Evaluation of the Local Incidence and Determinants of Bronchopulmonary Dysplasia and Pulmonary Morbidity in Extremely Preterm Infants

by

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Dedication

For my husband and my wonderful two boys who inspire me every day to grow and learn.

Abstract

Prevention and management of bronchopulmonary dysplasia (BPD) and resulting pulmonary morbidity remains one of the greatest challenges of neonatal intensive care. This study of infants from northern and central Alberta had three goals: first, to estimate the incidence and risk factors contributing to the development of BPD; second, to estimate the incidence and risk factors contributing to the development of pulmonary morbidity in early infancy; and third, to evaluate the use of two specific early scoring systems in the prediction of BPD and early pulmonary morbidity.

Methods: This observational prospective study was conducted on a cohort of 103 premature infants born at < 29 weeks gestational age or birth weight ≤ 1250 grams who were discharged from the Royal Alexandra Hospital, Edmonton, Alberta from August 1, 2008 to July 31, 2009. Hospital data were collected retrospectively through patient chart review and telephone and in person questionnaires administered when the study subjects were three and six months adjusted age. The incidence of bronchopulmonary dysplasia, defined as mild if oxygen was needed at 28 days of life, moderate if <30% supplemental oxygen was needed at 36 weeks post-menstrual age and severe if >30% oxygen was needed, the infant required ventilator support at 36 weeks post-menstrual age or oxygen support was required at hospital discharge. Maternal, antenatal and post-natal risk factors, including two pulmonary scoring systems: the Chronic Oxygen Dependency (COD) Score and the Pulmonary Severity (PS) Score, were evaluated by logistic regression in the prediction of BPD and pulmonary morbidity in early infancy. Infants in this cohort

were evaluated for the presence of major pulmonary morbidity in the first 6 months post-discharge, including 1) death from a pulmonary cause; 2) pneumonia or sepsis with a positive blood culture or requiring antibiotics for 5 days or more; 3) continued hospitalization or rehospitalization for a pulmonary cause; 4) continued use of oxygen, diuretics or systemic steroids for pulmonary disease; or 5) use of pulmonary medications, including systemic or inhaled bronchodilators and/or corticosteroids or leukotriene receptor antagonists.

Results: Overall incidence of moderate to severe BPD was 44.7%. In the univariate analysis, significant risk factors included lower gestational age, birth weight and male gender. Apgar scores at 1 and 5 minutes were significantly lower for infants developing moderate or severe BPD and these infants were significantly less likely to have received antenatal corticosteroids. When controlling for antenatal and postnatal variables, such as duration of ventilation and presence of retinopathy of prematurity, pulmonary scores applied at days 2 and 7 were not significantly associated with the development of BPD. Overall, at 3 months 20.5% of infants were reported as having one or more of the above morbidities. Similarly, 24.5% of infants with six-month follow-up data were reported as having one or more of the above morbidities. In the multivariate analysis, risk factors associated with pulmonary morbidity at six months corrected age included the presence of moderate to severe BPD, younger maternal age, duration of invasive and non-invasive ventilation, COD score at day 7 and history of atopy. The COD and PS scores were significant predictors of pulmonary morbidity at 6 months corrected age, but the prediction improved when applied at 2 days of age compared with scoring at day 7, however

the prediction of pulmonary morbidity was not significant at 6 months when controlling for other risk factors.

Conclusion: In spite of improvements in neonatal care, the incidence of bronchopulmonary dysplasia remains high in infants requiring prolonged ventilation in spite of improvements in neonatal care. Infants born prematurely are at risk for pulmonary morbidity in early infancy however early prediction models are of limited clinical utility.

Preface

This thesis is an original work by Amber E. Reichert. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name “Bronchopulmonary Dysplasia”, Pro00003364. No part of this thesis has been previously published.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
BLES	Bovine Lipid Extract Surfactant
BPD	Bronchopulmonary Dysplasia
CI	Confidence Interval
COD	Chronic Oxygen Dependency (score)
CPAP	Continuous Positive Airway Pressure
CT	Computed Tomography
GA	Gestational Age
GBS	Group B *Streptococcus*
HFOV	High Frequency Oscillatory Ventilation
FEV_1	Forced Expiratory Volume in 1 second
FOT	Forced Oscillation Technique
FVC	Forced Vital Capacity
iNO	inhaled Nitric Oxide
INSURE	Intubation, SURfactance, Extubation
IPPV	Intermittent Positive Pressure Ventilation
IUGR	Intrauterine Growth Restriction
IVH	Intraventricular Hemorrhage
LFNC	Low Flow Nasal Cannula
NCPAP	Nasal Continuous Positive Airway Pressure
NEC	Necrotizing Enterocolitis
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal Intensive Care Unit
NIPPV	Nasal Intermittent Positive Pressure Ventilation
NPIPPV	NasoPharyngeal Intermittent Positive Pressure Ventilation
OR	Odds Ratio
PDA	Patent Ductus Arteriosus
PDI	Psychomotor Developmental Index
PEEP	Positive End-Expiratory Pressure
PIP	Positive Inspiratory Pressure

PPV	Positive Pressure Ventilation
PS	Pulmonary Severity (score)
RDS	Respiratory Distress Syndrome
RFS	Respiratory Failure Score
ROC	Receiver Operating Characteristic (curves)
ROP	Retinopathy of Prematurity
RSV	Respiratory Syncytial Virus
VLBW	Very Low Birth Weight

CHAPTER 1:
Bronchopulmonary Dysplasia in Premature Infants

1.1 Bronchopulmonary Dysplasia

Premature infants are at increased risk for developing bronchopulmonary dysplasia (BPD), a disorder of respiratory function defined by a persistent need for supplemental oxygen beyond the neonatal period (1). In addition to preterm birth, many factors contribute to increased risk, including baseline differences in genetic and somatic susceptibility and exposure to protective or harmful intrauterine and post-natal factors (2). In addition to low birth weight and gestational age, many other risk factors have been identified that result in inflammation, such as invasive ventilation and infection. These risk factors have a role in lung injury and the development of BPD. The purpose of this research is to evaluate the incidence of BPD in a local cohort of extremely premature infants and to determine the relative influence of key risk factors that occur in the perinatal and post-natal environment.

BPD is a well-known cause of lung morbidity in the preterm population, however the extent of pulmonary morbidity in the early post-discharge time period is quite variable. This study will also be used to evaluate the relative incidence of pulmonary morbidity and risk factors in addition to BPD that are related to pulmonary morbidity during the first 6

months of life. A further goal of the study is to evaluate the ability of simple clinical scoring tools applied early in the neonatal period in the prediction of BPD and early pulmonary morbidity.

Diagnostic criteria for BPD have changed over time with technological advances in ventilation and better understanding of the role of perinatal and post-natal risk factors in pathogenesis and management. Through the 1970s to mid 1990s, BPD was defined as persistent oxygen need at 28 days of life (3,4). In more recent decades, the definition has changed with descriptions of degrees of BPD severity based on ventilation support at different time points in the neonatal period, with less emphasis on radiographic changes as a requirement for diagnosis (5-7). In a landmark paper, Shennan, Dunn and Lennox demonstrated that oxygen and ventilation needs at 36 weeks adjusted age in infants with birth weights of 1500 grams or less was more predictive of abnormal lung function in the first two years of life than oxygen and ventilation needs during the first 28 days of life (5). Although improved care practices have led to the survival of increasingly immature infants, the incidence of BPD has changed little in the past few decades, ranging from 23 to 46% in infants born below 29 weeks gestational age (8-12). Over time, trends in neonatal care such as increasing use of antenatal corticosteroids and post-natal surfactant have resulted in increasing survival of the smallest and lowest gestational age infants (8). Improvements in care may also improve rates of BPD in older infants, but with increasing survival of smaller infants, the overall rate of BPD is relatively unchanged (8,9). In addition, the

use of potentially harmful therapies that may have improved the rates of BPD, such as post-natal corticosteroids and lower oxygen targets have decreased in recent years due to increased risk of disability and death (11,13). The use of individualized lung-targeted therapies such as antenatal corticosteroids, post-natal surfactant, with early extubation, and gentle or non-invasive ventilation strategies are of prime importance in the medical care of very premature infants reducing early illness severity and improving survival but at the potential cost of higher overall rates of morbidities such as BPD (8,12).

Premature infants with and without a history of BPD are at increased risk for chronic respiratory morbidity, including recurrent hospitalization, chronic dependency on bronchodilators and corticosteroid therapy, reduced activity tolerance and athletic ability and increased risk of chronic obstructive pulmonary disease (14). The use of validated scoring criteria applied early in the neonatal period may facilitate early recognition of infants at higher risk for BPD and pulmonary morbidity. Validated scoring systems would allow for targeted management strategies that optimize the use of potentially harmful therapies, such as postnatal corticosteroids. Critical review of changes in practice will enable caregivers to assess the effects of changing care strategies over time and determine if rates of BPD are changing and if long term pulmonary outcomes are improved.

1.2 Defining BPD

Over time, as understanding of the pathophysiology and consequences of BPD have increased and management strategies have been refined, the criteria for diagnosing BPD have evolved. Historically, the term "bronchopulmonary dysplasia" was used to describe clinical, radiographic, and histopathologic changes seen in the lungs of infants dying from the complications of prematurity (3,15). Advances in the understanding of how lung development is affected by premature birth have led to improvements in neonatal resuscitation and management, and consequently lower morbidity and mortality (15). For example, researchers evaluating the use of room air during resuscitation compared with the use of 100% inspired oxygen in order to decrease early oxidative stress found that BPD rates were significantly reduced from 25% to 7% in infants born between 24 and 34 weeks gestation (16). Improvements in clinical care, especially in ventilation strategies, have increased survival of very early preterm infants resulting in a different clinical picture of lung disease compared with that described in 1967 (15).

In 1989, in an attempt to standardize diagnostic criteria for BPD, the BMCHRD Guidelines were generated (1). They included:

1. positive pressure ventilation during the first two weeks of life for a minimum of three days;
2. clinical signs of respiratory compromise persisting longer than 28 days of age;

3. requirements for supplemental oxygen longer than 28 days of age to maintain a P_aO_2 above 50 mmHg;
4. chest radiographs with findings characteristic of BPD (1).

However, these guidelines were problematic because determining ventilatory need in the first two weeks of life and interpreting radiographic findings were subjective and based on the clinical judgment of the attending physician. As more extremely preterm infants survive our understanding of the pathophysiology of the disease has progressed but the clinical definition of BPD has become more challenging (7,17,18). The definition was revised in 2001 at the National Institute of Child Health and Human Development /National Heart, Lung and Blood Institute/Office of Rare Diseases Workshop, such that infants born before 32 weeks gestation were classified based on need for supplemental oxygen at 28 days and either 36 weeks post-menstrual age or at discharge (Table 1-1) (7).

Today, the term BPD commonly refers to the clinical picture of prolonged oxygen dependency after premature birth; an alternative, equivalent term is “chronic lung disease of infancy” or “neonatal chronic lung disease” (7). Clinicians continue to rely on physiologic parameters such as arterial saturation and clinical assessment of overall health and nutritional status to determine need for supplemental oxygen (7). The 2001 NICHD/NHLBI/ORD has simplified the definition of BPD, basing it solely on the use of supplemental oxygen; however, this has not eliminated the subjective nature of determining which infants need oxygen or ventilation

support and how much support should be provided (7). More recently a physiologic definition of BPD has been proposed using an oxygen reduction test with oxygen saturation monitoring to provide a more objective evaluation of oxygen dependency at 36 weeks corrected gestational age (9,10).

Table 1-1. NICHD/NHLBI/ORD Definition of BPD in Infants Born <32 Weeks Gestation

(modified from: (7)**)**

	Assessment at 28 days	**Assessment at 36 weeks PMA or Discharge Home**
No BPD	breathing room air	breathing room air
Mild BPD	need for oxygen > 21%	breathing room air
Moderate BPD	need of oxygen > 21%	need for <30% oxygen
Severe BPD	need for oxygen > 21%	need for ≥30% oxygen and/or positive pressure (PPV or NCAP)

1.3 Incidence of BPD in North America and Regionally

Advances in the care of the preterm lung have resulted in an expectation that the incidence of BPD would improve over time, however it seems to vary more with birth weight than with the decade when the care was provided. Since the early 1980s the use of antenatal corticosteroids, postnatal surfactant and gentle ventilation strategies increased; however, the incidence of BPD continued to be high, ranging from 29% to 52% of infants with birth weights under 1000 grams (8,19,20). The Caffeine therapy for apnea of prematurity (CAP) trial demonstrated similar rates of BPD in babies born < 1250 grams between 1999 and 2004: 48% and 36% in the placebo and caffeine treatment groups respectively (21). In a randomized, double-blind, placebo-controlled trial of inhaled nitric oxide conducted between 2000 and 2005, infants with birth weight< 1250 grams had an incidence of BPD of 50.7% in the treatment group versus 56.9% in the placebo group, though these infants were selected for this study based on a need for ventilation, which may have introduced bias into the results (22). Data from the Canadian Neonatal Network also demonstrate the inverse relationship of BPD rates with birth weight (23,24). Overall, 26% of infants with birth weights of < 1500 grams developed BPD; with the highest rate (54%) in those at the lowest birth weights (23). Contrary to the expectation of improved outcomes over time, results from the Canadian Neonatal Network (CNN) database demonstrated that oxygen dependency at 36 weeks post-menstrual age in infants born less than 29 weeks gestation increased

from 34.7% in 1996-97 to 46.1% in 2006-07 in 15 Canadian Neonatal Intensive Care Units, possibly due to higher rates of infants with exposure to partial antenatal corticosteroid treatment, higher rates of cesarean delivery and sicker infants as reflected by lower SNAP scores (12). In Edmonton, the overall incidence of BPD in the period from 1997 to 2003 was 31% for infants born between 24 and 29 weeks gestation, with approximately 83% of mothers receiving antenatal corticosteroids (retrospective review of inborns < 1250 grams from the Royal Alexandra Hospital – personal communication, L. Hendson). The incidence continues to be inversely proportional to gestational age with rates as high as 50-70% in infants born between 24 and 26 weeks gestation decreasing to 10% at 29 weeks gestation (local review of data – personal communication, L. Hendson). There is some evidence that the use of benchmarking may reduce overall incidence of bronchopulmonary dysplasia. Using the Evidence-based Practice for Improving Quality (EPIQ) method, CNN investigators demonstrated that a reduction in the baseline risk of BPD does occur when specific management practices targeting organizational culture are implemented and compared between geographically separate neonatal units (25)

1.4 Pathogenesis of BPD

Injury to developing lungs is thought to arise from the combined effects of structural and functional immaturity and is affected by inflammatory mediators such as barotrauma, volutrauma, oxygen toxicity and infection. The complex interplay of these factors leads to a chronic

disease state balanced between ongoing tissue development and the scarring and fibrosis resulting from reparative processes (3,26,27). With Northway's historical classification of BPD, which was based on radiographic features and clinical symptomatology, infants developing BPD had a characteristic pattern of apparent resolution of respiratory distress syndrome if they were supported with intensive ventilation and supplemental oxygen (3). These infants then developed clinical pulmonary morbidity with cyanosis and typical cystic changes on chest radiographs (3). Lung histology showed abnormal and hyperactive development of the bronchial and bronchiolar mucosa and of the vascular bed and associated signs of inflammation and edema (28). Many infants died during this phase; survivors gradually improved but continued to have abnormal chest radiographs with patchy areas of increased lucency interspersed with areas of increased density (3).

Advances in antenatal care and postnatal resuscitation and ventilation practices have reduced the incidence of pulmonary sequelae in the larger preterm infant such that these infants no longer follow the pattern described by Northway et al. and have also resulted in improved survival of infants born at earlier gestations (29-31). Today, this pattern of pulmonary morbidity is rare in neonates born after 30 weeks gestation with birth weights above 1200 grams but can occur in infants with lower birth weights and gestational ages (7,31). Very low birth weight infants are in better condition after delivery as a result of antenatal corticosteroid therapy, postnatal surfactant and standardized resuscitation practices; they require

less invasive ventilation and lower levels of supplemental oxygen initially, however, the inverse relationship between gestational age and risk of BPD persists, suggesting that lung immaturity is an important factor in pathogenesis, independent of ventilator-induced or oxygen-related injury (29,32,33).

1.4.1 The Role of Lung Development in BPD

Animal and post-mortem data indicate that abnormal or delayed angiogenesis and interruption of alveolar growth and arborization are important factors in the pathogenesis of BPD (29,34,35). Lung development through the second and third trimester involves differentiation of conducting airways into gas-exchanging airways by primary and secondary alveolarization from the pseudoglandular phase through to the alveolar phase (7,36,37) (See Figure 1-1). Growth and development of lung architecture depends on complex interactions between the alveolar epithelium and vascular endothelium for normal branching and development of both the alveolar and supporting capillary bed, and for support of the maturation of type I epithelial cells that form the gas exchange surface in the lungs (36,38). Along with airway development, the pulmonary vascular bed undergoes a parallel process of arborization and expansion (7,38). The complex relationship between angiogenesis and alveolar development depends on many factors including the expression of vascular endothelial growth factor, production of nitric oxide and synthesis of angiopoietin;

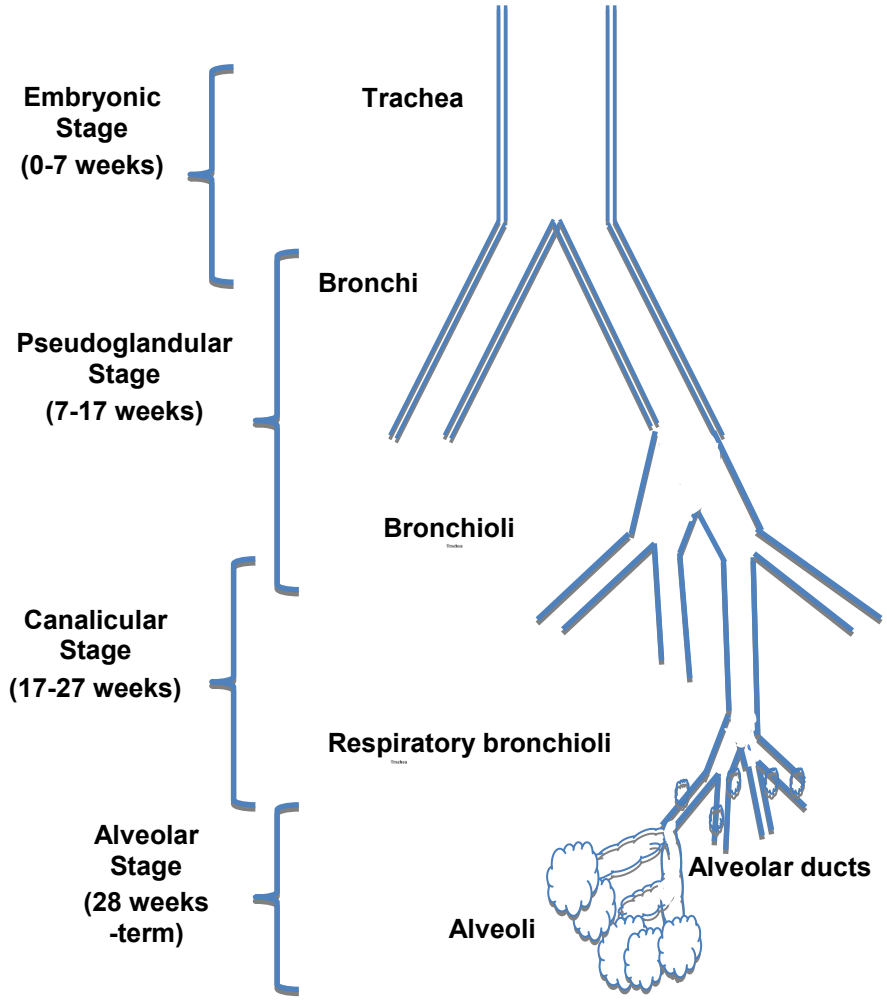
abnormal signaling and expression of these growth factors has been demonstrated in neonatal chronic lung disease (38).

Functionally, decreased levels of pulmonary surfactant also characterize lung immaturity. Produced in type II pneumocytes, pulmonary surfactant is an amphiphilic phospholipoprotein that stabilizes the alveoli by minimizing the gradient between alveolar surface tension and transpulmonary pressure through the respiratory cycle (39). Surfactant deficiency in the premature infant results in respiratory distress syndrome and contributes to lung injury by allowing cycles of alveolar collapse leading to inflammation (7,36,40). Antenatal corticosteroids have been demonstrated to accelerate lung maturity in the fetus resulting in higher levels of functional endogenous surfactant in the prematurely born infant and reduced need for, but not duration of, post-natal ventilation support, thereby improving survival (41-43). Postnatal administration of exogenous surfactant reduces injury but does not eliminate it altogether (36). A suggested sequence of events resulting in BPD includes the presence of pre- and post-natal factors, such as infection, inflammation and oxidative stress interacting with the vulnerable developing lung and leading to lung injury and subsequent inflammatory response (16,44). This inflammatory response is thought to contribute to scarring of lung tissue and disruption of ongoing alveolar and pulmonary vascular bed development (44).

Delivery in the second trimester results in the birth of infants in early stages of lung development. Infants born at 24 to 25 weeks gestation, during

the canalicular/early alveolar stages of lung development, can now survive but will very likely have altered lung development (45). Their lungs will have fewer but larger alveoli with “marked simplification of acinar structure” and abnormal morphology of the capillary vascular bed; however, in contrast to “old BPD”, there is less evidence of interstitial or alveolar fibrosis (29,35,36,46). Airway injury during the canalicular stage of development has been associated with prenatal factors, such as chorioamnionitis, and with postnatal trauma from ventilation, oxygen toxicity or inflammation secondary to infection (44,47). In addition, genetic differences in the expression of lung “morphoregulators” may contribute to the susceptibility of certain premature infants to developing BPD as cellular injury progresses to either cell death, apoptosis or subsequent scarring (7,47).

Figure 1-1. Stages of Lung Development Through the Fetal Period (Modified from: [48]**)**



1.4.2 The Role of Antenatal Corticosteroid, Respiratory Distress Syndrome and Surfactant in BPD

Respiratory distress syndrome (RDS) due to surfactant deficiency in the premature infant results in uneven lung aeration with atelectasis and alveolar over-distension contributing to small airway injury and inflammation (47). Produced in type II pneumocytes, surfactant reduces surface tension at the alveolar-capillary interface thereby preventing collapse of the small airways (48). Cuboidal immature pneumocytes first appear in the pseudoglandular phase and differentiate into type I and type II cells as lung development progresses through the canalicular phase (37). Surfactant production in type II pneumocytes is usually detectable after 23-24 weeks gestation, coincident with the development of primitive alveoli and the alveolar capillary barrier such that gas exchange becomes possible (37). However, at this stage gas exchange is less efficient; overall lung surface area is small relative to the size of the infant, the distance between the alveolar interface and supporting blood vessels is high, and surfactant production is suboptimal in both quantity and quality (37). Surfactant deficiency results in small airway collapse, which leads to intrapulmonary shunting and ventilation-perfusion mismatch. In addition to hypoxia, as RDS progresses there is evidence of inflammatory change in the lung parenchyma, which is enhanced by concurrent baro- and volutrauma and by hyperoxia (44). Inflammatory processes, perpetuated by an ongoing cycle of increased oxygen need and ventilator dependence, are postulated to disrupt

subsequent vascularization and alveolar septation and, if severe, contribute to scarring and fibrosis ultimately leading to a diagnosis of BPD (44).

Advances in the management of RDS of the premature neonate have decreased the impact of RDS on the development of BPD, but they have not substantially reduced the rate of BPD (26). Without surfactant therapy, adequate functional residual capacity is not established and lung injury occurs (34). Some infants develop a form of necrotizing bronchiolitis with squamous metaplasia of the larger airways and connective tissue proliferation, while others demonstrate arrest of terminal alveolarization with subsequent scarring of the lung parenchyma (34).

Despite more widespread use of antenatal glucocorticoids and exogenous surfactant, some infants require prolonged mechanical ventilation and high inspired oxygen concentrations (26). These treatment strategies help the more extreme preterm infant survive, but they then have a higher risk of developing the "new" BPD (31,49). This form of BPD occurs in a population where premature "initiation of pulmonary gas exchange interrupts normal alveolar development" and subsequent inflammatory changes resulting from mechanical ventilation and premature birth contribute to lung injury (49). In infants dying from severe cases of BPD, autopsy findings confirm milder forms of alveolar septal fibrosis with more uniform lung inflation but decreased numbers of alveoli and less well developed pulmonary microvascular architecture (7).

The NICHD ELGAN study, a review of infants born at 28 weeks or less, described three patterns of early postnatal respiratory function and evaluated how each relates to the development of BPD, as defined by supplemental oxygen need at 36 weeks post-menstrual age (33). Infants were divided into three groups based on supplemental oxygen need during the first weeks of life: low FiO2 Group (persistently low supplemental oxygen need (<0.25) by 14 days of age), pulmonary deterioration group (low oxygen during the first week but increased need by 14 days of age), and early and persistent pulmonary dysfunction group (persistently high oxygen needs) (33). Risk factors were evaluated over three time periods amongst the three groups to identify risk factors that significantly contributed to the development of BPD (33). Sixty nine percent of infants in the early and persistent pulmonary dysfunction group, and 52% of the pulmonary deterioration group developed BPD, but only 17% in the low FiO_2 group (33). In addition to younger gestation at birth, low birth weight and growth restriction contributed to BPD risk for all three groups; however, there were differences between the three groups with respect to the antenatal and neonatal risk factors associated with subsequent BPD (33). In the low FiO_2 group, growth restriction (birth weight z score < -1) and high Score for Neonatal Acute Physiology-II (SNAP-II) scores were associated with later development of BPD, along with later use of analgesics (33). In the pulmonary deterioration group, gestational age < 27 weeks, growth restriction and male gender increased the risk for BPD, along with elevated

SNAP-II scores, confirmed neonatal bacteremia and need for mechanical ventilation at 1 week of age (33). Similar risk factors were observed for the early and persistent pulmonary dysfunction group (33).

1.4.3 The Role of Inflammation in BPD

Several factors influence the development of inflammation in the immature lung, including antenatal exposure to inflammatory mediators or infection, postnatal exposure to infection, high concentrations of oxygen, pressure and volume effects of assisted ventilation, and pulmonary fluid overload secondary to patent ductus arteriosus (28,50,51). True clinical chorioamnionitis, defined as maternal symptoms of uterine tenderness, fever, malodorous amniotic fluid and elevated white count, is less common in preterm delivery, occurring in approximately 15 percent of cases, however histologic chorioamnionitis occurs in as many as 33-57% of the placentas of VLBW infants (52-54). In a small cohort of very low birth weight infants who had not received surfactant or antenatal corticosteroid, exposure to histologic chorioamnionitis resulted in higher levels of inflammatory markers in tracheal aspirates and increased BPD risk (55). Subsequent studies are more equivocal, however there is variability in the definitions used for inflammation and for BPD. Local experience has demonstrated a clear link between histologic chorioamnionitis and increased rates of BPD, but this may be mediated by other variables (54,56).

1.5 Modifiable Risk Factors and BPD

Since the initial description of BPD by Northway and colleagues in 1967, changes in the care and management of the premature infant have had a profound impact on the presentation and outcome of neonatal respiratory disorders and subsequently on morbidity and mortality of the premature infant (3,26). It has become increasingly clear that there are significant prenatal, perinatal and postnatal risk factors that collectively influence the developing lungs during fetal and neonatal life (see Table 1-2). A variety of nutritional, medical and mechanical therapies to treat and manage respiratory distress syndrome and resultant pulmonary insufficiency have been evaluated, however no single therapy or combination of therapies have been shown to completely eliminate the disease, particularly in the smallest preterm infants.

Risk factors for BPD can be divided into intrinsic relatively fixed variables, such as gestational age at birth and birth weight, or extrinsic, potentially modifiable risk factors including infection exposure and hemodynamic instability resulting from patent ductus arteriosus; however there is overlap between these categories (see Table 1-2). Risk factors can also be classified by the timing of occurrence as antenatal, perinatal or post-natal and include factors such as presence of maternal illnesses such as chorioamnionitis, group B *Streptococcus* colonization and gestational hypertension, and neonatal factors such as need for surfactant therapy, pneumothorax, patent ductus arteriosus, pulmonary hemorrhage and

infections or necrotizing enterocolitis (49,57-60). Maternal care strategies that may moderate the development of BPD include the use of antenatal corticosteroids to minimize RDS, intrapartum antibiotics to treat or prevent neonatal infection, and careful management of maternal illnesses such as gestational hypertension and gestational diabetes (47). Neonatal therapeutic strategies that may alter the course of BPD include targeted oxygen saturation and permissive hypercapnia, gentle ventilation with optimal peak inspiratory and end-expiratory pressure (PIP/PEEP) targets, minimal total duration of invasive pressure ventilation, fluid resuscitation and nutritional status, including overall caloric intake and total duration of parenteral nutrition (47,49,57-59). It is commonly thought that many of these risk factors or determinants contribute to or modify an overall inflammatory state, resulting in a process of lung injury and repair that eventually culminates in either recovery of the lung parenchyma or delayed and abnormal lung alveolarization (61).

Table 1-2. Risk Factor Classification for BPD

(based on**:** (16,60,62))

	Intrinsic	Modifiable
Antenatal	multiple pregnancy gender maternal age gestation hypertension gestational diabetes	maternal infection chorioamnionitis group B *Streptococcus* status
Perinatal	gestational age birth weight duration of rupture of membranes pulmonary hypoplasia chorioamnionitis group B *Streptococcus* status birth order in multiple pregnancy mode of delivery Apgar score	ventilation strategies at delivery oxygen targets peak pressures end-expiratory pressures respiratory distress syndrome
Postnatal	PDA pulmonary hemorrhage infection/inflammation sepsis/meningitis necrotizing enterocolitis	ventilation strategies oxygen targets $PaCO_2$ targets mode/duration non-invasive ventilation hypotension fluid balance nutritional status NIDCAP care

Chorioamnionitis has an important role in the etiology of premature birth, affecting over half of infants born prematurely (63). When used in the clinical setting, chorioamnionitis is a subjective diagnosis based on nonspecific signs and symptoms of maternal inflammation, such as maternal fever and leukocytosis, foul smelling amniotic fluid and uterine tenderness (53). Often, cases identified as clinical chorioamnionitis are found not to have evidence of intrauterine inflammation (64). However, large studies have shown an association of clinical chorioamnionitis with increased rates of early onset sepsis in premature infants (53). Histologic changes attributed to chorioamnionitis include the presence of polymorphonuclear cellular infiltrate and is graded by location and depth of infiltration and by severity (63). Histologic chorioamnionitis has an important role in the etiology of premature birth, associated with over half of infants born prematurely (63). In addition to lower gestational age and weight at birth, infants with exposure to histologic chorioamnionitis are more likely to develop early onset sepsis, severe retinopathy of prematurity and BPD (54).

Antenatal corticosteroids have been shown to decrease the rates of respiratory distress syndrome, intraventricular hemorrhage and mortality in preterm neonates, but not bronchopulmonary dysplasia (43). Randomized controlled trials have not demonstrated any advantage of single versus multiple courses of antenatal corticosteroid in reducing the incidence of BPD, although there may be some benefit in infants born < 32 weeks gestation (65-68).

Many proposed therapies have been evaluated in randomized controlled trials to modify the development of BPD, but only a few have demonstrated apparent benefit: prophylactic surfactant followed by early extubation, early institution of caffeine therapy, post-natal corticosteroid therapy, use of volume-targeted ventilation, and shorter duration of invasive mechanical ventilation (21,69-73).

Surfactant prophylaxis and treatment have been extensively reviewed in the Cochrane Database of Systematic Reviews for managing respiratory distress syndrome and preventing BPD (72-80). Natural surfactant preparations have been proven to be safer than synthetic surfactant preparations with respect to risks for pneumothorax, but have not been shown to be more effective in reducing BPD, and may result in marginal increases in the risk of intraventricular haemorrhage (78). Regardless of preparation, prophylactic surfactant therapy with early extubation in comparison to delayed, selective therapy decreases the rates of BPD (72,73). Geary et al. evaluated two cohorts of extremely low birth weight infants (< 1000 grams) born in two periods (2001-2002 vs 2004-2005) to evaluate the impact of three early management changes, including early administration of prophylactic surfactant with immediate extubation to nasal continuous positive airway pressure, early institution of parenteral amino acid therapy and lower targets for oxygenation (70). These practice changes resulted in a significant reduction in the combined outcome of moderate and severe BPD, from 43% to 24% in the population studied (70).

Caffeine therapy has recently been shown to improve the rates of BPD if given in the first 10 days of post-natal life, possibly because it acts as a mild diuretic and decreases the total duration of invasive ventilatory support (21,81). In the Caffeine for Apnea of Prematurity study, placebo treated infants required an additional week of invasive ventilation as compared with infants treated with caffeine, and subsequently had rates of BPD of 48% versus 36%, respectively with an adjusted odds ratio of 0.63 [95% CI: 0.52 to 0.76] (21,69). In addition, caffeine significantly decreased the rate of neurodevelopmental disability in infants surviving to a corrected age of 18 to 21 months, odds ratio 0.77 [95% CI: 0.65 to 0.93] (69).

An umbrella review of the Cochrane Database of Systematic Reviews identified over 36 systematic reviews evaluating various medical therapies to prevent or treat BPD. Medical therapies evaluated include anti-inflammatories (super-oxide dismutase, α-1 proteinase inhibitor, inhaled and systemic corticosteroids), anti-infective agents (erythromycin, IVIG), bronchodilators, diuretics (loop diuretics and distal-tubule active agents), nutritional supplements (vitamins A and E) in addition to supplemental surfactant therapy (synthetic and natural preparations) (72-80,82-98). Of these, only post-natal steroids have been shown to have benefit in terms of reducing the rates of BPD but at a significant potential neurodevelopmental cost (85,92,95). In a meta-analysis of 21 studies evaluating the impact of post-natal corticosteroid therapy on mortality and risk for cerebral palsy, Doyle et al. demonstrated that rates of cerebral palsy

are elevated after therapy with post-natal corticosteroids (99). This risk is somewhat dependent on the underlying risk of developing BPD; infants at lower risk of oxygen dependence at 36 weeks corrected gestation were much more likely to die or develop cerebral palsy if they were exposed to post-natal corticosteroids than infants at higher risk of developing BPD (99). The use of inhaled nitric oxide has been shown to have a marginal effect on the rate of BPD or death in one meta-analysis, with a trend toward an effect on BPD, however variability in study design limits conclusions drawn overall (100,101). Optimal nutrition strategies should promote growth and development as well as facilitate healing, however there is no single dietary strategy that has been shown to reduce the incidence of BPD (102). In this study data regarding fluid management and nutrition support was not examined.

Ventilation strategies that use pressure or volume targets have been developed with the goal of reducing baro- and volutrauma which could then potentially decrease the rate of BPD (70,71,103,104). There are many conventional ventilation strategies available for use in the premature infant, including pressure limited strategies, such as assist control, synchronized intermittent mandatory ventilation, pressure support, proportional assist ventilation or volume-targeted ventilation, however none have been rigorously evaluated in the reduction of BPD (47,105). Volume-targeted ventilation strategies have been shown to have some benefit in the reduction of BPD however the effect on long-term neurodevelopmental outcome is

unknown (106). Volume Guarantee mode on the Draeger Babylog 8000+ ventilator uses a hot wire anemometer at the airway opening to detect the exhaled tidal volume to minimize variability in delivered breaths and functions to optimize the pressures needed to delivery an appropriate tidal breath for the infant with variability responsive to the infant's changing needs (71,106). Volume-targeted ventilation has been shown in a meta-analysis of 4 randomized controlled trials to decrease the total duration of ventilation, a known risk factor for BPD, resulting in a borderline significant reduction in the risk of BPD (71).

High frequency, oscillatory and jet ventilation use high ventilator rates to achieve ventilation and oxygenation. These modalities rely on complicated pressure and flow dynamics to improve aeration in heterogeneous lung disease. Systematic review of 15 randomized controlled trials on the use of elective high frequency oscillatory ventilation demonstrated decreased rates of BPD in subgroup analysis if high-volume strategies, piston oscillators and inspiratory:expiratory times of 1:2 were used (103). Unfortunately this strategy has been associated with increased risk of pneumothorax and severe intraventricular hemorrhage or periventricular leukomalacia (103,104). Elective use of high frequency jet ventilation has been evaluated in a similar fashion, and has also been shown to decrease the rates of BPD, but has also been associated with a trend toward increased risk of periventricular leukomalacia (104). There may be some benefit with selective use of high

frequency jet ventilation, however availability and comfort level with this modality precludes widespread use (104,107).

Recent trials have focused on targeted intubation and minimizing the duration of mechanical ventilation, using strategies such as INSURE (Intubation SURfactant Extubation) followed by NCPAP either immediately after surfactant therapy or with resolution of the symptoms of RDS (47,108). Not surprisingly, duration of mechanical ventilation has been shown to be inversely proportional to survival rates and is associated with increasing rates of deafness, blindness and cerebral palsy and decreasing Mental and Psychomotor Developmental indices on the Bayley Scales of Infant Development II (109). There is some suggestion that avoidance of intubation may be preferable with only rescue intubation and surfactant for those with intractable oxygen needs however in those infants at highest risk for RDS, intubation with administration of prophylactic surfactant is still considered best practice with careful consideration for the need for ongoing ventilation support (73,110,111). Other strategies using minimally invasive approaches to surfactant administration have been attempted, including the use of nebulized surfactant, however with minimal success (110,112,113). Current ventilation strategies to minimize lung damage employ permissive hypercapnia, combined with lower oxygen saturation targets to limit baro- and volutrauma along with earlier extubation and less invasive ventilation modalities to promote and maintain functional residual capacity (110). Permissive hypercapnia has been evaluated as a way to reduce or prevent

injury resulting from pulmonary over-distension; however, there have been no randomized control trials of sufficient power to demonstrate a statistically significant benefit and reported studies have used different targets (47).

1.6 Non-Invasive Ventilation and BPD

Many infants will need immediate mechanical ventilatory support through an endotracheal tube. This is required for both administration of artificial surfactant in the treatment of RDS so as to provide alveolar stability and also to overcome the work of breathing placed on the fragile newborn thorax (114). Despite advances in technology, endotracheal intubation and mechanical ventilation continue to be associated with progressive lung injury and the development of BPD in the premature infant, largely due to inflammation resulting from baro- and volutrauma, lung injury resulting from recurrent atelectasis, and oxygen toxicity (114,115).

Gentler ventilation strategies, including initiation of non-invasive ventilation to establish FRC at resuscitation, limiting duration of mechanical ventilation, and using non-invasive ventilation to promote extubation success are now recognized as important ways to minimize damage to the fragile developing lung of the premature infant (47,62,114,116). These non-invasive or minimally invasive ventilation strategies provide oxygen and end-expiratory pressure to facilitate the infant's own ability to establish and maintain functional residual capacity and prevent alveolar collapse (114).

In a recent meta-analysis of four randomized controlled trials evaluating the use of nasal CPAP from birth, the authors found a statistically

significant reduction in the relative risk of BPD and/or death in the nasal CPAP group (62). In this meta-analysis, 2780 infants born between 24 and 29 weeks gestation were randomized to intubation or nasal CPAP at birth (62). Infants randomized to the nasal CPAP group were less likely to require any mechanical ventilation and were less likely to need any surfactant treatment (62). The authors found a borderline significant reduction in the incidence of bronchopulmonary dysplasia in the nasal CPAP group compared to the intubation group (RR 0.91; 96% CI: 0.82 to 1.01) (62).

When the extremely premature infant requires invasive ventilation support, three potential strategies may be used. The first and most invasive strategy involves the placement of an endotracheal tube for administration of surfactant where required, and for ongoing mechanical ventilation. The second strategy, described as INSURE [Intubation, SURfactant, Extubation] includes endotracheal tube placement for surfactant treatment and, in some circumstances, a brief period of mechanical ventilation support but for shorter duration with the expectation for early extubation to either a non-invasive support mode or directly to low flow nasal cannula or room air (117-119). The least invasive approach entails the use of non-invasive ventilation support with intubation reserved for rescue surfactant administration only as with INSURE but on a more selective basis or with alternative minimally invasive means of delivering surfactant to the lungs (112,113,120-126). It is well known that the development of RDS and subsequent need for intubation are independent risk factors for the

development of BPD, however the total duration of intubation has also been directly and indirectly implicated as a risk factor for more severe disease and with long term neurodevelopmental disability (109,127-131).

There are multiple modalities to provide non-invasive ventilation strategies. These include both nasal and nasopharyngeal support systems as well as various pressure and flow devices. This has made systematic evaluation difficult. Neonatal respiratory care at the Royal Alexandra Hospital NICU uses nasal continuous positive airway pressure (NCPAP) and unsynchronized nasal intermittent positive pressure (NIPPV) modalities after extubation with the goal of reducing reintubation rates secondary to apnea of prematurity or respiratory failure. In practice, unsynchronized NIPPV is used either as a step-down from invasive ventilation, in order to promote extubation success, or as a step-up from single level NCPAP to avoid or minimize the need for invasive ventilation. The purpose of these strategies is to reduce the overall duration of intubation and thus rates of BPD. To achieve this, supplemental oxygen and ventilatory pressures must be titrated carefully so as to decrease the contribution of hyperoxia and barotrauma to lung injury while allowing the infant to breathe independently. Unfortunately, there are few data comparing these modalities in clinical practice.

1.6.1 Nasal Continuous Positive Airway Pressure

In treatment of RDS in the early 1970's, endotracheal continuous positive airway pressure was used in an attempt to minimize trauma

associated with mechanical ventilation (132). Since then, various methods of delivering positive pressure have been developed, including non-invasive approaches, such as nasal mask or prongs, that are equally effective in establishing alveolar aeration and minimizing atelectasis (116). Different interfaces and pressure generating devices have been developed and systematically evaluated in the management of RDS, apnea of prematurity, and prevention of extubation failure and many studies have reported possible reduction in the rates of BPD as a secondary benefit (111,133-136).

1.6.2 Non-invasive Intermittent Positive Pressure

VLBW infants are at higher risk of extubation failure due to central hypoventilation, residual airway disease and upper airway instability, which all contribute to atelectasis and ventilation failure (137,138). Using intermittent high pressure above a baseline pressure has been demonstrated to improve functional residual capacity by improving stability of the airway and increasing airflow transmitted to the lungs with enhanced alveolar recruitment (115,138,139). The use of bi-level positive airway pressure by non-invasive means is widely used in clinical practice to augment traditional nasal CPAP (116,140). Early modalities of noninvasive intermittent ventilation were poorly standardized, technically difficult and associated with significant non-pulmonary clinical complications (140,141). With advances in technology that allow for a gentler approach, interest in noninvasive intermittent ventilation methods has regained popularity in neonatal intensive care. Intermittent noninvasive ventilation is hypothesized

to reduce the need for intubation or reintubation by improving functional residual capacity and minute ventilation and thereby improving gas exchange and also reducing the overall work of breathing (140). The goal of non-invasive ventilatory support is to minimize the adverse consequences of prolonged invasive mechanical ventilation that contribute to BPD, including baro- and volutrauma, oxygen toxicity and nosocomial infections (139). Different patterns and frequencies of pressure cycles may be used, which may or may not be synchronized with spontaneous breaths, complicating systematic evaluation of its effectiveness in different clinical settings (116,142). With this method, different settings can also be applied for PIP, PEEP, inspiratory time and rate, however ideal settings have not been rigorously evaluated and most trials published to date have evaluated synchronized NIPPV (116).

1.6.3 Synchronized Non-invasive Intermittent Positive Pressure

Early studies of non-invasive IPPV were designed to allow an extension of synchronized intermittent mandatory ventilation settings using a non-invasive interface and as a result synchronization with the infant's spontaneous respiratory efforts was by default (115,139). However, detailed analysis of pulmonary mechanics demonstrated improvements in tidal volume and minute ventilation with synchronous ventilator breaths compared to asynchrononous breaths (139). Synchronized nasal intermittent positive pressure ventilation has been used to facilitate successful extubation and as a result has contributed to decreased rates of BPD in comparison with

extubation to nasal continuous positive airway pressure (143,144). Meta-analyses have not shown a clear benefit of synchronized NIPPV over NCPAP in the reduction of BPD though there is a trend favoring NIPPV (134,145). Unfortunately, synchronized non-invasive positive pressure ventilation requires the use of specialized equipment in order to coordinate pressure increases with the infant's spontaneous breathing efforts. Synchronized non-invasive intermittent positive pressure is not currently used in this centre.

1.6.4 Unsynchronized Non-invasive Intermittent Positive Pressure

Unsynchronized non-invasive IPPV provides two levels of positive airway pressure support that is not coordinated with the infants' intrinsic respirations, allowing the patient to breathe spontaneously at both levels (146). Currently this centre uses unsynchronized bi-level non-invasive intermittent positive pressure administered through nasal prongs or nasal mask to prevent extubation failure or to defer the need for intubation. There are no meta-analyses of studies evaluating unsynchronized NIPPV published to date as primary studies are difficult to interpret due to the small number of studies, variability in type of interface, pressure and flow devices used, pressure settings, rate and pattern of pressure cycling and underlying study population variability. Initial strategies involved using nasal mask or prongs to deliver ventilator breaths from the same equipment used with endotracheal intubation and were unsynchronized due to inability to detect spontaneous respiratory effort (147,148). An early observational study of 10

premature infants requiring NCPAP for prematurity or severe RDS demonstrated some success using unsynchronized IPPV to avoid intubation (147). Other reports of unsynchronized non-invasive IPPV using nasopharyngeal prongs have demonstrated some benefit in prevention of extubation failure compared with NCPAP (142,149,150). The rate of BPD was not an outcome studied, however the authors of the most recent study noted a trend toward shorter duration of hospitalization in the NIPPV group (142).

A single observational study evaluated the use of unsynchronized non-invasive IPPV on the long-term outcome of BPD (149). This study evaluated the implementation of unsynchronized nasopharyngeal IPPV (NPIPPV) to prevent extubation failure as part of the Vermont Oxford Network Collaborative for quality improvement (149). In the initial phase, infants were started on NPIPPV if they met criteria for reintubation from NCPAP, which included worsening apnea/bradycardia, increasing desaturations or progressive hypercapnea (149). In the final phase of the project, retrospective chart comparisons in the pre- and post-study periods demonstrated decreases in the duration of intubation and frequency of discharge home on supplemental oxygen (149). The authors concluded that introduction of non-invasive ventilation improved overall success of extubation and reduced indicators of BPD (149). These conclusions are limited by the observational nature of the study and by the small sample size, however they provide some promising evidence that this ventilation strategy may be useful in the reduction of BPD.

The evidence published to date regarding unsynchronized non-invasive IPPV is limited and plagued by methodological limitations; however this modality offers a simple, potentially effective way to reduce extubation failure and overall duration of invasive mechanical ventilation. Despite this lack of evidence, some neonatal units, including this local neonatal program use unsynchronized non-invasive IPPV as a "step up" from straight NCPAP for infants with refractory apnea, progressive hypoxemia or hypercapnea in an attempt to prevent extubation failure, often because of lack of availability of ventilators with options for synchronization (146,150). A recently published clinical trial evaluated the use of NIPPV compared with NCPAP as either initial ventilation support to prevent intubation or support for extubated infants with the primary outcome of survival without BPD (151). In this multi-centre trial, individual centres were allowed to use synchronization as per their usual centre care practices with an a priori plan for subgroup analysis of infants treated with synchronized NIPPV compared to unsynchronized NIPPV (151). There was no significant difference between groups for the primary outcome survival without BPD between the NCPAP and NIPPV groups (151).

1.7 Summary

The original definition of bronchopulmonary dysplasia as defined by Northway nearly five decades ago has shifted from persistent oxygen need and characteristic radiographic and clinical findings at 28 days of life to the more commonly accepted classification as mild, moderate or severe based on

supplemental oxygen need at both 28 days of life and 36 weeks corrected gestational age (3,7). In the late 1980s it was recognized that ongoing pulmonary dysfunction at 36 weeks corrected gestational age was more predictive of persistent abnormalities beyond the neonatal period and into early childhood than need for supplemental oxygen at 28 days (5).

There are many intrinsic and modifiable risk factors contributing to the pathophysiology of bronchopulmonary dysplasia however the common denominator appears to be the combination of immature, underdeveloped lungs and inflammatory processes resulting in preterm labor or arising in the neonatal period. Early prognostication of infants at high risk for BPD will enable individualized approaches to neonatal care.

CHAPTER 2:

Prediction Models and Pulmonary Outcomes in Premature Infants

2.1 Prediction Models for BPD

Bronchopulmonary dysplasia has been viewed as a consequence of immature lungs, inflammation resulting from both prenatal and immediate postnatal factors including respiratory distress, and a complication of mechanical ventilation. Early prediction of chronic oxygen dependency allows targeted therapy for clinical trials to evaluate which populations are at highest risk and to determine which subgroups of infants are most likely to benefit. Additionally, scoring tools can be used to classify infants who are in the most severe category in whom the risk of using controversial or potentially hazardous therapies, such as systemic corticosteroids, may be justified.

A number of scoring systems using clinical data have been developed to predict and classify BPD early in order to target treatments for those infants at highest risk and to allow comparison of outcomes between centres (152-157). These scoring systems are often complex and multifactorial or based on logistic regression analysis of various risk factors and determinants of BPD and are difficult to apply easily in the clinical setting. For example, the scoring system of Palta et al requires interpretation of chest radiographs, peak inspiratory pressures, respiratory rate, plus partial pressures of oxygen

and carbon dioxide in the vascular system (152,153). Other scoring systems, also based on logistic regression analysis, have found that a large number of potential risk factors contribute to the development of BPD. These use complex equations or systems for risk prediction (154-160). Some prediction tools using pulmonary function testing show that premature infants often have early abnormalities such as elevated airway resistance and decreased lung compliance with low lung volumes, which have been associated with later development of BPD (161). The use of these measures is imprecise as it is unclear which measure performs best and which age at measurement provides the most prognostic value, given the dramatic changes in lung compliance and resistance over the first days to weeks of life.

Sinkin's SCORE which is applied at 12 hours and 10 days of age, was developed to predict the need for oxygen at 28 days, thus including infants categorized as having mild BPD (158). This SCORE included ventilation parameters (peak inspiratory pressure and main airway pressure), 5 minute Apgar, gestational age, and birth weight (158). Interestingly, though prospective testing was done on patients who were eligible to receive surfactant therapy, which should have improved outcome, the SCORE underestimated adverse outcomes (158). Like Sinkin's prediction tool, that of Corcoran was also used to predict oxygen need at 28 days with the additional criteria of radiographic changes consistent with BPD as defined by Northway (162).

A respiratory failure score (RFS) was created in an attempt to provide a simpler tool with which to predict the development of BPD (160). This score included factors such as gestation, birth weight, fraction of inspired oxygen, ventilator rate, peak inspiratory pressures, and mean airway pressures (160). In comparison with the Sinkin SCORE applied at 12 hours of age and the Ryan score applied at 72 hours of age, the RFS at 72 hours of age demonstrated the largest area under the curve for receiver operating characteristic curves (158-160). Though this model is somewhat simpler than previous models, it is unclear as to which cutoff values are most appropriate for use in differentiating infants at highest risk and it remains somewhat cumbersome in the determination of the various factors included in the model. Other models have included ventilation parameters however these methods are prone to difficulty in interpretation given the various ventilation strategies in use, varied methods of measuring airflow and pressure within each system, and by known changes in management strategies over time (156,161). In general these models have high specificity and sensitivity as is evident in that the area under the curve on receiver operating characteristic curves were generally high (0.76 to 0.94) (154,156,159).

The Pulmonary Severity score of Madan et al. was developed to quantify BPD severity in infants enrolled in the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial (163). It was observed that supplemental oxygen resulted in higher rates of BPD

and thus the scoring system was developed to allow comparison of the study groups at randomization and to predict pulmonary outcome at three months follow-up (163). Elements in the pulmonary severity score included medication use (systemic steroids, methylxanthines or diuretics), level of inhaled oxygen and level of ventilation (163). In the calculation of the score, the fraction of inhaled oxygen is multiplied by the ventilation support, scored as 2.5 for invasive mechanical ventilation, 1.5 for nasal CPAP and 1.0 for low flow nasal cannula or room air (163). This value is then added to a medication score, the sum of: 0.2 for systemic steroids given for treatment of BPD, 0.1 each for regular diuretics or inhaled steroids and 0.05 each for methylxanthines or intermittent diuretics (163). Scores ranged from 0.21 where no supplemental oxygen, no medications and no ventilation support was required, to 2.95 for a fully ventilated baby requiring all three classes of medication and 100% supplemental oxygen (163). The median value of the pulmonary score was higher for those who subsequently developed pulmonary morbidity than for those who did not ($p < 0.0001$, Kruskal-Wallis test) (163). The Pulmonary Score was then evaluated using the area under the receiver operating characteristic curve and the Akaike Information Criterion method, which measures the quality of a statistical model for a given set of data (163). After controlling for other covariates, regression modelling demonstrated that for every increase of 1 unit in the Pulmonary Score, the odds of subsequent pulmonary morbidity increased by a factor of 7 (163). The utility of this scoring system above that of the current definition of

BPD by NICHD criteria is that it provides a continuous quantitative estimate of BPD severity, rather than a categorical definition, but remains simple to calculate and interpret (163). The Pulmonary Score has not been validated in any other populations of premature infants, nor has the score been extrapolated to older age groups.

More recently, May et al. modified the Pulmonary Score of Madan by excluding the need for medications in the model and applying the score earlier in the neonatal course at 2 and 7 days of age to predict chronic oxygen dependency at 28 days or 36 weeks corrected gestational age among very low birth weight infants less than 33 weeks gestational age at birth (164). The tool was developed to identify those infants at highest risk who might benefit from treatments such as systemic corticosteroids (164). The scoring system of May et al. demonstrated highest area under receiver operator characteristic curve for predicting oxygen dependency at 28 days and 36 weeks corrected gestational age when applied at 7 days chronologic age (164). Sensitivity and specificity for the score on day 7 are presented in table 2-1. This Chronic Oxygen Dependency (COD) score has not been validated in other populations, nor has it been used to predict pulmonary morbidity in early infancy.

Table 2-1. Sensitivities and Specificities of the COD Score Applied at 7 Days of Age

(Modified from: (164)**)**

COD Score at 7 days of age	Prediction of COD at 28 days chronologic age		Prediction of COD at 36 weeks corrected gestational age	
	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)
≥ 0.323	95	78	80	73
≥ 0.42	97	72	85	73
≥ 0.65	100	53	90	55

The scoring system of May et al (2007) has similar areas under the curves for receiver operating characteristics and has equal face validity to many of these scoring tools but it has the big advantage of simplicity (154-160,164). Madan's scoring system is equally simple to apply, and unlike the majority of other tools, has been shown to have clinical and research value in the prediction of longer-term pulmonary outcomes (163). The clinical utility of these scoring systems by Madan and May are that they are simple to use, and can be calculated early in the neonatal course: at 2 and 7 days of age for the COD score by May and at 35.7 weeks corrected gestational age for the Pulmonary Score by Madan (163,164). The COD score allows for prediction of oxygen dependency at both 28 days of age and 36 weeks corrected gestational age (164). A goal of this study is to evaluate whether the COD score (which is a modification of the Pulmonary Score by Madan) or the Pulmonary score will prove useful in predicting longer term pulmonary morbidity at three and six months corrected age in infants born <29 weeks gestation or <1250 grams birth weight.

2.2 Pulmonary Morbidity in Early Childhood

2.2.1 Impact of BPD on Pulmonary Morbidity

In the pre-surfactant era, a cohort study of 605 survivors born <1500 grams birth weight demonstrated that 20% of infant experienced abnormal pulmonary symptoms or death during a two year follow up period (5). Those with pulmonary abnormalities on follow-up were more likely to be male

gender, have lower birth weights and gestational ages, have RDS, and longer duration of ventilation and oxygen therapy (5). The authors observed that the infants who had normal pulmonary outcomes were able to wean off oxygen by 30 to 33 weeks corrected age (5). Oxygen requirement persisting to 34 to 36 weeks corrected age was the turning point at which the probability of having pulmonary morbidity in the first two years of life crossed 50%. As such, the authors concluded that the use of oxygen at 36 weeks gestation was a better predictor of pulmonary morbidity than oxygen use at 28 days in infants born ≤ 32 weeks gestation (5).

Today, BPD continues to have a significant impact on mortality rates and long term morbidity affecting long term growth, lung health and neurodevelopment, particularly for extremely low birth weight neonates requiring prolonged ventilation (7,49,109). In contrast with classical BPD as described by Northway, infants with BPD in the current era of neonatal intensive care experience an acute injury to immature lungs resulting in arrested alveolar and vascular development (49). What follows is a period of recovery of alveolarization and vascular development, which is negatively influenced by dynamic inflammatory processes from necessary supportive therapy during and after neonatal intensive care (49). Though lung development continues beyond the newborn period it is possible that lung tissue development does not achieve normal levels. It has been postulated that this process is inversely related to gestational age at birth, such that in the youngest infants, the acute injury occurs at an earlier stage and the

ongoing cycle of injury and repair occurs for longer, which results in more severe long term damage (49).

Lung injury may continue beyond the NICU. These infants are prone to a vicious cycle of increased vulnerability to and risk for additional lung injury resulting from subsequent respiratory infection. Infants with BPD have higher rates of community resource use related to lung health, hospital readmission, abnormalities on pulmonary function testing, increased susceptibility to respiratory infections and airway hyper reactivity, particularly if they were discharged from the NICU with home oxygen therapy (165-167).

Overall estimates of rehospitalization during infancy and early childhood ranged from 22 to 70%, particularly for respiratory illnesses (167-171). In the era before widespread use of antenatal corticosteroids and RSV prophylaxis, up to 67% of rehospitalizations in the first year of life for infants who were ventilator dependent at 21 days of age were attributable to cardiac or respiratory causes (167). In general 11.3% of infants born prior to 37 weeks gestation are at risk for pulmonary morbidity and frequent rehospitalization; BPD elevates that risk up to 49% (165,172). In a cohort of 1597 infants born <33 weeks gestation, 49% of those with BPD required rehospitalization during the first year of life as compared with 23% of preterm infants without BPD (165). The primary diagnosis was classified as respiratory in 36% and 34% of these two groups respectively (165). Factors associated with rehospitalization for respiratory illness in the BPD cohort

included predisposition to atopy, exposure to cigarette smoke, and poor air quality (165). More recent Canadian data similarly demonstrated that respiratory illnesses, such as airway infection, breathing problems and BPD-related morbidities account for a higher proportion of hospital re-admission in infants born <29 weeks gestation (171).

Bronchiolitis remains a leading cause of hospital admission for infants and children with pulmonary morbidity. In particular, Respiratory Syncytial Virus (RSV) has historically accounted for 20% of hospitalizations in infants with a history of premature birth and BPD (173). In the PREVENT trial, RSV prophylaxis with intravenous RSV immunoglobulin resulted in a 41% reduction in RSV hospitalization and 53% reduction in duration of stay related to RSV bronchiolitis in children with a history of premature birth and BPD. There was no difference in the duration of intensive care unit admission or mechanical ventilation (173). The IMpact-RSV randomized controlled trial demonstrated a similar reduction in hospitalization in infants with a history of BPD treated with prophylaxis (174,175). Widespread use of RSV prophylaxis will prevent some but not all hospitalizations in infants with a history of BPD.

Data from the NICHD have demonstrated that BPD was independently associated with increased specialized outpatient service use (OR 2.22; 95% CI: 1.56 – 2.98). This association was higher than with other significant risk factors such as sepsis, gestational age, or birth weight (176). BPD was also independently related to increased need for pharmacy services in a cohort of

infants in the Infant Functional Status Study (177). These children required more antibiotic (29%) and respiratory (49%) prescriptions (177). Follow-up data from the Irish/UK EPICure study demonstrated that up to 84% of extremely preterm infants required ongoing oxygen, medication or therapy for lung related issues (178). On subgroup analysis those with a history of BPD were significantly more likely to require these treatments (178). By 5-6 years of age the relative difference between the children with and without BPD had lessened, however those with BPD continued to have a higher likelihood of wheeze in the past year and greater use of inhaled bronchodilators and steroids (178).

A study of Canadian infants demonstrated that about 30% of infants born <29 weeks gestation required regular prescription medication; of those infants, 25% were for respiratory medications such as inhaled corticosteroid or bronchodilators (171). The odds of needing outpatient services were increased in those who had BPD (OR 1.85, 95% confidence interval 1.08 – 3.14) (171). A longer cohort study demonstrated that the need for increased medical services persisted through to late adolescence and young adulthood. Individuals with a history of BPD had higher rates of outpatient visits, increased rates of asthma, episodes of acute respiratory illness, and respiratory infection (179). The same study demonstrated that individuals with history of BPD required almost twice as many prescriptions per person-year compared with those who had history of RDS only. Overall costs

for medication use, medical consultations and hospitalization was significantly higher (179).

Airway reactivity in prematurely born infants with a history of BPD appears to have different physiologic characteristics than airway reactivity seen with asthma, although on pulmonary function testing, flow limitations are similar, and children tend to be treated similarly with bronchodilators and inhaled corticosteroids (180-182). Airway reactivity in school-aged children with a BPD history has been demonstrated to have variable responsiveness to bronchodilators, unlike children with airway reactivity secondary to asthma (180). Exhaled nitric oxide has been used as a marker of inflammation and eosinophil activation in reactive airways disease as it is known to regulate airway and vessel tone (180). Comparison of spirometry and exhaled nitric oxide (Fe_{NO}) in healthy term born children, children with asthma who were matched for airflow limitation, children with a history of prematurity but no BPD, and children born prematurely with BPD (defined as persistent oxygen need at 28 days) demonstrated that the BPD group had the lowest values of Fe_{NO} (180). It is unclear whether this is a reflection of decreased capacity to generate or release nitric oxide or whether it is related to dysfunctional growth of the pulmonary vascular bed related to BPD (180).

In a Norwegian study of two preterm birth cohorts who were assessed for airway reactivity in comparison to controls with and without asthma, researchers found that those with moderate to severe BPD were more likely to have symptoms of wheeze or diagnosis of asthma at 10 and 17 years

(181). When ex-premature children with asthma symptoms were compared to ex-preterms without symptoms there were no differences in markers of allergy whereas when controls with asthma were compared to controls without, there were significant differences in the same markers (181). The authors demonstrated that family history of atopy, exposure to cigarette smoke and elevated markers of airway inflammation were associated with asthma symptoms in term children but not prematurely born children who had airway reactivity; however, small sample size may have limited this conclusion (181). In prematurely born children, history of bronchopulmonary dysplasia and prolonged treatment with oxygen during the neonatal period was more relevant to current symptoms of wheeze (181).

Assessment of lung health using pulmonary function testing in ex-premature infants and children reveal persistent abnormalities that may contribute to clinical morbidity such as repeated hospital readmission with respiratory illness and chronic reactive or obstructive airway diseases. At preschool age, forced oscillation technique (FOT) demonstrated that children with a history of BPD have signs of decreased lung compliance and higher resistance on FOT (183). The children with BPD in this study also reported higher rates of hospitalization with bronchiolitis related to Respiratory Syncytial Virus (RSV) compared to controls (183). Pulmonary function testing reveals differences in observed versus predicted expiratory volume at 1 second (FEV_1) and forced vital capacity (FVC) in up to 46% of infants born

with very low birth weight (< 1500 grams) with statistically significant differences between those with BPD compared to those without BPD (184). There is evidence of impairment in lung function, ranging from mild to moderate airway obstruction, to air trapping and airway restriction (47).

Follow-up assessment of lung function in later childhood in the two cohorts of Norwegian children previously described in the study of airway reactivity demonstrated reduction in all lung function parameters except total lung capacity, particularly if they were diagnosed with moderate to severe bronchopulmonary dysplasia and required prolonged oxygen therapy (mean 85 days, range 55 to 257 days) (185). In the later cohort born 1991 to 1992 survival at lower gestational ages resulted in relatively longer exposure to oxygen; unfortunately the use of exogenous surfactant did not improve long term outcome (185).

Assessing pulmonary function testing using a raised-volume rapid thoracoabdominal compression technique and whole body plethysmograph in a cohort of early preschool age ex-premature children demonstrated that BPD was correlated with decreased forced expiratory flows but increased functional residual capacity and residual volume (186). Children with more severe obstructive changes were more likely to demonstrate bronchodilator responsiveness and have a history of recurrent wheeze treated with inhaled corticosteroid (186).

Chest computed tomography of one- to two-year old ex-premature infants with “new” BPD demonstrated hyperlucent areas and linear and sub

pleural opacities that correlate with low functional residual capacity with an obstructive pattern on pulmonary function testing (187). These abnormalities, specifically triangular subpleural opacities and linear opacities, were most strongly related to oxygen exposure during the neonatal period (187). Australian data demonstrated that about 84% of adult survivors of BPD with follow up data in early adulthood had changes consistent with emphysema on chest CT, primarily centrilobar type, and abnormalities on pulmonary function testing including emphysema and airflow limitation although clinical symptomatology was not as yet prominent (188). Evaluation of adult data is difficult in the current context given the large time lag in obtaining results of follow-up data. It is reasonable to infer that changes in practice management may influence long-term outcomes over time.

In summary, while many premature infants recover from the symptoms of BPD, there is evidence of continued respiratory morbidity in early childhood, such as bronchial hyper reactivity and airway obstruction (183,184). Many of these children require pulmonary medications such as inhaled bronchodilators and corticosteroids; and are rehospitalized in the first few years of life (165,189,190). Objective evidence of differences in lung development and overall function persist into later childhood and young adulthood.

2.3 Impact of BPD on Neurodevelopment

Bronchopulmonary dysplasia and extreme prematurity have been linked to adverse neurodevelopmental outcome with increased need for educational and other specialized community services (176). In a cohort of extremely low birth weight infants, BPD was associated with Mental Developmental Index < 70 on the Bayley Scales of Infant Development – 2nd edition (BSID-II) (OR 2.18; 95% CI: 1.20 – 3.94) and neurologic abnormality (OR 2.46; 95% CI: 1.12 – 5.40) on assessment at 20 months adjusted age (191). Vohr et. al. further corroborated this amongst a cohort of ELBW infants in the NICHD Neonatal Research Network born in the early 1990s (192). The authors demonstrated elevated risk for abnormal neurologic exam, PDI <70, inability to walk independently and inability to feed independently at 18 to 22 month assessment (192). Factors significantly associated with increased neurodevelopmental morbidity included BPD, steroids for BPD, grades 3 to 4 IVH/periventricular leukomalacia, necrotizing enterocolitis, male gender and severe ROP (192,193).

Schmidt et al have shown that infants born < 1000 grams have a baseline risk for neurodevelopmental disability of 20% at 18 months corrected age (193). With each additional neonatal morbidity (BPD, severe ROP or severe IVH), the probability of neurodevelopmental impairment increases by 20%, so that if all three conditions are present, the risk of poor outcome is > 80% (193). In extremely low birth weight infants with the most severe lung disease, prolonged ventilation has been shown to be an

independent risk factor for death and poor neurodevelopmental outcome (109).

Whether pulmonary morbidity and neurodevelopmental outcomes have been affected by trends in neonatal care over the past two decades continues to be an important research question. It has been postulated exogenous surfactant to treat respiratory distress syndrome, antenatal steroids to promote lung maturation and risk-stratified use of post-natal corticosteroid will reduce lung morbidity and long term neurodevelopmental sequelae (20). In a comparison of two birth cohorts of infants born < 1000 grams and < 28 weeks gestation before and after these widespread changes, investigators did not find any difference with respect to the overall duration of oxygen therapy or the rates of BPD (20). Moreover, there were significant increases in the duration of mechanical ventilation and length of time CPAP was required (20). Though there was less neurosensory disability at 20 months adjusted age, there were no statistically significant changes in the rates of cerebral palsy or the number of surviving infants with severe cognitive delays on assessment with the BSID-II (20). The authors hypothesize that the potential improvement from decreased use of post-natal corticosteroid may be offset by the increased morbidity associated with severe BPD, including longer duration of ventilation and supplemental oxygen (20). Further data from the ELGAN study group demonstrated that premature infants born < 28 weeks gestation with the most severe BPD were

at significantly increased risk for cerebral palsy (OR 5.7, 95% confidence interval 2.5 to 13) (194).

In order to determine whether persistent need for oxygen at initial hospital discharge had an impact on development, Australian researchers compared developmental outcomes at 1, 2 and 4 years follow-up between children who continued to require oxygen at discharge compared to those who were in room air but had BPD based on oxygen need at 36 weeks (195). These two groups were also compared with a group of premature infants who did not have BPD (195). Interestingly though statistically significant differences were noted on Griffiths Mental Development Scales at 1 and 2 year assessments, developmental assessment at 4 years demonstrated that children with BPD (both groups) had slightly lower developmental scores on the McCarthy Scales of Children's Abilities than did prematurely born children without BPD (195). This difference was not statistically significant and their results were still within the average range (195). There was also no statistically significant difference between the developmental scores of the BPD room-air group compared with the BPD home-oxygen group (195) The authors postulated that the children with BPD and home oxygen requirements experienced "catch-up" in development once supplemental oxygen was discontinued as a result of decreased stress, improved family functioning, and increased opportunity for developmentally supportive care (195). This study is not generalizable to the entire population of premature infants with BPD as the non-BPD group had significantly higher gestational

ages and birth weights than the two BPD groups and the authors excluded children with sensory and motor disabilities (195).

There is an association between the presence of BPD, duration of oxygen use and the use of post-natal corticosteroids with lower cognitive, academic achievement, motor, and attention skills at school age; however, this finding is controversial in the literature (196,197). Using data from the pre-surfactant era local researchers demonstrated a clear difference in outcomes at school age (8 years) in infants with BPD of any severity (including mild) compared to matched controls (196). However, the difference between the BPD group and the matched preterm comparison group was less clear, and thus it was difficult to conclude that the difference in school age outcomes was due exclusively to BPD or to the effects of prematurity in general (196). This study was limited by a relatively small sample size due to strict inclusion and exclusion criteria (196).

Adults with a history of BPD born in the late 1980s and early 1990s had increased rates of cerebral palsy compared with prematurely born adults without BPD history or with term subjects on health-related quality of life self-reports (198). Additionally these adults have higher rates of outpatient services including prescription medications, more frequent hospital admissions per person-year, longer hospital stays and higher rates of intensive care unit admissions per person-year (198). Study investigators also reported higher rates of ADHD symptoms and subjects were less likely to access higher education than were their preterm-born counterparts

without a history of BDP or subjects born at term (198). It is unknown whether treatment practice changes in neonatal intensive care in the last two decades will result in improvements in these co-morbidities for survivors of prematurity and BPD.

CHAPTER 3:

Local Incidence and Determinants of Bronchopulmonary Dysplasia and Pulmonary Morbidity in Premature Infants

3. 1 Background

The short and long-term respiratory health of premature infants is influenced by specific pulmonary care practices in the neonatal intensive care unit, such as surfactant administration, caffeine therapy and post-natal corticosteroid use. Management strategies in neonatal intensive care vary over time and geographic location as prescribed by evidenced based practice, yet BPD and pulmonary morbidity after discharge continue to be problematic in prematurely born infants (183). Review of infants born in this center between 1997 and 2003 and with birthweight ≤ 1250 grams revealed that rates of BPD range from just under 10% for those born at 29 weeks gestation to 70% in infants born at 24 weeks.

3.2 Study Hypothesis:

The primary hypothesis of this study is that BPD rates continue to be high in infants with prolonged mechanical ventilation in addition to those with the lowest gestational ages. Rates of hospitalization and burden of disease attributable to pulmonary morbidity are unknown for this centre. In addition to BPD, other hypothesized risk factors for pulmonary morbidity in early infancy include exposure to smoke in the home, daycare environment

and family history of atopy. Pulmonary scoring may provide a useful clinical tool to differentiate infants who are likely to develop severe BPD, thus allowing targeted approach to management.

3.3 Objectives

Prevention and management of bronchopulmonary dysplasia (BPD) and resulting pulmonary morbidity, remains one of the greatest challenges of neonatal intensive care. This observational cohort study had three goals: first to estimate the incidence and risk factors contributing to the development of BPD, second to estimate the incidence and risk factors contributing to the development of pulmonary morbidity in early infancy and third to evaluate the use of two specific early scoring systems in the prediction of BPD and early pulmonary morbidity.

The first objective of this observational study was to estimate the incidence of BPD and to evaluate risk factors including mode and duration of ventilation in a cohort of infants who develop BPD compared with infants without BPD. In this centre unsynchronized non-invasive bi-level positive airway pressure ventilation (NIPPV) is often used to prevent reintubation however evidence is lacking regarding efficacy of this strategy. Early extubation using the INSURE technique (intubation and surfactant administration followed by early extubation) combined with the use of NIPPV may reduce the rate of reintubation, thereby decreasing overall length of intubation and thus improve rates of BPD (117,118,199). In this centre

prophylactic surfactant was used for extremely preterm infants, in addition to early initiation of regular caffeine therapy for apnea of prematurity. The use of inhaled nitric oxide, diuretics and post-natal corticosteroid was primarily targeted as rescue therapy for those infants with more severe neonatal lung disease. These care practices are hypothesized to influence the development of BPD.

The second objective of this study was to determine the incidence of pulmonary morbidity during the first year of life in the survivors of the study cohort. Pulmonary morbidity is defined as any of 1) death from a pulmonary cause; 2) pneumonia or sepsis with a positive blood culture or requiring antibiotics for 5 days or more; 3) continued hospitalization or rehospitalization for a pulmonary cause; 4) continued use of oxygen, diuretics or systemic steroids for pulmonary disease; or 5) use of pulmonary medications, including systemic or inhaled bronchodilators and/or corticosteroids or leukotriene receptor antagonists (163).

The third objective of this study was to evaluate the clinical utility of two pulmonary scoring tools, the chronic oxygen dependency (COD) score and the pulmonary severity (PS) score in the prediction of BPD and pulmonary morbidity during the first year of life (163,164). Receiver operating characteristic curve analyses were used to determine if one score has any advantage over the other when the scores are applied within the first two days of life or at one week of age.

Early identification of patients at risk for BPD and pulmonary morbidity facilitate review of local practices and potentially modifiable determinants of short-term lung health. The clinical significance of this study is that it will assess the rate of disease in a local population and thus facilitate comparison with historical rates of disease and rates of disease in other centres, so that management practices can be critically evaluated with respect to continuing quality assurance and improvement.

3.4 Methods

3.4.1 Study Design and Study Subjects

This observational prospective study was conducted on a cohort of premature infants discharged from the Royal Alexandra Hospital, Edmonton, Alberta from August 1, 2008 to July 31, 2009. The cohort included infants born at < 29 weeks gestational age or with a birth weight of ≤ 1250 grams that were followed prospectively to 6 to 8 months corrected age. Corrected age was calculated by subtracting the number of weeks prematurity from the infant's chronological age. Infants with major lethal anomalies were excluded if the anomaly was felt to influence the likelihood of hospitalization or lead to major medical morbidity, as this would skew the results of the study. Infants enrolled in another study evaluating oxygen saturation targets were also excluded from this study due to conflicting study goals. Parental consent was obtained to collect demographic information on the mother and infant from the infant's hospital records, and information about lung health was collected

from parents and caregivers at 3 and 6 months corrected age by telephone and face-to-face interview questionnaire respectively. Gestational age was defined by best estimate based on early ultrasound or last menstrual period or by neonatal evaluation according to the method of Ballard and Dubowitz (200). Fenton growth charts were used to determine whether infants were classified as growth restricted, based on birth weight, head circumference and total length below the 3rd percentile (201). There were too few growth restricted infants to determine the influence of symmetric versus asymmetric growth restriction.

3.4.2 Respiratory Management

In this centre infants born < 25 weeks gestation were treated with prophylactic bovine lipid extract surfactant (BLES Biochemicals Inc. DIN 02245464) via endotracheal intubation prior to 30 minutes of age. Infants born > 26 weeks gestation were given early rescue surfactant before 2 hours of age if they required supplemental oxygen with FiO2 > 0.30 on nasal CPAP (6 cm H_20) or mechanical ventilation. Any infant with persistent or recurrent oxygen and ventilation requirements were given repeat doses of surfactant up to a maximum of three doses within the first 72 hours of life.

For the purposes of this analysis, infants were classified as having BPD if they require supplemental oxygen and/or ventilatory support at 36 weeks post-menstrual age or at final hospital discharge, equivalent to moderate or severe BPD as outlined in the NICHD Bronchopulmonary Dysplasia Workshop (7). Mild BPD or no BPD groups were assessed together as it has

been previously shown that oxygen dependency at 36 weeks corrected gestational age is more predictive of pulmonary morbidity in infancy (5). In addition, this study evaluated perinatal and neonatal determinants of BPD within the context of early extubation after surfactant prophylaxis, the use of NIPPV and decreased use of post-natal corticosteroid therapy.

3.5 Data Collection

Data were abstracted from hospital records using a standardized data collection sheet. Information collected included demographic data for the mother (maternal age and parity) as well as maternal comorbidities, labor and delivery history, and gender, gestational age, weight, length and head circumference of the infant at time of birth. Specific variables included duration of rupture of membranes, presence or absence of chorioamnionitis or evidence of maternal infection, presence of maternal gestational hypertension or antepartum hemorrhage, number of courses of antenatal steroids, and mode of delivery. Chorioamnionitis was defined clinically based on the suspicion of the attending obstetrician or histologically confirmed on pathology report based on the presence of polymorphonuclear leukocytes infiltrating the chorion or amnion.

Pulmonary management data, including ventilatory support, medication use and oxygen support were collected at specific time points for infants during their hospitalization (specifically at days 2, 7 and 28 of life; and at 35 and 36 weeks corrected gestational age). The total number of days

of ventilation support was recorded for each category: room air, low flow nasal cannula, nasal CPAP or high flow nasal cannula, biphasic nasal CPAP or mechanical ventilation through an endotracheal tube. Partial days on each type of ventilation support were counted as one day if the study participant was treated for 6 or more out of 24 hours on a given day, thus the total days on ventilation support exceeded the actual cumulative days of ventilation support. Mean and median values of inhaled oxygen were calculated for each time point; days 2, 7, 28 and week 36 post-menstrual age. Medications used to manage respiratory distress syndrome and evolving BPD included caffeine, diuretics (aldactazide or furosemide), or systemic dexamethasone. In this centre, dexamethasone has also been used for post-extubation stridor, however this particular use was not observed in this study cohort. Bronchopulmonary dysplasia was diagnosed as mild if the subject required oxygen or ventilatory support at 28 days of age but not at 36 weeks corrected gestational age; moderate if the subject requires < 30% supplemental oxygen at 36 weeks corrected gestational age; severe if the subject requires > 30 % supplemental oxygen or ongoing invasive ventilatory support at 36 weeks corrected gestational age (7). For the purposes of risk factor analysis, study participants were classified as having BPD only if oxygen or mechanical ventilation was required at 36 week corrected gestational age.

Other morbidities recorded included pulmonary hemorrhage, clinical or echocardiographic diagnosis of patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC) as defined by Bell's criteria as stage 2 or

higher, intraventricular or parenchymal hemorrhage (IVH) of any severity, retinopathy of prematurity (ROP) classified according to international ROP classification system, hypotension requiring hydrocortisone therapy, and clinical sepsis (202,203). The use of inhaled nitric oxide (iNO) was also documented. PDA was defined clinically with echocardiographic confirmation left to the discretion of the attending physician caring for the infant. Subjects with PDA were further categorized into those requiring no treatment, medical therapy only or surgical ligation. Medical therapy during the study period was intravenous indomethacin with a 3-dose course of 0.2 mg/kg followed by 0.1 mg/kg 12 hours and 36 hours after the first dose. Infants were classified in the surgical ligation group whether or not they had received earlier medical therapy. Intracranial hemorrhage was categorized as none, unilateral, bilateral, periventricular or complicated (developing post-hemorrhagic hydrocephalus). Necrotizing enterocolitis was classified using Bell's criteria and only stage II and above was considered(202). Clinical sepsis was defined as any positive blood, cerebral spinal fluid, endotracheal tube secretions, or urine culture. Superficial infections such as cellulitis or external wound infections were not counted as an episode of clinical sepsis.

At 3 and 6 months corrected age, pulmonary morbidity was defined as per Madan et al. as any one of 1.) death from a pulmonary cause, 2.) pneumonia or sepsis with a positive blood culture or requiring antibiotics for 5 days or more, 3.) continued hospitalization or rehospitalization for a pulmonary cause, 4.) continued use of oxygen, diuretics or systemic steroids

for pulmonary disease or 5.) use of pulmonary medications, including systemic or inhaled bronchodilators and/or corticosteroids or leukotriene receptor antagonists (163). In a post-hoc analysis, “minor” pulmonary morbidity, defined as any one of 1.) persistent or recurrent symptoms of cough or wheeze; 2.) recurrent physician visits for pulmonary symptoms; 3.) need for chest radiographs any time after initial hospital discharge; or 4.) continued abnormal symptoms related to feeding, such as choking, gagging or coughing with feeds was also assessed.

Pulmonary outcomes were assessed by questionnaire format with the parents or legal guardians of the study subjects by telephone at three months corrected age and by face-to-face interview in the Neonatal and Infant Follow-up Clinic at six months corrected age. At the six-month evaluation, anthropomorphic parameters and physical assessment of the child was recorded. In addition, pulmonary risk factors were evaluated, including family history of atopy (history of asthma, eczema or allergy in a first degree relative), environmental risk factors such as smoking in the home and attendance at or exposure to day care or day home environments.

3.6 Statistical Analysis

The overall incidence of the composite outcome of BPD or death was calculated at 36 weeks corrected gestational age according to the diagnostic criteria of the NICHD, with further sub classification of severity for mild, moderate, or severe BPD (7). The incidences of mild, moderate, severe BPD,

and death were also calculated separately for the whole cohort by gestational age. The overall incidence of pulmonary morbidity as defined above was determined for the surviving sub-cohort and risk factors for pulmonary morbidity were analyzed using univariate and multivariate analysis.

Means, medians, standard deviations and ranges were used to describe the continuous variables for absence/ presence of BPD. Proportions and frequency distributions were used to summarize binary outcome variables. For all variables of primary interest, 95% confidence intervals (CIs) for summary measures were reported. Groups were compared on maternal demographic variables and data, and neonatal demographics and data. Anthropomorphic parameters were compared for study participants with and without BPD and survivors with and without pulmonary morbidity at 6 months corrected age. Two-independent sample Student t-tests and/or Mann-Whitney U tests were used to assess the equality of the means of continuous variables between two groups whereas Pearson chi-square tests or the Fisher's exact test were used to assess the equality for categorical variables. Logistic regression analysis was conducted for one variable at a time to determine which were significantly related to the outcome of BPD using $p<0.2$ as inclusion. Continuous variables with significant pair-wise correlations, such as birth weight and gestational age, were evaluated to determine which would be more clinically relevant for inclusion in the model to reduce or eliminate colinearity within the model. For the multiple logistic regression analysis, variables included maternal

characteristics (age, mode of delivery, number of fetuses, prolonged rupture of membranes, chorioamnionitis, hypertension, antepartum hemorrhage, Group B *Streptococcus agalactiae* status, antenatal corticosteroids and intrapartum antibiotic use), infant perinatal factors (gestational age at birth, birth weight, 1 and 5 minute Apgar scores, presence of respiratory distress syndrome, need for more than one dose of surfactant) and neonatal morbidities and management factors (duration of ventilation support, pulmonary hemorrhage, use of inhaled nitric oxide, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), sepsis, hypotension requiring hydrocortisone treatment and overall length of stay).

A second logistic regression analysis with one variable at a time was conducted with select neonatal and post-natal variables (birth weight, antenatal and post-natal glucocorticoid exposure, histologic chorioamnionitis, surfactant exposure, BPD, sepsis, necrotizing enterocolitis, PDA and ROP) to determine which were significantly related to the outcome of pulmonary morbidity at either 3 or 6 months corrected age using $p<0.2$ as inclusion. Other risk factors evaluated include environmental exposure to cigarette smoke in the home, family history of atopy and enrollment in daycare. For the purposes of this analysis, the study participant was classified as experiencing pulmonary morbidity if any of the 5 specified pulmonary outcomes were identified at either time point. As with the previous analysis, pair-wise correlation was used and judgment was used to

determine clinically relevant variables for inclusion in the model to reduce colinearity. Logistic regression analysis with purposeful/stepwise variable selection methods was conducted to determine the clinical utility of the pulmonary scoring tools in the prediction of pulmonary morbidity at 6 months adjusted age. Post-hoc analysis of the incidence of less severe pulmonary morbidities was also determined, defined as any one of 1.) need for chest radiographs, 2.) physician or emergency department visits for pulmonary cause, 3.) pulmonary signs and symptoms (wheeze, cough or shortness of breath), or 4.) feeding difficulties related to choking, gagging, coughing, spitting up, poor growth, pulling away from feeds or incoordination of swallowing. These outcomes were observed clinically far more often than overall pulmonary morbidity as defined for the study purposes during the first few months after hospital discharge.

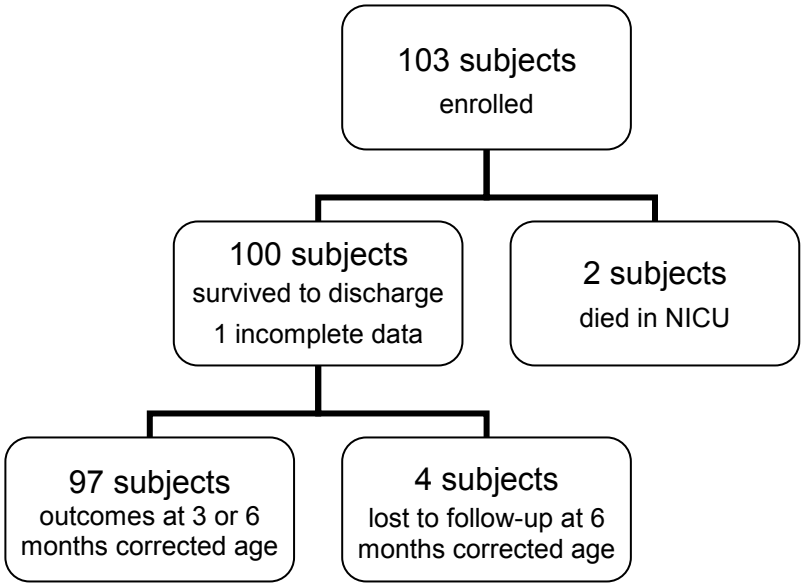
COD (FiO_2 X ventilator support) and PS ({FiO_2 X ventilator support } + medication) scores were evaluated separately in the models to determine whether these scores are clinically useful independent of confounders for BPD and pulmonary morbidities. All analyses were performed using STATA 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP).

3.6.1 Sample Size

Based on admissions in the Northern Alberta Neonatal Intensive Care Program in 2006, 154 infants were admitted with gestational age < 29 weeks or weight < 1250 grams at birth. Anticipating a participation rate of 75-80%

with loss to follow up of 10-15% the goal was to recruit 100 to 110 study participants. Using PASS 2008 © software for sample size calculation based on the assumption of a 50% event rate in the study population, estimated from data by Madan et al., a total sample size of 92 patients (46 subjects with BPD and 46 with no BPD) was required to detect a difference of 0.15 between the areas under the curves of the ROC curves generated by the two pulmonary scoring systems to predict pulmonary morbidity, assuming 80% power and an alpha of 0.05(163,204). An inception cohort of 103 infants born < 29 weeks gestation and/or birth weight ≤ 1250 grams was recruited to this study from August 1, 2008 to July 31, 2009 (see figure 3-1).

Figure 3-1. Description of Study Sample



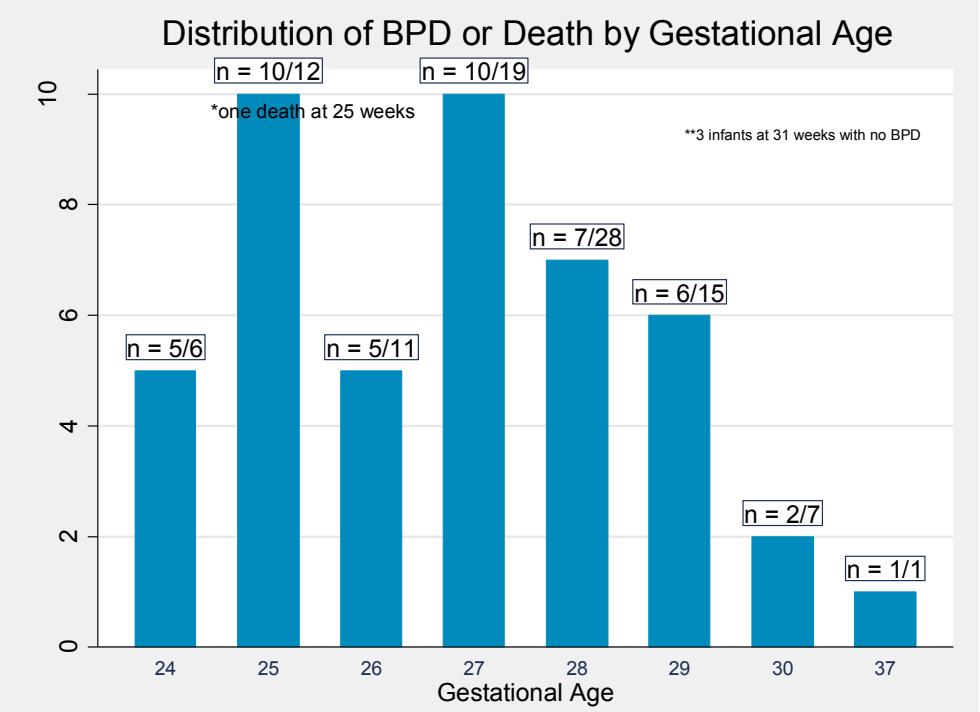
CHAPTER 4:

Results

4.1 Characteristics of Participants

In this study, 102 study participants were recruited between August 1, 2008 to July 31, 2009. One study participant was transferred to a different centre prior to determination of the primary study outcome (BPD). Mean gestational age (± SD) at was 27 ± 2 weeks (range 24 to 37 weeks) with a mean birth weight of 1022 ± 203 grams (range 640 to 1570 grams). 65% of the study subjects recruited were male and 43% were singleton pregnancies. 40% were primigravida mothers and average maternal age (± SD) at delivery was 29.6 ± 5.7 years. Overall the rate of moderate to severe BPD or death defined as supplemental oxygen need at 36 weeks corrected age was 43.7% (95% CI: 34.9, 54.8) in this population. Gestational age was inversely related to BPD (see Figure 4-1). Classifying by the NICHD Workshop categories, 16.5 % (95% CI: 9.9, 25.1) of infants had no BPD, 37.9% (95% CI: 28.4, 48.0) had mild BPD, 35.9% (95% CI: 26.7,46.0) had moderate BPD and 7.8% (95% CI: 3.4, 14.7) had severe BPD. (See Table 4-1) Two infants died prior to hospital discharge; one infant died at 4 weeks of age from necrotizing enterocolitis totalis, the other died at 45 weeks corrected age of cardiorespiratory failure.

Figure 4-1. Distribution of BPD or Death by Gestational Age.



[Boxes: Number with BPD over total number within each gestational age category]

Table 4-1. BPD Severity by Gestational Age

GA (n)	BPD Severity n (%) (95% CI)				
	None	**Mild**	**Moderate**	**Severe**	**Death**
24 – 26+6 (n=29)	1(3.4) (0.09-17.8)	8 (27.6) (12.7-47.2)	14 (48) (29.4-67.5)	5 (17.2) (5.8-35.8)	1 (3.4) (0.09-17.8)
27 – 29+6 (n=62)	9 (14.5) (6.9-25.8)	30 (48.4) (35.5-61.4)	19 (30.6) (19.6-43.7)	3 (4.8) (1-13.5)	1 (1.6) (0.04-8.7)
30 – 32+6 (n=10)	7 (70) (34.8-93.3)	1 (10) (0.3-44.5)	2 (20) (2.5-55.6)	0	0
≥ 33 (n=1)	0	0	1 (100) (2.5-100)	0	0
All (n=102)	17 (16.7) (10-25.3)	39 (38.2) (28.8-48.4)	36 (35.3) (26-45.4)	8 (7.8) (3.4-14.9)	2 (2) (0.2-6.9)

4.2 Factors Associated with BPD

Demographic analysis of maternal and neonatal data demonstrated significant differences between infants with mild or no BPD compared to infants with moderate or severe BPD or death (table 4-2). There were no differences noted between infants with and without the outcome of BPD or death in terms of antepartum and perinatal characteristics, such as singleton pregnancy, use of antenatal steroids or antibiotics and presence of prolonged rupture of membranes, chorioamnionitis, maternal GBS status or mode of delivery. Infants who died or required ongoing respiratory support at 36 weeks corrected age were more likely to be male, of younger gestational age and smaller birth weight and be delivered to slightly younger mothers. With respect to potentially modifiable risk factors, infants with BPD or death were more likely to have received multiple doses of surfactant, required more days of invasive and non-invasive respiratory support and higher initial supplemental oxygen needs. They were also more likely to require inhaled nitric oxide. All infants with sepsis or pulmonary hemorrhage developed BPD or died (results not shown). Infants with PDA, IVH and ROP were more likely to develop BPD or death (see table 4-3). The overall length of stay was also significantly longer for infants with BPD (64 ± 16 vs 113 ± 70 days, $p < 0.0001$).

Table 4-2. Characteristics of Infants With and Without BPD

Characteristics	No BPD	BPD	*P* value
Number of infants, n (%)	56 (55)	46 (45)	
Gestational age, weeks (mean ± SD)*	28.3 (1.5)	27.3 (2.3)	0.01
Mean birth weight, g (mean ± SD)*	1096 (184)	929 (188)	<0.0001
IUGR (%)**	0 (0)	3 (3)	0.08
Male gender (%)**	30 (54)	37 (80)	0.004
Apgar at 1 min (mean ± SD)*	5 (2)	4 (2)	0.006
Apgar at 5 min (mean ± SD)*	7 (2)	6 (2)	0.004
Length of Stay (days, mean ± SD)	64 (16)	113 (70)	<0.0001
Maternal age at delivery, y (mean ± SD)*	31 (5)	28 (6)	0.03
Primigravida (%)**	24 (43)	16 (35)	0.4
Singleton pregnancy (%)**	32 (55)	26 (45)	0.9
Cesarean section (%)**	32 (57)	31 (67)	0.2
Prolonged rupture of membranes (%)** (known in 100)	13 (24)	10 (22)	0.8
chorioamnionitis (%)** (known in 75)	16 (38)	13 (39)	0.9
Maternal Group B *Streptococcus* (%)** (known in 47)	4 (19)	6 (23)	0.7
Intrapartum antibiotics (%)** (known in 84)	42 (62)	9 (56)	0.7
Antenatal steroids (%)** (known in 98)	47 (89)	40 (89)	0.97
Pregnancy induced hypertension (%)** (known in 50)	12 (30)	2 (20)	0.7
Antepartum hemorrhage (%)** (known in 64)	28 (56)	6 (43)	0.6

*Student t-test with unequal variances ** Pearson Chi Square test

Table 4-3. Predictors of Moderate/Severe BPD or Death: Results from Univariate Logistic Regression

Variable	Mean (± SD) or Frequency (%) n = 46 with BPD	OR for BPD	95% CI	P value
Gestational age at birth, weeks	27 (± 2)	0.72	0.57 to 0.92	0.009
Female gender	9 (20)	0.28	0.11 to 0.69	0.006
Apgar at 1 minute	4 (± 2)	0.78	0.65 to 0.94	0.009
Apgar at 5 minutes	6 (± 2)	0.71	0.55 to 0.90	0.006
Birth weight, grams	928 (± 188)	0.995	0.992 to 0.998	<0.001
Maternal age, years	28 (± 6)	0.92	0.86 to 0.99	0.03
Antenatal Steroid*	40 (89)	1.02	0.29 to 3.60	0.97
Surfactant therapy				
1 dose	27 (59)	3.66	0.94 to 14.19	0.06
2 doses	11 (24)	5.30	1.14 to 25.55	0.03
3 or more doses	5 (11)	10.83	1.37 to 85.44	0.02
Days of invasive ventilation	30 (± 32)	1.17	1.09 to 1.26	<0.001
Days of non-invasive ventilation	81 (± 66)	1.07	1.04 to 1.10	<0.001
COD Score at day 2	0.59 (± 0.28)	82.58	7.03 to 969.89	<0.001
PS Score at day 2	0.63 (± 0.28)	72.32	6.19 to 844.80	0.001
COD Score at day 7	0.51 (± 0.16)	2590	97.47 to 68862	<0.001
PS Score at day 7	0.55 (± 0.15)	2823	95.45 to 83491	<0.001
Need for inhaled nitric oxide	7 (15)	9.87	1.17 to 83.49	0.04
Patent ductus arteriosus	23 (7.5)	3.31	1.42 to 7.72	0.006

*known for 45

Table 4-3. Predictors of Moderate/Severe BPD or Death: Results from Univariate Logistic Regression (Continued)

Variable	Mean (± SD) or Frequency (%) n = 46 with BPD	OR for BPD	95% CI	P value
Necrotizing enterocolitis (stage 2 or more)	9 (20)	3.16	0.91 to 11.05	0.07
Intraventricular hemorrhage	19 (41)	3.24	1.31 to 7.97	0.01
Retinopathy of prematurity***				
Stage 1	15 (34)	3.58	1.28 to 10.01	0.015
Stage 2	7 (16)	5.43	1.31 to 22.45	0.02
Stage 3	2 (5)	3.1	0.39 to 24.95	0.29
Laser Therapy	10 (23)	31	3.52 to 273	0.002

** known for 44

Logistic regression analysis was used to determine risk factors associated with developing moderate to severe BPD or death. Logistic regression analysis with one variable at a time was used to determine which independent variables to include in the logistic regression model to predict the outcome, using $p<0.2$ for inclusion in the main effects model. Maternal factors initially included in the model building included maternal age and administration of antenatal steroids. In addition to weight and gestational age at birth, labor and delivery factors that were significant in the univariate analysis included gender and Apgar scores at 1 and 5 minutes. Significant factors predicting BPD in the univariate analysis demonstrated that the COD and PS scores at both days 2 and 7 were significantly associated with the development of moderate or severe BPD or death, in addition to treatment with surfactant, duration of invasive and non-invasive ventilation, continued mechanical ventilation at day 2, treatment with inhaled nitric oxide, presence of any patent ductus arteriosus, necrotizing enterocolitis stage 2 or higher, and any intraventricular hemorrhage (see Table 4-3). Logistic regression analysis with purposeful/ stepwise variable-selection methods revealed that the COD and PS scores were no longer significant when controlling for gestational age, duration of invasive and non-invasive ventilation. There was significant interaction between the duration of invasive ventilation and the duration of non-invasive ventilation (see Table 4-4).

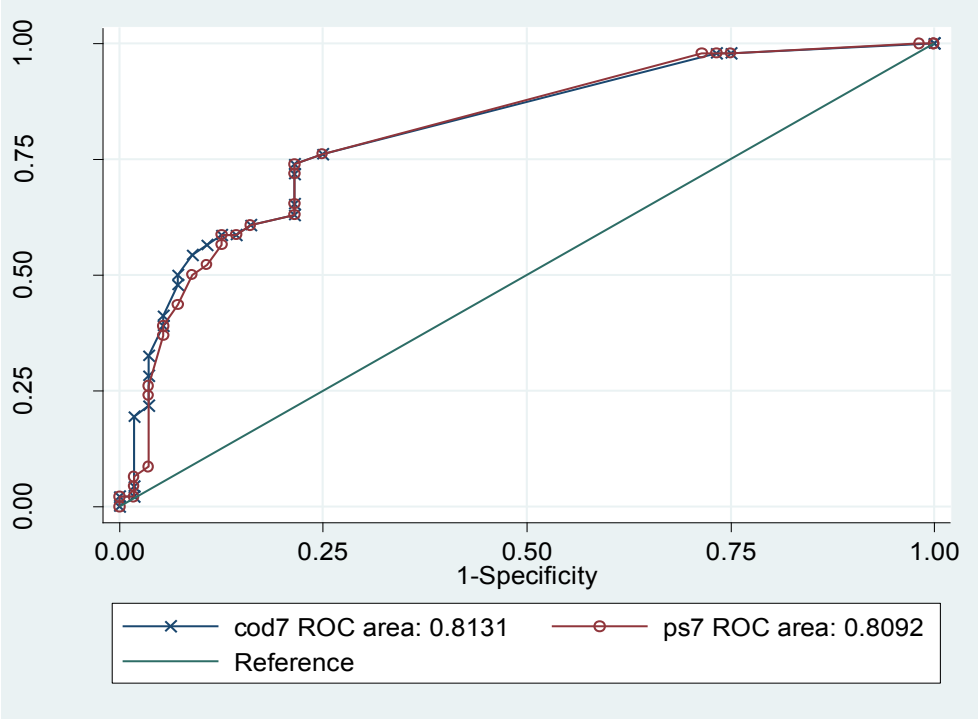
Table 4-4. Predictors of Moderate/Severe BPD or Death: Results from Multiple Logistic Regression

Variable	OR for BPD	95% CI	P value
Gestational age at birth, weeks	2.6	1.3 to 5.1	0.008
Days of invasive ventilation	1.5	1.2 to 1.8	<0.001
Days of non-invasive ventilation	1.1	1.1 to 1.2	0.001
Interaction Term (invasive ventilation*non-invasive ventilation)	0.997	0.995 to 0.999	0.005
Patent ductus arteriosus	3.8	0.8 to 18.9	0.1
Necrotizing enterocolitis (stage 2 or more)	1.7	0.06 to 51	0.8
Intraventricular hemorrhage	0.3	0.05 to 2.3	0.3

4.3 Chronic Oxygen Dependency & Pulmonary Severity Score

Comparison of receiver operating characteristic curves to determine whether the chronic oxygen dependency (COD) score or pulmonary severity (PS) score performed better in the prediction of moderate to severe BPD or death revealed that COD and PS scores at day 7 performed slightly better than COD and PS scores at day 2, with an area under the curve of 0.81 (for both COD and PS at day 7) compared with 0.72 (for both COD and PS at day 2) however these differences were not statistically significant ($p=0.07$ for both comparisons). Comparison of the COD and PS at day 7 demonstrated similar areas under the curve (see Figure 4-2). Neither score was superior in the prediction of moderate to severe BPD ($p=0.33$).

Figure 4-2. Receiver Operating Characteristic Curves - COD7 and PS7



4.4 Predictors of Pulmonary Morbidity at 3 and 6 Months

Of 88 infants with three month adjusted age data available, 18 (20.5%) demonstrated pulmonary morbidity. Many more infants, 52 (59%) of the 88 infants, experienced "minor" pulmonary morbidity.

There were no differences in gestational age at birth or mean birth weight between infants with pulmonary morbidity at three months adjusted age compared with those without (see Table 4-5). However infants with pulmonary morbidity at three months were less likely to have exposure to antenatal steroids, more likely to be treated with multiple doses of surfactant, intubated and required low flow nasal cannula for a longer period, more likely to have been treated with inhaled nitric oxide and to have longer overall hospital stay. These infants were characterized by higher oxygen requirements at day 2 and ongoing mechanical ventilation at the end of the first week of life. Infants with pulmonary morbidity were also significantly more likely to have neonatal morbidities, such as hemodynamically significant PDA, intraventricular hemorrhage and moderate or severe bronchopulmonary dysplasia (see Tables 4-5, 4-6). Not surprisingly, pulmonary morbidity at three months was also associated with increased frequency of symptoms such as wheeze and increased need for physician assessment and chest radiographs for pulmonary symptoms (see Table 4-7).

Table 4-5. Demographic Characteristics of Infants With and Without Pulmonary Morbidity at 3 Months Corrected Age (n = 88)

Characteristics	No PMORB	PMORB	*P* value
Number of infants, n (%)	70 (80)	18 (20)	
Gestational age, weeks (mean ± SD)*	28 (1.5)	27.7 (3.1)	0.68
Mean birth weight, g (mean ± SD)*	1066 (194)	989 (200)	0.16
IUGR (%)**	2 (3)	1 (6)	0.6
Male gender (%)**	40 (57)	15 (83)	0.04
Maternal age at delivery, y (mean ± SD)*	31 (5)	27 (6)	0.02
Singleton pregnancy (%)**	36 (51)	15 (83)	0.01
Antenatal steroids (%)** (known in 85)	63 (93)	12 (71)	0.01

*Student t-test with unequal variances ** Pearson Chi Square test

Table 4-6. Neonatal & Respiratory Characteristics of Infants With and Without Pulmonary Morbidity at 3 Months Corrected Age (n = 88)

Characteristics	No PMORB	PMORB	*P* value
RDS (%)**	55 (79)	17 (94)	0.12
Multiple doses of surfactant (%)**	14 (20)	9 (50)	0.01
Days of mechanical ventilation (mean ± SD)*	8 (13)	27 (30)	0.02
Days of biphasic CPAP (mean ± SD)*	10 (11)	11 (10)	0.6
Days of nasal CPAP (mean ± SD)* (known for 87)	24 (15)	26 (15)	0.65
Days of LFNC (mean ± SD)* (known for 87)	15 (12)	31 (22)	0.007
Day 2 FiO2 (mean ± SD)*	0.24 (0.05)	0.29 (0.08)	0.01
Day 7 FiO2 (mean ± SD)*	0.22 (0.02)	0.23 (0.03)	0.15
Ongoing Ventilation at Day 2 (%)**	20 (29)	9 (50)	0.09
Ongoing Ventilation at Day 7 (%)**	12 (17)	7 (39)	0.05
Bronchopulmonary Dysplasia (%)**	25 (36)	12 (67)	0.02
Pulmonary hemorrhage (%)**	4 (6)	3 (17)	0.12
inhaled NO (%)**	2 (3)	5 (28)	<0.001
PDA (%)**	20 (29)	10 (56)	0.03
NEC (%)**	7 (10)	2 (11)	0.89
IVH (%)**	14 (20)	8 (44)	0.03
ROP (%)** (known in 82)	32 (49)	11 (65)	0.3
Sepsis (%)**	3 (4)	3 (17)	0.06
Hypotension treated with steroids (%)** (known in 87)	5 (7)	3 (18)	0.2
Length of stay, days (mean ± SD)*	74 (22)	97 (35)	0.01

*Student t-test with unequal variances ** Pearson Chi Square test

Table 4-7. Risk Factors in Infants With and Without Pulmonary Morbidity at 3 Months Corrected Age (n = 88)

Characteristics	No PMORB	PMORB	*P* value
Family History of Atopy (%) (known for 87)**	45 (65)	13 (72)	0.57
History of Atopy (%)**	3 (4)	2 (11)	0.27
Exposure to smoking at home (%)**	19 (27)	8 (44)	0.16
Chest radiographs (%) (known for 85)**	1 (1)	8 (44)	<0.001
Physician attendance for lung symptoms (%)**	14 (20)	12 (67)	<0.001
Symptoms of wheeze, cough, shortness of breath (%)**	14 (20)	9 (50)	0.01
Feeding difficulties (%)**	18 (26)	5 (28)	0.9
Received palivizumab prophylaxis (%) (known for 84)**	48 (72)	13 (76)	0.60

*Student t-test with unequal variances ** Pearson Chi Square test

Similarly, 24.5 % (23/94) infants had ongoing pulmonary morbidity and 56.4% (53/94) infants had ongoing "minor" pulmonary symptoms at six months adjusted age follow-up. Gestational age at birth and birth weight was similar between infants with and without pulmonary morbidity. Male gender and younger maternal age at birth were associated with pulmonary morbidity at six months. Singleton pregnancy and exposure to antenatal steroid was not associated with pulmonary morbidity at six months adjusted age unlike at three months (see Table 4-8). Of the neonatal characteristics, longer duration of invasive ventilation support as well as biphasic CPAP and LFNC, need for inhaled nitric oxide, and hypotension requiring corticosteroid therapy were significantly associated with pulmonary morbidity. Of the associated comorbidities, only moderate or severe bronchopulmonary dysplasia and intraventricular haemorrhage remained statistically significantly different between groups (see Table 4-9). Similar to three months adjusted age, infants at six months adjusted age with pulmonary morbidity were more likely to have respiratory symptoms, need physician care and have required chest radiographs, but at six months had also increasing reports of atopy symptoms and feeding difficulties (see Table 4-10). Interestingly, treatment with palivizumab was not associated with less pulmonary morbidity either at three or six months adjusted age (see Tables 4-7 & 4-10).

Table 4-8. Demographic Characteristics of Infants With and Without Pulmonary Morbidity at 6 Months Corrected Age (n = 94)

Percent (unless otherwise specified	No PMORB	PMORB	*P* value
Number of infants, n (%)	71 (76)	23 (24)	
Gestational age, weeks (mean ± SD)*	28 (1.6)	27 (2.8)	0.17
Mean birth weight, g (mean ± SD)*	1036 (201)	957 (174)	0.08
IUGR (%)**	2 (3)	1 (4)	0.7
Male gender (%)**	41 (58)	20 (87)	0.01
Maternal age at delivery, y (mean ± SD)*	31 (5)	27 (6)	0.02
Singleton pregnancy (%)**	39 (55)	15 (65)	0.39
Antenatal steroids (%)** (known in 91)	60 (87)	21 (95)	0.27

*Student t-test with unequal variances ** Pearson Chi Square test

Table 4-9. Neonatal & Respiratory Characteristics of Infants With and Without Pulmonary Morbidity at 6 Months Corrected Age (n = 94)

Percent (unless otherwise specified)	No PMORB	PMORB	*P* value
RDS (%)**	58 (82)	21 (91)	0.27
Multiple doses of surfactant (%)**	17 (24)	9 (39)	0.16
Days of mechanical ventilation (mean ± SD)*	9 (15)	35 (41)	0.01
Days of biphasic CPAP (mean ± SD)*	9 (10)	16 (9)	0.003
Days of nasal CPAP (mean ± SD)* (known in 93)	23 (14)	41 (54)	0.126
Days of LFNC (mean ± SD)* (known in 92)	17 (15)	35 (38)	0.04
Pulmonary hemorrhage (%)**	5 (7)	3 (13)	0.4
inhaled NO (%)**	3 (4)	4 (17)	0.04
PDA (%)**	22 (31)	10 (43)	0.27
NEC (%)**	8 (11)	3 (13)	0.8
IVH (%)**	16 (23)	11 (48)	0.02
ROP (%)** (known in 88)	39 (60)	13 (57)	0.77
Sepsis (%)**	4 (6)	4 (17)	0.08
Hypotension treated with steroids (%)** (known in 93)	5 (7)	6 (26)	0.02
Length of stay, days (mean ± SD)*	75 (24)	128 (93)	0.01
Bronchopulmonary Dysplasia (%) (known in 93)	28 (40)	15 (65)	0.04

*Student t-test with unequal variances ** Pearson Chi Square test

Table 4-10. Characteristics of Infants With and Without Pulmonary Morbidity at 6 Months Corrected Age (n = 94)

Percent (unless otherwise specified)	No PMORB	PMORB	*P* value
Family History of Atopy (%) (known for 92)	46 (65)	14 (67)	0.9
History of Atopy (%)	8 (11)	8 (35)	0.01
Exposure to smoking at home (%)	22 (31)	8 (35)	0.7
Chest radiographs (%)	2 (3)	16 (70)	<0.001
Physician attendance for lung symptoms (%)	17 (24)	20 (87)	<0.001
Symptoms of wheeze, cough, shortness of breath (%)	9 (13)	12 (52)	<0.001
Feeding difficulties (%)	8 (11)	10 (43)	0.001
Received palivizumab prophylaxis (%) (known for 84)	50 (71)	16 (70)	0.9

*Student t-test with unequal variances ** Pearson Chi Square test

Evaluation of the receiver-operating characteristic curves demonstrated that there was a trend for the COD and PS scores at day 7 to perform better than the scores at day 2 for predicting bronchopulmonary dysplasia ($p = 0.07$ for each, respectively). There was a reverse trend noted for predicting three month outcome, in that the scores at day 2 seemed to perform better than the scores at day 7 however this was not statistically significant ($p = 0.2$ for COD day 2 vs. COD day 7 and for PS day 2 vs. PS day 7 in predicting three month outcome, see Figure 4-3). At six months, the scores had lower areas under the curve overall and there appeared to be no difference between the scores or between the scores at day 2 versus day 7 ($p = 0.7$ for COD day 2 vs. COD day 7 and for PS day 2 vs. PS day 7 for predicting six month outcome, see Figure 4-4). Overall the areas under the curve for the scores were not significantly different in the prediction of any of the three outcomes (see Table 4-11). Direct comparison of COD and PS scores at day 2 or at day 7 did not demonstrate superiority of either score.

Figure 4-3. Comparison of Receiver Operating Characteristic Curves for COD and PS Scores at Days 2 and 7 for 3 Month Pulmonary Morbidity

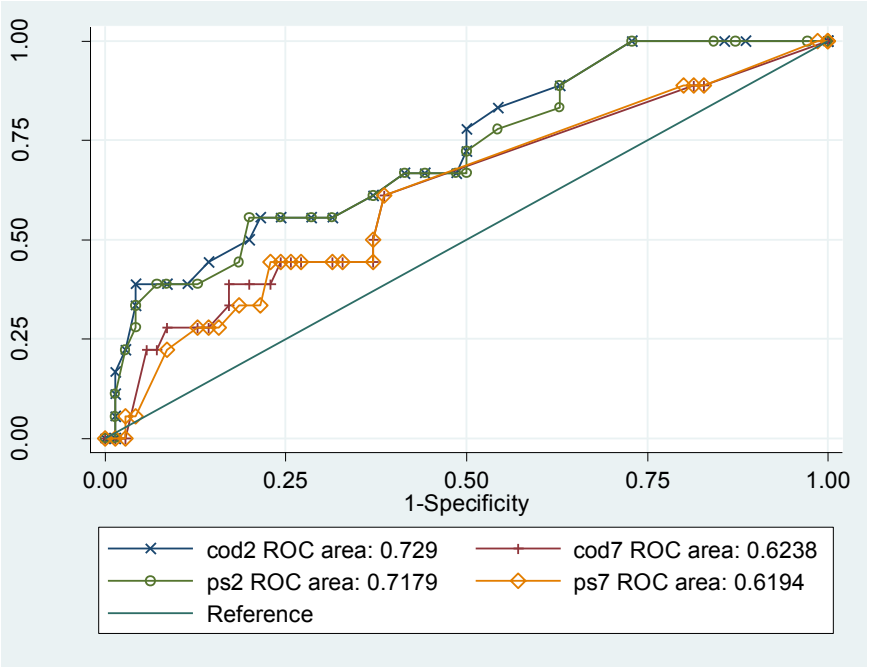


Figure 4-4. Comparison of Receiver Operating Characteristics Curves for COD and PS Scores at Days 2 and 7 for 6 Month Pulmonary Morbidity

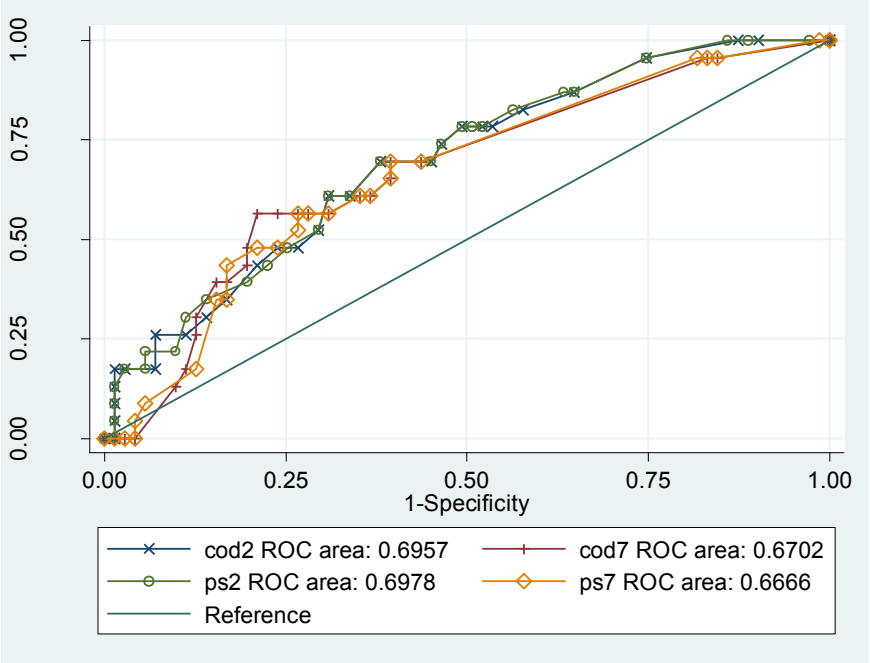


Table 4-11. Area Under the Curve for COD and PS Scores at Days 2 and 7 for BPD and Pulmonary Morbidity at 3 and 6 Months Corrected Age

Score	BPD (n = 102)	3 Months Adjusted Age	6 Months Adjusted Age
COD Day 2	0.72	0.73	0.7
COD Day 7	0.81	0.62	0.67
PS Day 2	0.72	0.72	0.7
PS Day7	0.81	0.62	0.67
p-value*	0.14	0.17	0.89

*test of equality of the receiver operating characteristic curve areas using graph 1 (COD day 2) as the reference

Table 4-12. Univariate Analysis of Factors Associated With Pulmonary Morbidity at 6 Months Corrected Age (n = 94)

Variable	Mean (± SD) or Frequency (%) n = 23 with PMORB	OR for PMORB	95% CI	P value
Gestational age at birth, weeks	27 (± 2.7)	0.77	0.58 to 1.02	0.06
Birth weight, grams	957 (± 174)	1.0	0.995 to 1.00	0.1
Female gender	3 (13)	0.21	0.06 to 0.75	0.02
Maternal age, years	27 (± 6)	0.9	0.8 to 0.98	0.01
Surfactant therapy				
1 dose	12 (52)	1.9	0.4 to 9.6	0.4
2 doses	5 (22)	2.3	0.4 to 14.1	0.4
3 or more doses	4 (17)	8.7	1 to 72	0.05
COD Score				
Day 2	0.63 (± 0.3)	18	2.2 to 142	0.007
Day 7	0.49 (± 0.2)	26	1.6 to 421	0.02
PS Score				
Day 2	0.67 (± 0.3)	20	2.3 to 170	0.007
Day 7	0.53 (± 0.1)	25	1.3 to 454	0.03
Week 35	0.45 (± 0.2)	0.97	0.85 to 1.11	0.7
BPD				
Mild	7 (30)	2.8	0.3 to 25	0.4
Moderate	9 (39)	4.2	0.5 to 37	0.2
Severe	6 (26)	36	2.7 to 481	0.007
Days of invasive ventilation	35 (± 41)	1.04	1.02 to 1.07	0.001
Days of non-invasive ventilation	92 (± 91)	1.04	1.02 to 1.06	0.001
Inhaled Nitric Oxide	4 (17)	4.8	0.98 to 23	0.05
Intraventricular hemorrhage	11 (48)	3.2	1.2 to 8.5	0.02
Hypotension	6 (26)	4.6	1.2 to 16.9	0.02
Clinical sepsis	4 (17)	3.5	0.8 to 15.4	0.09
Length of Stay	129 (± 93)	1.03	1.01 to 1.05	0.001
History of Atopy	8 (35)	4.2	1.4 to 13	0.01

Logistic regression demonstrated that maternal and neonatal characteristics, such as gestational age, maternal age, duration of invasive and non-invasive ventilation, history of bronchopulmonary dysplasia and atopy in the first year of life, the chronic oxygen dependency and pulmonary severity scores at days 2 and 7 were predictive of pulmonary morbidity at 6 months corrected age. This effect was reduced to non-significance however, with the inclusion of multiple confounding variables including gestational age, gender, maternal age, duration of invasive and non-invasive ventilation, history of moderate to severe BPD or atopy; however, any conclusions drawn from this result are limited by small outcome numbers (see Tables 4-12, 4-13).

Table 4-13. Stepwise Logistic Regression: Pulmonary Morbidity at 6 Months Corrected Age (n = 91)

Variable	OR for Pulmonary Morbidity	95% CI	P value
Gestational age, weeks	1.2	0.8 to 2	0.4
Gender	0.5	0.1 to 2.2	0.4
Maternal age, years	0.9	0.8 to 0.996	0.04
COD Score at Day 2	2.6	0.06 to 113	0.6
Days of invasive ventilation	1.03	0.99 to 1.08	0.1
Days of non-invasive ventilation	1.05	1.01 to 1.1	0.02
Moderate to Severe BPD	0.09	0.01 to 0.7	0.02
History of Atopy	7.3	1.4 to 39	0.02

CHAPTER 5:

Discussion & Conclusions

In this prospective cohort study conducted from August 1st, 2008 to July 31st, 2009, 102 study participants with gestational ages between 24 and 37 weeks and birth weights <1250 grams had sufficient outcome data to evaluate the incidence and determinants of BPD and pulmonary morbidity in early infancy. There were two neonatal deaths and four subjects were lost to follow-up. The overall rate of BPD, defined as supplemental oxygen need at 36 weeks corrected gestational age, was 43.7% in survivors, consistent with rates in the literature ranging from 23 to 46% in infants of similar gestational ages (8-12). This rate is slightly increased from 31% in infants born between 24 and 29 weeks gestation in this centre between 1997 and 2003 (retrospective review of inborns < 1250 grams from the Royal Alexandra Hospital – personal communication, L. Hendson). BPD rates in the literature have changed little in recent years in spite of evolution in the classification of BPD and advances in the care of extremely low gestational age infants (11,12). The use of a physiologic definition for oxygen dependence, where supplemental oxygen need is determined using a standardized approach with targeted oxygen saturation, may improve diagnostic specificity and decrease the subjective nature of determining oxygen dependency (10). This centre does not use the physiologic test for supplemental oxygen need in infants with moderate BPD.

When considering the severity classification proposed by the NICHD/NHLBI/ORD Workshop, rates of BPD were 38% in the mild BPD group (oxygen dependence at 28 days but not at 36 weeks corrected gestational age), 35% in the moderate group (oxygen dependence at 28 days and at 36 weeks corrected gestational age in ≤ 30% supplemental oxygen) and 8% in the severe group (oxygen dependence at 28 days and continued mechanical ventilation or > 30% supplemental oxygen need at 36 weeks corrected gestational age) (7). Moderate to severe bronchopulmonary dysplasia rates were highest in the lowest gestational ages in this cohort. Similar rates of moderate BPD have been described in the literature, however the rates of both mild and severe BPD were lower than other published reports, perhaps reflecting differences in determination of supplemental oxygen need or baseline population difference (205).

5.1 Risk Factors Associated with BPD

In the analysis of risk factors for BPD, it is important to consider the potential etiologic relationship between the risk factor and the disease state. New BPD is related to the combination of effects of preterm birth with post-natal events. Categorization of risk factors into intrinsic versus modifiable allows for a targeted approach to management of critically ill premature infants. In this particular cohort, intrinsic factors related to BPD on univariate analysis included gender, gestational age and birth weight. In spite of literature evidence suggesting that antenatal inflammation and placental vascular insufficiency play a role in the development of BPD,

maternal conditions such as pregnancy induced hypertension and chorioamnionitis were not shown to be related consistently with the development of moderate to severe BPD or death for this cohort; however, these data were limited by the number of infants with documentation about the presence of chorioamnionitis (206).

In the Durrmeyer et al. study, preterm birth resulting from vascular disorders was related to increased risk for BPD compared with preterm birth resulting from intrauterine inflammation (206). Multivariate analysis demonstrated that the odds of BPD in the inflammation group were significantly increased at the lowest gestational ages whereas in the vascular disorders group, who tended to have higher gestational ages, the odds of developing BPD were increased if infants had intrauterine growth restriction below the 3rd percentile (206). A study from this centre has demonstrated increased risk for BPD when there is antenatal exposure to histologically confirmed chorioamnionitis (54). Forty-two percent of infants with exposure to histologic chorioamnionitis developed BPD compared with 31.9% in those not exposed (54). These infants had lower gestational age and weight at birth and were more likely to have early onset sepsis (54). In this study it was not possible to determine accurately whether preterm birth resulted from placental vascular insufficiency or inflammatory/infectious causes, which may have influenced the results of the multivariate analysis. In addition, there was insufficient data to evaluate the adequacy of intrapartum antibiotic

therapy and whether this would have provided a protective effect for the neonate.

Perinatal factors associated with BPD on univariate analysis included Apgar scores at 1 and 5 minutes and younger maternal age at delivery. Although the administration of antenatal corticosteroids has been associated with improved survival of extremely premature infants the relationship with the incidence of BPD is less clear (17,41,43). Similar to other published literature, the administration of antenatal corticosteroid was associated with a non-significant increase in the odds of developing moderate to severe BPD or death in this cohort when controlling for gestational age and weight at birth, reflecting the increased administration of antenatal corticosteroid at younger gestational ages (205,207). Though the overall rate of antenatal corticosteroid administration was high at 85.4%, a limitation of this study is that maternal data was recorded from neonatal health records. It was not possible to determine the timing of antenatal corticosteroid administration in relation to the delivery nor was it possible to determine whether multiple courses of antenatal corticosteroids had been administered.

Over time, events that occur during the infant's course in the NICU contribute to ongoing inflammation and injury to the developing lung, such as infection, necrotizing enterocolitis (Bell's stage 2 or higher) and pulmonary congestion secondary to patent ductus arteriosus. In this cohort, the rates of both culture proven sepsis and necrotizing enterocolitis were relatively uncommon at 9% and 12.6% respectively. The presence of any

PDA, treated or not, was more common at 35% however given the relatively small sample size and subjective determination, it was not feasible to determine whether the ductus was considered hemodynamically significant or not. The presence of clinical sepsis was not significantly related to the development of moderate to severe BPD or death on univariate analysis whereas the presence of PDA or Bell's stage 2 or higher NEC were both statistically associated with increased odds of developing moderate to severe BPD or death. After controlling for gestational age, birth weight, surfactant therapy and duration of ventilation support, the presence of NEC or PDA was no longer significant, but both were retained in the final model due to confounding, reflecting the relationship of these complications of prematurity with lower gestational ages and birth weights. We speculated that the relationship of gestational age with moderate to severe BPD or death was somewhat complicated by non-linearity in the relationship between gestational age and moderate to severe BPD or death. This may have been influenced by the inclusion of a near term infant with severe intrauterine growth restriction, however when the analysis was repeated excluding this outlier, similar results were obtained (data not shown). It is possible that using gestational age <29 weeks gestation rather than both gestational age and birth weight <1250 grams for inclusion may have resulted in cleaner data, however with this cohort there were insufficient numbers to evaluate this.

In this cohort, only one infant received post-natal corticosteroids as the use of dexamethasone was extremely limited in this centre during the observation period, because of literature evidence suggestive of neurodevelopmental impairment after exposure to post-natal corticosteroids. In more recent years, low dose dexamethasone has been used as per the DART protocol to facilitate extubation in infants with severe lung disease (208). This treatment is reserved for infants with more severe lung pathology who remain ventilator dependent for prolonged periods of time. Dexamethasone use for management of airway inflammation and subglottic stenosis resulting from intubation and prolonged mechanical ventilation has become more common in this centre in recent years, however there is a lack of standardized criteria for treatment and treatment regimens vary based on physician preference. The short and long term implications of this treatment are unclear. Most infants in this cohort were treated with daily caffeine therapy for apnea of prematurity at days 2 and 7 as well as at week 35. A few infants were treated with intermittent or daily diuretics by week 35 but few were on diuretic therapy during the first week of life. In this region, diuretic therapy is usually implemented for management of a hemodynamically significant PDA and less commonly for management of evolving moderate to severe BPD.

The use of early extubation to unsynchronized non-invasive positive pressure ventilation (NIPPV) to maintain extubation in the first days of life has become standard practice in this centre. Use of this modality did not

result in decreased rates of BPD compared with single pressure level NCPAP, however this may have been due to small numbers of infants extubated to NCPAP rather than NIPPV and would need to be assessed in a randomized controlled trial. Infants who required ongoing invasive mechanical ventilation at day 7 of life were much more likely to develop BPD. Overall length of both invasive and non-invasive mechanical ventilation support was associated with the development of BPD and remained statistically significant in the logistic regression model after controlling for gender, gestational age and weight at birth. Duration of invasive ventilation has implications not just for ventilation but also for risk of disability later in life. Increasing duration of invasive mechanical ventilation has also been shown to decrease the rate of survival free of long term neurodevelopmental impairment at 18 months adjusted age (109).

On univariate analysis the chronic oxygen dependency and pulmonary severity scores at day 2 and 7 were both associated with the development of BPD. Areas under the receiver operating characteristic curves were slightly higher for day 7 scores than day 2 scores with fairly equal performance for both scores, indicating relatively high sensitivity and specificity. When the scores were included in the logistic regression analysis, however, the association became statistically non-significant. This may be reflective of differences in practice in the use of medications, oxygen targets and preference for non-invasive and gentler ventilation practices in this centre during this time period.

Contrary to data from this cohort, a larger observational study of data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Benchmarking Trial demonstrated that a model incorporating levels of supplemental oxygen and ventilation support is useful in estimating severity of BPD (209). This data demonstrated that a model incorporating oxygen and ventilation along with gender, ethnicity, gestational age and weight at birth was predictive of BPD severity when applied at days 1, 3, 7, 14, 21 and 28 with areas under the curve ranging from 0.771 to 0.823 (209). When applied in the first days of life, gestational age had the highest weight whereas level of ventilation support was more important in subsequent time points (209).

Predicting BPD severity is clinically useful in evaluating the potential clinical benefit of therapies with theoretical risk of harm, such as post-natal dexamethasone. It has been shown that the population with the most severe form of BPD has lower risk of mortality or cerebral palsy after dexamethasone therapy than those who had milder forms of BPD (99). Earlier treatment may be of benefit to decrease overall duration of invasive ventilation. Using a scoring system in both research and clinical settings may be of use to evaluate the application of such therapy.

Future applications of this study would be to evaluate the application of similar models to the prediction of short and long term pulmonary morbidity and to the prediction of other neonatal morbidities. Evaluation of the predictive capacity of models such as the Neonatal Research

Benchmarking Trial in other settings may be clinically useful in development and application of medical therapies or protocols to decrease clinical risk (209). The ultimate goal is to decrease long-term health and neurodevelopmental morbidity in the vulnerable preterm population.

5.2 Risk Factors Associated With Pulmonary Morbidity in Early Infancy

BPD is directly related to the development of pulmonary morbidity in early infancy and childhood as well as with impairments in neurocognitive outcome (206,210). In this study cohort, 20.5% of infants developed pulmonary morbidity at three months adjusted age compared with 24.5% of infants at six months adjusted age. There is a risk of bias that may influence these results given the different follow-up rates at these two time points as well as recall bias as these outcomes were based on parent interview by telephone and face-to-face interview respectively. In addition, the relatively small numbers of infants with the outcomes of interest limits the conclusions that can be drawn from the analysis. Minor pulmonary symptoms were more common, at 59% and 56.4% for three and six months adjusted age respectively. On univariate logistic regression analysis younger gestational age and lower birth weight, male gender, younger maternal age, need for 3 or more doses of surfactant, COD scores at day 2 and 7, PS Scores at days 2 and 7, moderate to severe BPD, duration of ventilation (both invasive and non-invasive), and the presence of neonatal morbidities including use of

inhaled nitric oxide, hypotension requiring treatment with hydrocortisone, clinical sepsis and length of stay during initial hospitalization were all associated with a history of pulmonary morbidity at 6 months adjusted age. Multivariate assessment was limited by very small numbers of infants with the outcome of interest. Higher COD score at day 2 was not significantly associated with the pulmonary morbidity at 6 months adjusted age when controlling for gestational age at birth, gender, maternal age, duration of invasive and non-invasive ventilation, history of BPD and history of atopy. There was no significant benefit of either the COD or PS scores at day 2 or 7 in the prediction of 6 month pulmonary morbidity; however, these results are also limited by the small number of outcomes observed for this sample cohort. The prediction of BPD and early pulmonary morbidity was not possible using these simple models when adjusting for individual differences, which would render them less useful in the clinical setting. These factors would need to be taken into account when building a model. Although the risk at a given time point may be calculated, it may not hold over time given the variations in the clinical course of the infant and the additional morbidities they may develop. The relative contribution of individual comorbidities change over time as the infant continues to mature and develop and may be influenced by additional factors; however, clear relationships are difficult to delineate in this small dataset.

The development of a comprehensive, multidisciplinary BPD care program that promotes lung health, better nutrition and developmentally

supportive care has been shown to improve rates of rehospitalization and improvements in the rates of low cognitive and language scores on developmental follow-up of infants with severe BPD(210). In this particular program, infants diagnosed with BPD are started on a care plan that incorporates family-centered inpatient management, facilitation of transition to community care and ongoing coordinated management after hospital discharge (210). Targets of this program include prevention of infection, optimal nutrition support and the provision of neurodevelopmental care in addition to managing ventilation needs and preventing progressive pulmonary hypertension (210). Measurement of pulmonary morbidity as a research outcome is useful in the evaluation of comprehensive care and management programs designed to reduce the overall impact of BPD as well as to evaluate centre-specific outcomes as part of national benchmarking standards.

5.3 Conclusion

In conclusion, this cohort study demonstrated that the incidence of BPD continues to remain high especially in infants who require prolonged invasive and noninvasive ventilation, in spite of improvements in neonatal care practices, including high rates of antenatal corticosteroid use. Assessment of risk factors associated with the development of BPD demonstrated that the most important potentially modifiable factors include the number of doses of surfactant required and the duration of invasive and

non-invasive ventilation. The use of COD and PS scores may have limited clinical utility in that they did not perform as well as in the original studies, perhaps due to differences in early neonatal management. Little difference was seen between the two scores at days 2 and 7 of life as in this centre, most infants are treated early with caffeine therapy and few receive other medications such as diuretic or steroid that early in the neonatal course. Overall, the scores were not as robust in the prediction of pulmonary morbidity at either 3 or 6 months adjusted age. The strength of this study includes completeness of follow-up with limited loss of subjects over the study time period. These results reveal a clear difference in the rate of pulmonary morbidity between infants with and without BPD. Infants with moderate to severe BPD are at increased risk for pulmonary morbidity in early infancy. The study was limited by potential bias introduced by the use of parent recall for the pulmonary outcome data and by very small numbers of infants with the relevant long-term outcomes of interest. Models that predict outcomes early would be clinically useful if they were simple to apply and calculate in the clinical setting, as well as demonstrating high clinical reliability and validity. Unfortunately, while the COD and PS scores performed reasonably well in the prediction of BPD, they were less useful in the prediction of longer-term outcomes in this cohort of infants born <29 weeks gestation/<1250 grams birth weight. Modified scores that are better able to differentiate between the highest risk infants need further study.

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