aimed at reduction of nosocomial infection and 6 focused on reduction of CLD. Infants in the group attempting to limit infection were used as the control comparison for the CLD group and vice versa All infants born at less than 32 weeks' gestation were included. The participant hospitals in the study used a method (the Evidence-based Practice for Improving Quality) that focused on critical appraisal of evidence and examination of individual hospital data to identify hospital-specific practice changes and strategies. The study ran for 3 years and enrolled 3070 infants in the arm dedicated to reduction of CLD. No decrease in the rate of CLD was observed in the nosocomial infection (control) group but in the pulmonary group, a 15% decrease from baseline was observed in the study period. The investigators concluded that their QI method is effective in reducing the incidence of CLD in NICUs. The study was halted before the goal sample size and 1 large NICU withdrew from the study while it was ongoing. In addition, the potential for the Hawthorne effect (the effect that being observed has on the behaviors of individuals and the potential for bias) in this study limits its generalizability. Nevertheless, this report represents the first study to incorporate QI methods using a cluster trial technique, with the hospital as the unit of reference, to successfully reduce the incidence of CLD.

WHY HAVE QI INITIATIVES NOT BEEN UNIFORMLY SUCCESSFUL IN REDUCING CLD RATES?

Controversy exists on whether QI techniques can be successful on disease processes with heterogeneous causes and influences such as CLD. QI methods have given mixed results when studied systematically. Estimates of the effectiveness of specific

QI strategies may be limited by difficulty in classifying complex interventions, insufficient numbers of studies, publication bias, and selection bias.[120]

There are multiple contributing factors to the development of CLD. Nonetheless, the wide disparity of center-based BPD incidence (varying in the VON databank by a factor of 10) of a fairly homogenous population of premature infants (birth weight 400–1500 g) seems to highlight the varying implementation of evidence-based practices in individual hospitals. Clinicians may be hampered by the choice of multiple possible interventions and treatment strategies to reduce the incidence of BPD. Controversy exists on whether QI methods that implement multiple interventions will be effective in limiting pathology with multiple causes. Methods for continuous QI have been used to improve and change processes more easily and consistently than outcomes. Complex outcomes, such as CLD, often require changes in multiple practices over an extended hospitalization that involves multiple disciplines and caretakers. It may be that PBPs taken from the benchmarking centers with admired outcomes may not be beneficial to each center with less-than-desired outcomes. This concept may be especially possible in the cases for which only weak supporting evidence exists to support these practices. Of the multitude of interventions, processes, and strategies implemented by any given center, it is unknown which (or what combinations) contribute to improved outcomes. Critical appraisal of evidence is thereby of utmost importance. In addition, the importance of local customization of individual practices cannot be overemphasized. Interventions or strategies useful in one setting may not make clinically significant improvements in a separate setting. Lastly, centers aiming toward QI are susceptible to the Hawthorne effect: the NICUs that chose to participate in QI projects are self-selected, highly interested and motivated, and willing participants. Improvement in performance, especially in terms of intermediate and process measures, is noted when performance receives additional scrutiny. As noted earlier, these intermediate performance measures will not always translate to improved outcomes. Accordingly, caution in generalization of QI findings is encouraged. Finally, QI methods toward improvement in CLD or any other outcome should not be considered as a substitute for formal RCTs but as a tool for implementing evidence and studying the effects of change in complex adaptive systems.[121]

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