Jacobs, Linda M., Evaluation of respiratory outcomes in pre-term infants receiving nCPAP versus surfactant and mechanical ventilation during transport. Master of Public Health (Clinical Research), December 2012, 40 pp., 18 tables, 4 illustrations, references, 34 titles.

The initial respiratory treatment for premature infants is trending toward nCPAP but this therapy sometimes fails requiring surfactant plus mechanical ventilation. This retrospective review of respiratory interventions by referral hospitals and a neonatal transport team evaluated predictors of respiratory support at 72 hours. A unique variable of time between birth and transport arrival was added to the multivariate regression model.

This study confirmed that gestational age and high levels of respiratory support in the first hours of life are strong predictors for higher levels of respiratory support at 72 hours. Time to transport arrival was not a factor. The transport team has trended toward utilizing nCPAP more often over the past two years.

EVALUATION OF RESPIRATORY OUTCOMES IN PRE-TERM INFANTS RECEIVING NCPAP VERSUS SURFACTANT AND MECHANICAL VENTILATION DURING TRANSPORT

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TABLE OF CONTENTS

LIST OF TABLES iv

LIST OF ILLUSTRATIONS vi

Chapter

1. INTRODUCTION 1

   Purpose of the Study
   Background and Rationale
   Definition of Key Terms

2. LITERATURE REVIEW 6

   CPAP
   Surfactant
   Neonatal Transport

3. METHODS AND ANALYSIS 10

   Inclusion and Exclusion Criteria
   Sample Population
   Research Variables and Data Collection
   Delimitation and Limitations
   Analysis

4. RESULTS 17

   Study Population Characteristics
   Logistic Regression
   Secondary Outcome Bronchopulmonary Dysplasia

5. DISCUSSION AND CONCLUSIONS 27
   Main Outcome
   Limitations
   Conclusion

REFERENCES 31

APPENDICES 37

A. Tables 6 - 10 Respiratory Support by Year
B. Tables 16 – 18 Detailed Results for BPD and IVH

LIST OF TABLES

Table 1. Gestational Age Categories ……10

Table 2. Level of Respiratory Support Categorized ……11

Table 3. Multiple Logistic Regression Variables with Reference Values ….....11

Table 4. Study Population Characteristics with Comparison by Level of Respiratory Support at Admission ……..14

Table 5. Study Population Post-natal Support and Transport Variables ….....15

Table 11. Logistic Regression Analysis for Level of Respiratory Support at 72 Hours ……16 - 17

Table 12. Logistic Regression Model Fit Statistics for Level of Respiratory Support at 72 Hours ……18

Table 13. Logistic Regression Analysis for Presence of BPD ……21

Table 14. Logistic regression Model Fit Statistics for Presence of BPD …….22

Table 15. Mortality and Morbidity …….....23

LIST OF ILLUSTRATIONS

Figure 1. Frequency Chart for Gestational Age ……..……..……18

Figure 2. Overlay Plot of Sensitivity and Specificity versus All Possible Cutpoints ……..……19

Figure 3. ROC Curve Plot of Sensitivity versus 1 – Specificity for All Possible cutpoints ……..……...19

Figure 4. Plot of $\Delta\chi^2$ versus the estimated probability from the fitted model ……20

CHAPTER 1

INTRODUCTION

Purpose of the Study

The neonatal transport team for a regional Level III-C Neonatal Intensive Care Unit (NICU) travels to rural facilities to treat premature newborn infants with varying post-delivery experiences. Presently, there is not agreement among neonatal practitioners for initial respiratory intervention when a baby is born very prematurely (Diblasi, 2009; Morley et al., 2008; SUPPORT Study Group, 2010; Dunn et al., 2011). The Neonatal Resuscitation Chapter Collaborators, Perlman et al. (2010), recommend, "Spontaneously breathing preterm infants who have respiratory distress may be supported with CPAP or intubation and mechanical ventilation. The most appropriate choice may be guided by local expertise and preferences".

Prior to 2007, the neonatal transport team would respond to a premature infant exhibiting respiratory distress by placing an artificial airway, giving exogenous surfactant, and then utilizing positive pressure ventilation (PPV) during transport until the infant was admitted to the NICU. Since 2007, the transport team has increasingly utilized a less invasive intervention, nasal continuous positive airway pressure (nCPAP), but this therapy sometimes fails especially when the infant is born very prematurely requiring an urgent increase in the level of respiratory support.

The aim of this study was to identify variables such as time between birth and transport arrival, a specific gestational age group, early surfactant administration, referral interventions, or the use of nCPAP, to predict the level of respiratory support required at 72 hours after admission to the NICU.

Background and Rationale

Infants born between 8 to 16 weeks early, or between gestational ages of 24 – 32 weeks, have a high risk of respiratory insufficiency. The premature infant's lungs are underdeveloped and known to be surfactant deficient leading to varying degrees of respiratory distress requiring interventions such as nasal CPAP, mechanical ventilation, supplemental oxygen, or surfactant replacement therapy.

Nasal CPAP was first introduced in 1970 for the treatment of respiratory distress in the premature infant but was not widely utilized due to the development of mechanical ventilators specifically designed for infants around the same time (Pfister & Soll, 2102, Diblasi, 2009). Unfortunately, it was discovered that lung injury or endotrauma is a consequence of PPV. Since the 1980's, ventilation strategies have been continually revised as new insight about ventilator induced lung injury is discovered (Hutchison & Bignall, 2008; Peterson, 2009), however as a general strategy PPV is minimized in favor of less invasive respiratory support such as nCPAP.

Treatment of the premature lungs with exogenous surfactant to stabilize the infant's lungs and improve respiratory outcomes evolved rapidly in the 1980's and 1990's and has been credited with dramatically improving outcomes for premature infants (Pfister & Soll, 2012; Halliday, 2008). The drawback to administering surfactant is often the baby requires PPV, which is associated with ventilator induced lung injury and potential development of chronic lung disease.

A landmark study published by Avery et al. (1987) indicated that nCPAP instituted immediately after birth may avoid lung injury and therefore less chronic lung disease or bronchopulmonary dysplasia (BPD) than conventional ventilation. Since

1987, many centers have attempted to reproduce the Avery study with mixed results. Many of the nCPAP studies with promising outcomes are performed in hospitals where the newborn can be placed on nCPAP in the delivery room then transported immediately to the NICU. Hospitals that do not have a NICU capable of supporting infants requiring PPV rely on neonatal transport teams to stabilize and transport infants in distress to a higher level of care. The referral hospital may support the infant in respiratory distress by providing blow-by oxygen or manual ventilation until the transport team arrives. We hypothesized the benefits of early nCPAP are negated by the delay in application of nCPAP at referral hospitals making this study unique due to the addition of time to transport intervention as a predictor.

This study investigated the initial respiratory management at delivery by the referral hospital, respiratory support provided by the neonatal transport team, and the subsequent respiratory outcomes for pre-term newborn infants transported between January 2006 and December 2011. The primary outcome was the level of respiratory support at 72 hours, i.e., PPV versus non-invasive support (NCPAP, oxygen, or no support). The secondary outcome was the presence of bronchopulmonary dysplasia measured at 36 weeks gestational age.

Definition of Key Terms

Nasal CPAP provides respiratory support by applying pressure to the infants lungs through nasal prongs attached to a breathing circuit that provides humidified medical gas that can be adjusted to provide supplemental oxygen.

Fraction of inspired oxygen (FiO_2) is the fraction of supplemental oxygen. The range can be 0.21, which is the FiO_2 of room air to 1.0 or 100% oxygen.

Intubation is the process of placing an artificial airway into the trachea. The artificial airway, known as a tracheal tube, provides a stable interface for mechanical positive pressure ventilation (PPV).

Positive pressure ventilation is commonly provided using a conventional ventilator (CV). High-frequency jet ventilation (HFJV) and high-frequency oscillatory ventilation (HFOV) are advanced forms of PPV.

Surfactant is a substance secreted in the alveoli within the lung and serves as a stabilizer to overcome the surface tension and tendency of the alveoli to collapse on exhalation. Human secreted surfactant is called endogenous surfactant and is composed of phospholipids and proteins. Immature lungs have an impaired ability to maintain surfactant production. Pharmaceutically prepared or exogenous surfactant of many varieties can be administered to the lungs in an attempt to improve lung function.

Bronchopulmonary dysplasia (BPD) is chronic lung disease (CLD) of the newborn and is the result of progressive injury and inflammation from positive pressure ventilation, supplemental oxygen delivery, and surfactant deficiency.

CHAPTER 2

LITERATURE REVIEW

CPAP

A systematic review by Ho, Henderson-Smart, and Davis (2009) concluded that "Early application of [CPAP] has a clinical benefit in the treatment of RDS", but also noted the caveat that many of the studies included in the review were before the era of antenatal steroid use and more research is needed to understand the role of early surfactant administration. The Continuous Positive Airway Pressure or Intubation at Birth (COIN) trial determined that "in infants born at 25-to-28 weeks gestation, early nasal CPAP did not significantly reduce the rate of death or bronchopulmonary dysplasia, as compared with intubation" (Morley et al., 2008). A recent trial conducted by the SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network, (2010) supports consideration of CPAP as an alternative to intubation and surfactant in preterm infants. A recent review by Carlo (2012) summarized four recent trials from the United States and abroad by stating that CPAP soon after birth is a strategy to reduce BPD and death and does not put infants at increased risk if surfactant is either delayed or not utilized.

The drawback with nCPAP is that it is difficult to maintain the continuous pressure on tiny infants without large leaks thus allowing the lungs to collapse. There are many recent studies seeking variables associated with nCPAP failure. The reported failure rates are generally go up as gestational age goes down. Koti, Murki, Gaddam, Reddy and Reddy (2010) studied premature infants with a mean gestational age of 30 weeks and reported a 25% nCPAP failure rate. A recent study of infants at 26 – 29

weeks gestational age reported a 50% nCPAP failure rate (Fuchs, Lindner, Leiprecht, Mendler, & Hummler, 2011). Rocha et al. (2012) identified the following predictors of nCPAP failure, need for resuscitation with greater than 0.30 FiO_2, nCPAP pressures of 6 $\pm$1.2 cm H_2O, the need of a FiO_2 greater than 0.40 in the first 4 hours of life, male gender with need of a FiO_2 greater than 0.25 in the first 4 hours of life.

Surfactant

The establishment of surfactant therapy in the 1980's and 1990's was associated with an overall reduction of 6% in infant mortality in the United States (Halliday, 2008). Complications of respiratory distress syndrome such as pulmonary air leaks were also reduced. Surfactant does have adverse effects primarily related to method of administration. The infant often requires extended support with positive pressure ventilation, which is associated with a host of physiological changes that can be detrimental (Pfister & Soll, 2012).

As discussed in the previous section, nCPAP has made a big come back in the past 5 – 10 years, but there are many infants who require surfactant replacement therapy due to declining respiratory function. Research continues today to identify patients who would most benefit from early surfactant replacement therapy rather than early nCPAP without surfactant.

Neonatal Transport

Few studies have investigated the impact of transport team interventions on respiratory outcomes for premature newborns. Two studies were relevant to this investigation, one by Kumar, Kumar, Shaik, Yadav, Dusa, & Venkatlakshmi (2011) who studied all newborn babies transported to the authors unit in an Indian hospital. The

babies were transported to a higher level of care and showed a significant improvement in clinical condition. A second study carried out in Jerusalem by Arad, Braunstein, & Far-Oz (2008) concluded that extra-low birth weight outborn infants share comparable outcomes with inborn newborn infants.

CHAPTER 3

METHODS AND ANALYSIS

Inclusion and exclusion criteria

This was a retrospective review of existing records during the period 2006 to 2011. Data was collected regarding respiratory interventions provided by referral hospitals, the neonatal transport team, and a Level III-C Neonatal Intensive Care Unit (NICU) for premature newborn infants less than 33-weeks gestational age (GA) transported less than 24 hours after birth to a level III-C Neonatal Intensive Care Unit (NICU). Records of patients were excluded if the admission or discharge diagnosis included heart defects, genetic abnormalities, airway anomalies, septic shock, pneumonia diagnosis, facial anomalies, diaphragmatic hernia, meconium aspiration syndrome, neuromuscular disease, or cardio-pulmonary resuscitation of the mother during birth.

Sample population

The neonatal transport team provides transport services for approximately 700 neonatal patients annually in north Texas. Ambulance transfers usually are provided within 30 miles or less from the Level III-C NICU in Fort Worth, Texas. Helicopter transport was usually preferred for 30 to 150 mile distances such as Wichita Falls, Abilene, or Denton. An airplane was used for transporting patients greater than 125 miles from the medical center, including neighboring states.

Research Variables and Data Collection

The research population for this study was premature infants, therefore the investigators accounted for known contributing factors for respiratory distress and

bronchopulmonary dysplasia in the analysis. Antenatal variables obtained from the records include gestational age, gender, multiple births, and maternal steroids. Gestational age is considered a strong predictor for respiratory distress requiring intervention and for subsequent BPD (Ammari et al., 2005; Stoll & NICHD Neonatal Research Network, 2010; Trembath & Laughon, 2012). Male gender, multiple births, and lack of maternal steroids are associated with the need for respiratory support and subsequent BPD (Stoll & NICHD Neonatal Research Network, 2010; Rocha et al., 2012; Trembath & Laughon, 2012). The respiratory support variables extracted from the records include PPV before transport arrival (indicates delivery room resuscitation), early surfactant administration (pre-admission), and the level of respiratory support at admission. Time before transport arrival was included as a study variable to investigate the hypothesis of delayed respiratory intervention.

The initial data set was generated by searching the existing neonatal database maintained by the health care system for newborn infants meeting the inclusion criteria. This data set was augmented by an electronic medical record review. Each record was verified with two identifiers before review. Gestational ages were rounded to a full week. Level of respiratory support was carefully evaluated at exactly 72 hours after admission based on flow sheet documentation. The level of respiratory support at 36-weeks post-menstrual age (PMA) was assessed as oxygen only versus nCPAP or PPV. The number of days on oxygen between admission and 36-weeks PMA was counted precisely to evaluate the BPD criteria of greater than or equal to 28 days on oxygen with one-day equal to twelve hours or more on oxygen. The discharge summaries and diagnosis list prepared by the neonatologist was reviewed for presence of BPD.

Delimitation and Limitations

There were two main delimitations for this study, first the data collection was from one center, and second, the care provided by the referral centers may have had wide variability. The main limitation of the study was that a retrospective record review captures an uncontrolled group of subjects making it difficult to isolate significant findings.

Analysis

Primary Outcome

The data excluding all patient identifiers was exported to SAS 9.2© (SAS Institute Inc., Cary, NC). The baseline characteristics of the study population were determined. Gestational age was coded for the categories listed in Table 1. The level of respiratory support at admission, and the level of respiratory support at 72 hours were coded into the categories listed in Table 2. Multiple logistic regression was utilized to evaluate the primary outcome of level of respiratory support at 72 hours after admission (infants who died before 72 hours were excluded). Nine independent variables were selected for the multiple logistic regression model and are listed in Table 3 with the reference values.

Table 1.

Gestational Age Categories

	Gestational Age (Weeks)
1	22 – 24
2	25 – 27
3	28 – 30
4	31 – 32 (reference)

Table 2.

Level of Respiratory Support Categorized

Level	Chart Finding
0	▪ Room air ▪ Nasal cannula ▪ nCPAP ▪ High-flow nasal cannula
1	PPV: Intubated with conventional ventilation or high-frequency ventilation

Table 3.

Multiple Logistic Regression Variables with Reference Values

Primary Outcome	
Level of respiratory support at 72 Hours as noted in Table 2 (ref = 1)	
Predictors	
1. Gestational age, categorized per Table 1 (ref = 4)	6. Level of respiratory support at admission listed in Table 2 (ref = 0)
2. Maternal steroids (ref = no)	7. Did patient receive manual or mechanical ventilation before transport arrival (ref = no)
3. Gender (ref = female)	8. Was patient given surfactant pre-admission (ref = no)
4. Multiple birth (ref = no)	9. Birth Year (ref = 2006)
5. Time from birth to transport intervention (continuous)	
Multiple logistic regression model: $\ln(\hat{Y}/1 - \hat{Y}) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots \beta_i X_i$	
Categorical Variables Reference Value = ref	

Secondary Outcome

The secondary outcome was evaluated for the presence of Bronchopulmonary Dysplasia using the same multiple logistic regression variables. The presence of BPD was based on the National Institute of Health severity-based definition of BPD for infants less than 32 weeks' gestational age (Jobe & Bancalari, 2001):

- Mild BPD is defined as a need for supplemental oxygen (O_2) for greater than or equal to 28 days but not at 36 weeks' postmenstrual age (PMA) or discharge,
- Moderate BPD as O_2 for greater than or equal to 28 days plus treatment with less than 30% O_2 at 36 weeks' PMA,
- Severe BPD as O_2 for greater than or equal to 28 days plus greater than or equal to 30% O_2 and/or positive pressure at 36 weeks' PMA.

BPD presence was derived from the data according to the strict NIH definition and multiple logistic regression applied using BPD as the dependent outcome variable with a reference value of “yes”.

Assessing the Fit of the Logistic Regression Model

The multiple logistic regression model was assessed for goodness of fit using the Hosmer and Lemeshow chi-square test, the Wald confidence limits, and the area under the ROC (Receiver Operating Characteristic) curve (Hosmer & Lemeshow, 2000). Logistic regression diagnostics were also used to evaluate the model and included using classification tables for false positive and false negative rate and the proportion correctly classified. Regression diagnostics plots were created to assess for outlier leverage.

CHAPTER 4

RESULTS

Study Population Characteristics

The initial data set extracted from the neonatal database consisted of 39 variables that were used to contribute to the study variables required for analysis. There were 501 records eligible for review based on gestational age less than 33 weeks and transported at less than 24 hours after birth. Fifty-four patients were excluded after review for heart defects, genetic abnormalities, airway anomalies, septic shock, pneumonia (diagnosis at birth), facial anomalies, diaphragmatic hernia, meconium aspiration syndrome, or neuromuscular disease. One subject was excluded due to birth at home with subsequent transport by a local ambulance to the emergency room.

The demographic distributions of the study population are presented in Table 4 along with a comparison of the level of respiratory support at admission. Most notable is a significant difference, 27 versus 30 weeks, in the gestational age of the patients admitted at Level 0 (nCPAP, RA, or NC) which is almost three weeks older than the patients admitted at Level 1 (PPV or HFV). Also noted is the number of admissions at Level 0 (nCPAP, RA, or NC) is only 100 versus 346 admissions at Level 1 (PPV or HFV). Figure 1 illustrates the range and frequency of the gestational age in this study population and highlights the 59 infants born at 22 – 24 weeks gestational age.

Table 5 describes the key post-natal support and transport variables provided for the infants in the study. These variables were also contrasted by level of respiratory support at admission and predictably the patients who require less support at admission required less surfactant.

Table 4.

Study Population Characteristics with Comparison by Level of Respiratory Support at Admission

Characteristic	***All Subjects (N = 446)***	***Admit Level 0 nCPAP, RA or NC (n = 100)***	***Admit Level 1 CV or HFV (n = 346)***	***p*-value**
Gestational Age, weeks, mean (SD)	28.0 (2.8)	30.2 (1.9)	27.4 (2.7)	<.0001
Male gender, %	51.4	50.0	51.7	0.76
Multiple births, %	19.5	32.0	15.9	0.0003
Maternal steroids, %	39.2	43.0	38.2	0.38

nCPAP = nasal continuous positive airway pressure, RA = room air, NC = nasal cannula

CV = conventional ventilation, HFV = high-frequency ventilation

Figure 1.

Frequency Chart for Gestational Age

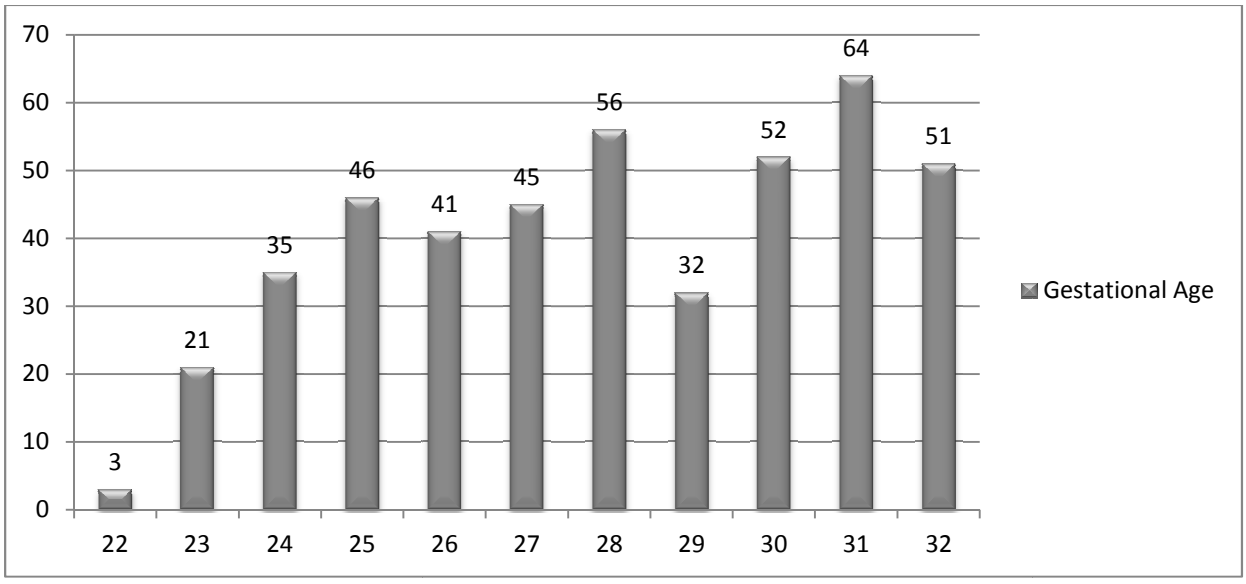


Table 5.

Study Population Post-natal Support and Transport Variables

Variable	***All Subjects (N = 446)***	***Admit Level 0 nCPAP, RA or NC (n = 100)***	***Admit Level 1 CV or HFV (n = 346)***	***p*-value**
Time of Birth to Transport Arrival, minutes, mean (SD)	88.3 (146.1) range 0 - 1224	68.7 (147.3)	93.9 (145.5)	0.13
PPV prior to transport arrival, *n*, (%)	251 (56.3)	27.0 (10.8)	224 (89.2)	<.0001
Surfactant pre-admission, *n*, (%)	343 (76.9)	8.0 (2.3)	335 (97.7)	<.0001
Time of Birth to First Surfactant Dose, minutes, mean (SD)	107 (256.5) range 0 - 2579	610 (685.6)	67.0 (117.5)	0.0003
Surfactant, total doses mean (SD)	1.3 (0.87) range 1 - 5	0.33 (0.64)	1.58 (0.72)	<.0001

SD = Standard Deviation

Table 6 in Appendix A, Type of Respiratory Support at Admission by Year, illustrates a trend over the six-year period toward more nCPAP and less conventional ventilation and high-frequency oscillatory ventilation. Table 7 shows the frequencies of Level of Respiratory Support at 72 Hours when admitted at Level 1 (PPV or HFV), noting that 46% of infants had “succeeded” to a lower level of respiratory support (nCPAP, NC, or RA). Conversely, Table 8 illustrates that infants admitted at Level 0, only 5% “failed” to a higher level of respiratory support (PPV or HFV). Table 9 details

respiratory support by year at 72 hours and Table 10 details respiratory support 2 weeks after admission. Inspection of the tables does not suggest there is a trend toward more advanced ventilation as more nCPAP is utilized at admission.

Logistic Regression

Primary Outcome Level of Respiratory Support at 72 Hours

The results for the multiple logistic regression are listed in Table 11 and show that higher level of respiratory support at admission and gestational age categories 1, 2, and 3 are significant predictors for higher level of respiratory support at 72 hours. Infants born in 2009 or 2010 were less likely to be at the higher level of respiratory support at 72 hours. Additional comparison of birth year by contrasting 2006 – 2008 versus 2009- 2011 revealed that there was a significant difference between the two groups of years with a parameter estimate of -0.9071 and a *p*-value of 0.0016.

Table 11.

Logistic Regression Analysis for Level of Respiratory Support at 72 Hours

Predictor (Reference)	***β Estimate***	***β SE****	***Wald χ^2***	***p***	***OR (95% CI)***
Intercept	-3.1138	0.6569	22.4706	<.0001	Not applicable
Time of birth to transport arrival	-0.00070	0.000991	0.4980	0.4804	0.999 (0.997 – 1.001)
Gestational age** (4)					
Category 1	4.0701	0.6498	39.2342	<.0001	58.564 (16.388 – 209.3)
Category 2	2.7211	0.4136	43.2852	<.0001	15.197 (1.201 – 5.705)
Category 3	0.9636	0.3968	5.8968	0.0152	2.621 (1.204 – 5.705)

Table 11 continued.

Logistic Regression Analysis for Level of Respiratory Support at 72 Hours

Predictor (Reference)	***β Estimate***	***β SE****	***Wald χ^2***	***p***	***OR (95% CI)***
Maternal steroids (No)	-0.3679	0.2773	1.7594	0.1847	0.692 (0.402 – 1.192)
Gender (Female)	-0.1502	0.2686	0.3127	0.5760	0.861 (0.508 – 1.457)
Multiple births (No)	0.4315	0.3667	1.3842	0.2394	1.540 (0.750 – 3.159)
Birth Year (2006)					
2007	-0.4694	0.4343	1.1681	0.2798	0.625 (0.267 – 1.465)
2008	-0.8298	0.4180	3.9404	0.0471	0.436 (0.192 – 0.990)
2009	-1.2487	0.4382	8.1213	0.0044	0.287 (0.122 – 0.677)
2010	-1.8847	0.5106	13.6235	0.0002	0.152 (0.056 – 0.413)
2011	-0.8871	0.4617	3.6918	0.0547	0.412 (0.167 – 1.018)
Respiratory Level at Admission (Level 0, nCPAP, NC, or RA)	2.6120	0.7305	12.7833	0.0003	13.626 (3.255 – 57.044)
Positive pressure ventilation before transport arrival (No)	0.4523	0.3157	2.0526	0.1519	1.572 (0.847 – 2.918)
Surfactant pre-admission (No)	-0.4221	0.6513	0.4201	0.5169	0.6560 (0.183 – 2.350)

* SE = Standard error

** Gestational age: category 1 = 22 -24 weeks, 2 = 25 – 27 weeks, 3 = 28 – 30 weeks, and 4 = the reference category 31 – 32 weeks

Logistic regression model fit statistics for level of respiratory support at 72 hours are described in Table 12. The Homer and Lemeshow goodness-of-fit test indicated that the model fits the data appropriately. Regression diagnostics plots were generated for additional assessment of the model. Figure 2 is an overlay plot of sensitivity and specificity versus all possible cutpoints, and the plot indicates an optimal cutpoint of ~ 0.4, which is near the SAS default cutpoint of 0.5. The ROC curve presented in Figure 3 represents the *c* statistic of 0.894, which indicates a good model fit, i.e., the larger the area the better. A plot of the change in the Pearson chi-square versus estimated probability reveals three potential outliers (see Figure 4) that may have exerted leverage on the model.

Table 12.

Logistic Regression Model Fit Statistics for Level of Respiratory Support at 72 Hours

Test	χ^2	***df***	***p***
Overall model evaluation			
Likelihood ratio test	211.6925	15	<.0001
Score test	172.8141	15	<.0001
Wald test	104.7449	15	<.0001
Goodness-of-fit test			
Homer & Lemeshow	7.1503	8	0.5205

Figure 2.

Overlay Plot of Sensitivity and Specificity versus All Possible Cutpoints

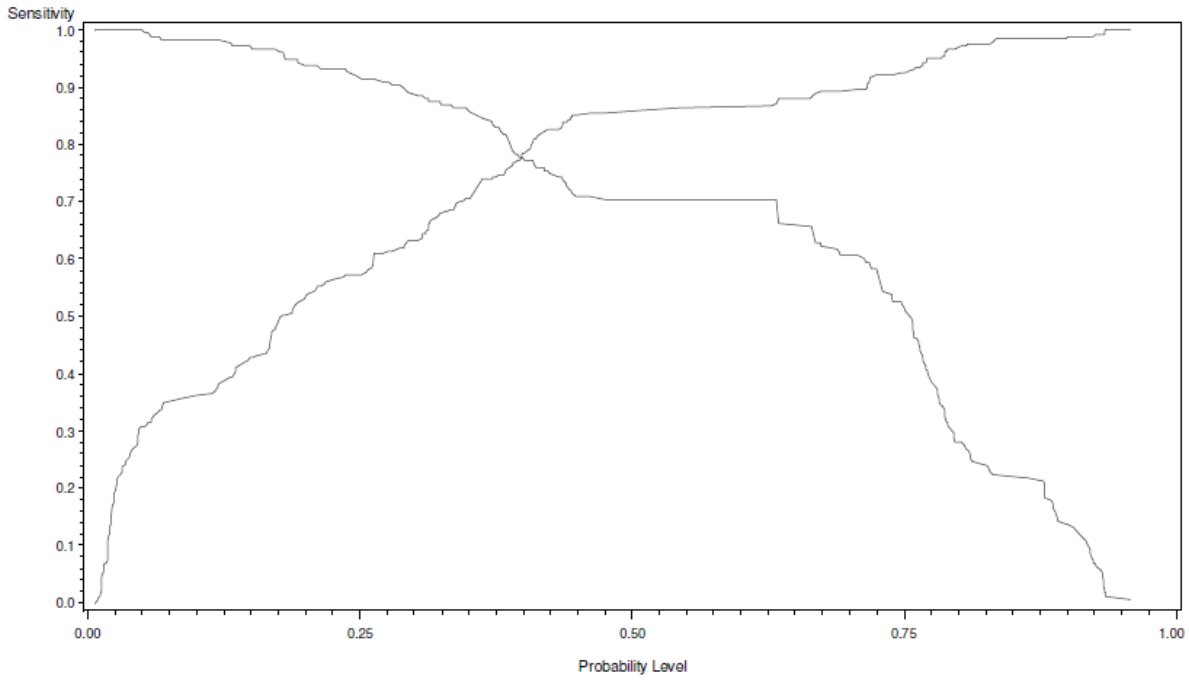


Figure 3.

ROC Curve Plot of Sensitivity versus 1 – Specificity

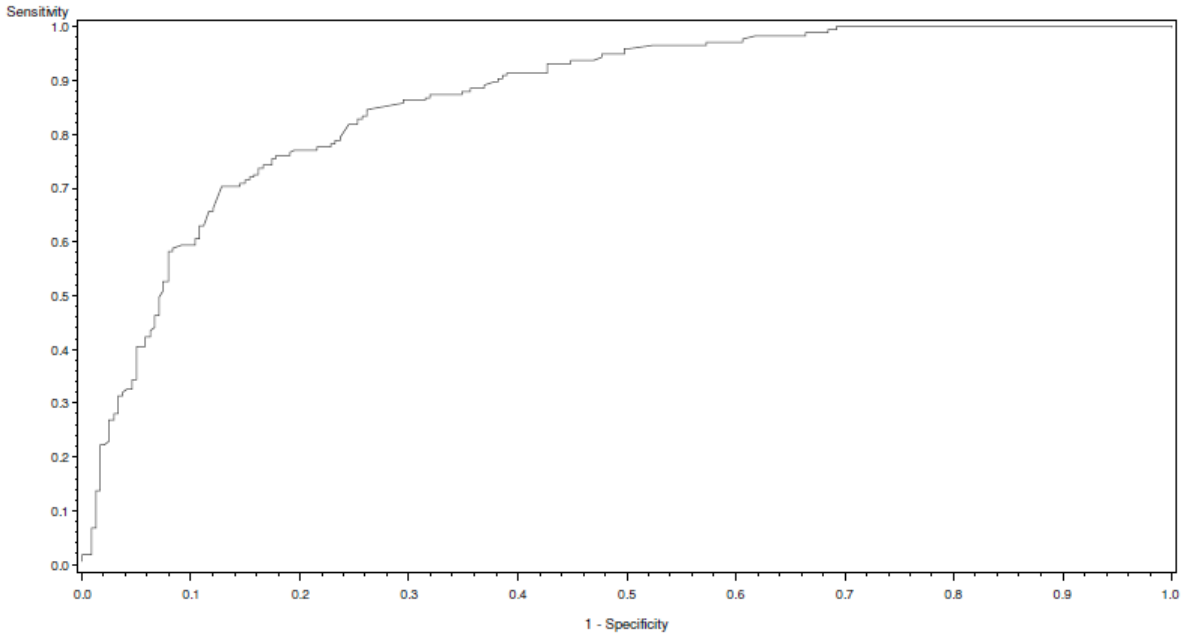
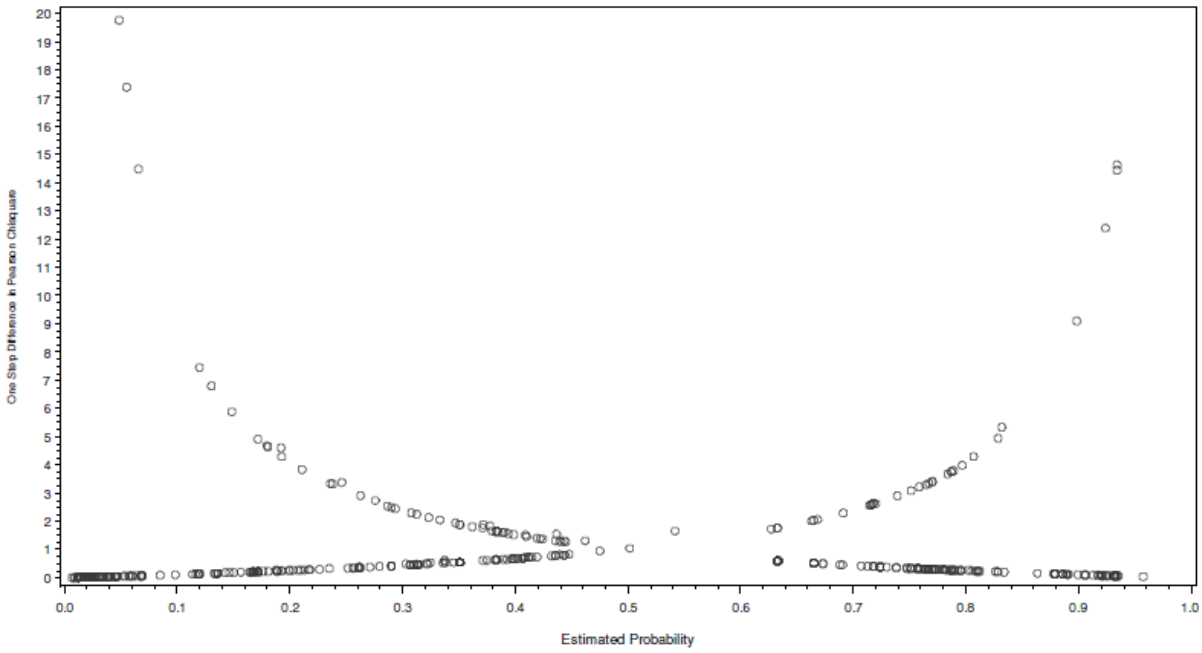


Figure 4.

Plot of $\Delta\chi^2$ versus the Estimated Probability from the Fitted Model



Secondary Outcome Bronchopulmonary Dysplasia

The results for the BPD multiple logistic regression are listed in Table 13 and show that birth year 2011 and gestational age categories 1,2, and 3 are significant predictors for the presence of BPD at 36 weeks PMA. Logistic regression model fit statistics for BPD are described in Table 14. The Homer and Lemeshow goodness-of-fit test indicated the model fits the data appropriately. Level of respiratory support at admission was not a significant predictor for BPD in our study.

Table 13.

Logistic Regression Analysis for Presence of BPD

Predictor (Reference)	***β Estimate***	***β SE****	***Wald χ^2***	***p***	***OR (95% CI)***
Intercept	-2.9750	0.6368	21.8287	<.0001	Not applicable
Time of birth to transport arrival	0.00190	0.00150	1.5943	0.2067	1.002 (0.999 – 1.005)
Gestational age** (4)					
Category 1	4.0890	0.8672	22.2330	<.0001	59.682 (10.906 – 326.6)
Category 2	3.8567	0.5059	58.1173	<.0001	47.309 (17.552 – 127.5)
Category 3	1.3188	0.4043	10.6398	0.0011	3.739 (1.693 – 8.259)
Maternal steroids (No)	-0.1181	0.2980	0.1572	0.6918	0.889 (0.495 – 1.594)
Gender (Female)	0.3542	0.2968	1.4241	0.2327	1.425 (0.797 – 2.549)
Multiple births (No)	-0.0108	0.3890	0.0008	0.9778	0.989 (0.462 – 2.120)
Birth Year (2006)					
2007	0.2935	0.4855	0.3656	0.5454	1.341 (0.518 – 3.473)
2008	0.4629	0.4577	1.0230	0.3118	1.589 (0.648 – 3.896)
2009	0.7178	0.4972	2.0837	0.1489	2.050 (0.774 – 5.432)
2010	0.0816	0.5060	0.0260	0.8719	1.085 (0.402 – 2.925)
2011	1.2034	0.5201	5.3545	**0.0207**	3.331 (1.202 – 9.233)
Respiratory Level at Admission (Level 0, nCPAP, NC, or RA)	0.4081	0.7471	0.2984	0.5849	1.504 (0.348 – 6.504)
Positive pressure ventilation before transport arrival (No)	-0.0831	0.3488	0.0568	0.8117	0.920 (0.465 – 1.823)
Surfactant pre-admission (No)	0.3794	0.7312	0.2692	0.6038	1.461 (0.349 – 6.126)

* SE = Standard error

** Gestational age: category 1 = 22 -24 weeks, 2 = 25 – 27 weeks, 3 = 28 – 30 weeks, and 4 = the reference category 31 – 32 weeks

Table 14.

Logistic regression Model Fit Statistics for Presence of BPD

Test	χ^2	***df***	***p***
Overall model evaluation			
Likelihood ratio test	139.1829	15	<.0001
Score test	119.8375	15	<.0001
Wald test	83.3730	15	<.0001
Goodness-of-fit test			
Homer & Lemeshow	6.8327	8	0.5548

The mortality and morbidity for this study population is detailed in Table 15 with comparison by level of respiratory support at admission. The BPD rate listed in Table 15 is 54.1%. An adjusted BPD rate excluding the Mild BPD category is 32.6%, which is equal to the 32% identified by the neonatologists in the discharge summaries. Tables 16 and 17 in Appendix B stratify BPD by birth year and gestational age categories respectively. Intraventricular hemorrhage (IVH) was reported in Table 15 as the sum of moderate and severe IVH. A complete listing of all IVH frequencies can be found in Table 18 in Appendix B.

Table 15.

Mortality and Morbidity

Variable	***All Subjects***	***Admit Level 0 nCPAP, RA or NC***	***Admit Level 1 CV or HFV***	***p*-value**
Mortality*, *n* (%)	81 (18.2)	2 (2.0)	79 (97.5)	<.0001
Died**, day of life, mean (SD)	13.7 (27.7)	15 (1.4)	13.6 (28.1)	<.0001
Severe IVH***, *n* (%)	56 (12.6)	1 (1.0)	55 (15.9)	<.0001
BPD†, *n* (%)	171 (54.1)	20 (29.9)	151 (60.6)	< .0001
Mild BPD††, *n* (%)	68 (21.5)	12 (17.9)	56 (22.5)	0.42
Moderate BPD††, *n* (%)	45 (14.2)	8 (11.9)	37 (14.9)	<.0001
Severe BPD††, *n* (%)	58 (23.3)	0 (0.0)	58 (23.3)	<.0001

* N = 446 all study subjects

** N = 81

*** N = 446, Severe intraventricular hemorrhage = Grade 3 or Grade 4

† N = 316 due to exclusions:

51 subjects = 32 Weeks GA when born,

77 subjects died before 36 Weeks GA,

2 subjects transferred before 36 Weeks GA

Admit Level 0, N = 67 and Admit Level 1, N = 249

†† Strict interpretation of National Institutes of Health Severity-Based definition of BPD (Jobe & Bancalari, 2001)

CHAPTER 5

DISCUSSION AND CONCLUSION

Main Outcome

The significant predictors of gestational age, and level of respiratory support in the first hours of life (in our study level of respiratory support at admission to the NICU) were similar to many studies investigating respiratory outcomes such as CPAP failure, need for surfactant, and BPD rates (Morley et al., 2008; Fuchs et al., 2011; Rocha et al., 2012; Dunn et al., 2011).

The study period began one year before the transport team transitioned to utilizing nCPAP for initial management rather than the standard practice of intubation and surfactant followed by positive pressure ventilation. There was a significant trend toward more nCPAP for birth years 2009 through 2011. When comparing the infants transported during 2006 -2008 versus 2009 – 2011, the latter group was significantly less likely to be at the higher level of respiratory support at 72 hours. A great illustration of this finding is found in Table 8. Infants transported on nCPAP generally remain on nCPAP or at the lower level. This finding may be correlated with the fact that these infants were in less distress thus a straightforward candidate for nCPAP transport. This observation of very few nCPAP failures leads to the question of attempting nCPAP on smaller infants in the 27 – 29 week gestational age group. More importantly, Table 7 suggests that an appreciable proportion of infants admitted with PPV transition to the lower level of respiratory support by 72 hours, e.g., in 2009 and 2010, 57% of infants were extubated to the lower level of respiratory support.

This study took a novel approach by including time to transport intervention as part of the analysis with the assumption that the transport team would provide a higher level of care, however the time variable did not have any detectable impact on the infants respiratory support at 72 hours or presence of BPD. One factor that may have influenced the lack of differentiation based on time is that the transport team attended 132 deliveries and arrived within 15 minutes of delivery for another 30 babies or 36% of the transports. A second factor to recognize is that the babies transported at Level 0, (room air, nasal cannula, or nCPAP), had a mean gestational age of 30 weeks, which was three weeks greater than the mean for the infants transported using PPV or 27 weeks gestational age. This finding might be a natural result of smaller babies requiring more support, or that the there is a bias toward infants with moderate to severe respiratory distress referred to a higher level of care while the infants with a mild degree of respiratory distress are kept successfully at the referral hospitals. This phenomenon would skew the outcomes for the regional NICU toward higher requirements for respiratory support and subsequent development of BPD.

It is possible that the actions of the delivery room team and the level of support provided by the referral hospital influences the transport team decisions when they arrive. One striking feature of Table 6 in Appendix A, respiratory support at admission, was that only 74 infants (16.6%) utilized nCPAP during the study period. This relatively low number may reflect that many infants were already intubated and were supported by conventional ventilation especially in the early study years 2006 – 2008. Future practice options for the transport team may involve the blended approach that includes early surfactant followed by nCPAP. A very recent pilot study by Attridge, Stewart,

Stukenborg, and Kattwinkel (2012) successfully used a less-invasive laryngeal mask airway to administer surfactant. There remains a great interest in protocolizing a blended approach of administering surfactant and utilizing nCPAP, thus minimizing mechanical ventilation for the treatment of respiratory distress syndrome.

Limitations

Premature infants are at increased risk for multiple medical complications including infections leading to sepsis or pneumonia, gastrointestinal challenges including reflux and necrotizing enterocolitis, and intracranial hemorrhage. Management of the respiratory system is difficult to isolate and to make direct inferences based on specified aspects of medical intervention is often impossible. Another challenge is to account for variation in practices especially in a large mixed rural and urban referral region. This study was limited by the complexity of statistically analyzing for clustering effects that inevitably occur when multiple centers care for patients. Initially we had proposed a longitudinal ordinal data regression with competing risks survival times, however the statistical programming for this analysis is relatively new and would require high functioning statistical support. The analysis performed for this study did not strictly evaluate for patients that died before 72 hours (n = 30, 6.8%).

Conclusion

This retrospective record review confirmed that gestational age and high levels of respiratory support in the first hours of life are strong predictors for higher levels of respiratory support at 72 hours. Time to transport arrival was not a factor in this investigation. An additional significant finding was infants transported during birth years 2009 and 2010 were less likely to require the higher level of respirator support at 72

hours. Birth year 2011 and gestational age categories 1,2, and 3 are significant predictors for the presence of BPD at 36 weeks PMA. BPD rates for these infants who were transported to a regional level III-C NICU were comparable to epidemiological data (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, 2010), and systematic reviews (Morley, et al., 2008; Carlo, 2012). The transport team has trended toward utilizing nCPAP more often over the past three years. The best approach for these complicated babies with immature lungs may include integrating the best practices from past – early surfactant with state of the art nCPAP.

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APPENDIX A

TABLES 6 - 10 RESPIRATORY SUPPORT BY YEAR

APPENDIX A

TABLES 6 – 10 RESPIRATORY SUPPORT BY YEAR

Table 6.

Respiratory Support At Admission By Year

Respiratory Support	***Birth Year***						
	2006	**2007**	**2008**	**2009**	**2010**	**2011**	**Total**
High Frequency Jet Ventilation, *n* (%)	1 (1.1)	3 (4.5)	2 (2.7)	1 (1.1)	1 (1.5)	1 (1.7)	9 (2.0)
High Frequency Oscillatory Ventilation, *n* (%)	13 (14.3)	6 (9.0)	11 (14.7)	7 (7.9)	3 (4.6)	6 (10.0)	46 (10.3)
Nasal Cannula, *n* (%)	3 (3.3)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	4 (0.9)
nCPAP, *n* (%)	2 (2.2)	8 (11.9)	10 (13.3)	20 (22.7)	20 (30.8)	14 (23.3)	74 (16.6)
Conventional Ventilation, *n* (%)	66 (72.5)	48 (71.6)	49 (65.3)	52 (59.1)	38 (58.5)	38 (63.3)	291 (65.2)
Room Air, *n* (%)	6 (6.6)	2 (3.0)	3 (4.0)	7 (8.0)	3 (4.6)	1 (1.7)	22 (4.9)
Totals, *n* (%)	91 (20.4)	67 (15.0)	75 (16.8)	88 (19.7)	65 (14.6)	60 (13.5)	446

Table 7.

Respiratory Support At 72 Hours By Year For Infants Admitted at Level 1

Level of Respiratory Support at 72 Hours	***Birth Year***						
	2006	**2007**	**2008**	**2009**	**2010**	**2011**	**Total**
Level 0 (nCPAP, NC, or RA), *n* (%)	28 (36.4)	24 (44.4)	26 (45.6)	29 (56.9)	20 (57.1)	19 (45.2)	146 (46.2)
Level 1 (CV or HFV), *n* (%)	49 (63.6)	30 (55.6)	31 (54.4)	22 (43.1)	15 (42.9)	23 (54.8)	170 (53.8)
Totals, *n*	77	54	57	51	35	42	316

Table 8.

Respiratory Support At 72 Hours By Year For Infants Admitted at Level 0

Level of Respiratory Support at 72 Hours	***Birth Year***						
	2006	**2007**	**2008**	**2009**	**2010**	**2011**	**Total**
Level 0 (nCPAP, NC, or RA), *n* (%)	11 (100)	7 (70.0)	13 (100)	28 (100)	23 (100)	13 (86.7)	146 (46.2)
Level 1 (CV or HFV), *n* (%)	0 (0.0)	3 (30.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)	170 (53.8)
Totals, *n*	11	10	13	28	23	15	100

Table 9.

Respiratory Support At 72 Hours By Year

Respiratory Support	***Birth Year***						
	2006	**2007**	**2008**	**2009**	**2010**	**2011**	**Total**
High Frequency Jet Ventilation, *n* (%)	5 (5.5)	11 (16.4)	5 (6.7)	7 (7.9)	5 (7.7)	4 (6.6)	37 (8.3)
High Frequency Oscillatory Ventilation, *n* (%)	5 (5.5)	4 (6.0)	7 (9.3)	5 (5.7)	1 (1.5)	6 (10.0)	28 (6.3)
Nasal Cannula, *n* (%)	3 (3.3)	0 (0.0)	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.1)
HFNC	8 (8.8)	7 (10.4)	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	17 (3.8)
nCPAP, *n* (%)	10 (11.0)	13 (19.4)	26 (34.7)	37 (42.1)	37 (56.9)	25 (41.7)	148 (33.2)
Conventional Ventilation, *n* (%)	39 (42.9)	18 (26.9)	19 (25.3)	10 (11.4)	9 (13.9)	15 (25.0)	110 (24.6)
Room Air, *n* (%)	18 (19.7)	11 (16.4)	9 (12.0)	20 (22.7)	6 (9.2)	7 (11.7)	71 (15.9)
Died	0 (0.0)	0 (0.0)	1 (1.3)	2 (2.3)	2 (3.1)	2 (3.3)	7 (1.6)
Died Prior to 72 hour time point	3 (3.3)	3 (4.5)	4 (5.3)	7 (7.9)	5 (7.7)	1 (1.7)	23 (5.2)
Totals, *n* (%)	91 (20.4)	67 (15.0)	75 (16.8)	88 (19.7)	65 (14.6)	60 (13.5)	446

Table 10.

Respiratory Support At 2 Weeks By Year

Respiratory Support	***Birth Year***						
	2006	**2007**	**2008**	**2009**	**2010**	**2011**	**Total**
High Frequency Jet Ventilation, *n* (%)	6 (6.6)	11 (16.4)	8 (10.7)	8 (9.1)	7 (10.8)	5 (8.3)	45 (10.1)
High Frequency Oscillatory Ventilation, *n* (%)	0 (0.0)	4 (5.9)	1 (1.3)	1 (1.1)	0 (0.0)	2 (3.3)	8 (1.8)
Nasal Cannula, *n* (%)	4 (4.4)	1 (1.5)	1 (1.3)	1 (1.1)	0 (0.0)	0 (0.0)	7 (1.6)
HFNC	9 (9.9)	5 (7.5)	1 (1.3)	0 (0.0)	1 (1.5)	6 (10.0)	22 (4.9)
nCPAP, *n* (%)	9 (9.9)	12 (17.9)	19 (25.3)	21 (23.9)	20 (30.8)	21 (35.0)	102 (22.9)
Conventional Ventilation, *n* (%)	19 (20.9)	8 (11.9)	6 (8.0)	2 (2.3)	5 (7.7)	4 (6.7)	44 (9.9)
Room Air, *n* (%)	34 (37.3)	18 (26.9)	25 (33.4)	38 (43.2)	22 (33.8)	13 (21.7)	150 (33.6)
Died	3 (3.3)	1 (1.5)	5 (6.7)	4 (4.5)	0 (0.0)	1 (1.7)	14 (3.1)
Died Prior to 2 Week time point	7 (7.7)	7 (10.5)	9 (12.0)	13 (14.8)	10 (15.4)	8 (13.3)	54 (12.1)
Totals, *n* (%)	91 (20.4)	67 (15.0)	75 (16.8)	88 (19.7)	65 (14.6)	60 (13.5)	446

APPENDIX B

TABLES 16 – 18 DETAILED RESULTS FOR BPD AND IVH

APPENDIX B

TABLES 16 – 18 DETAILED RESULTS FOR BPD AND IVH

Table 16.

BPD by Birth Year

Presence of BPD	***Birth Year***						
	2006	**2007**	**2008**	**2009**	**2010**	**2011**	**Total**
BPD = No, *n* (%)	35 (51.5)	21 (42.0)	27 (48.2)	23 (46.9)	24 (50.0)	15 (33.3)	145 (45.9)
BPD = Yes, *n* (%)	33 (48.5)	29 (58.0)	29 (51.8)	26 (53.1)	24 (50.0)	30 (66.7)	171 (54.1)
Totals, *n* (%)	68	50	56	49	48	45	316

Table 17.

BPD by Gestational Age Category

Presence of BPD	***Gestational Age Category***				
	22 – 24 W	**25 - 27 W**	**28 - 30 W**	**31 - 32 W**	**Total**
BPD = No, *n* (%)	2 (9.5)	10 (10.1)	79 (59.8)	54 (84.4)	145 (45.9)
BPD = Yes, *n* (%)	19 (90.5)	89 (89.9)	53 (40.2)	10 (15.6)	171 (54.1)
Totals, *n* (%)	21	99	132	64	316

Table 18

IVH by Birth Year

Presence of BPD	***Birth Year***						
	2006	**2007**	**2008**	**2009**	**2010**	**2011**	**Total**
IVH Grade 0, *n* (%)	56 (61.5)	42 (62.7)	34 (45.4)	40 (45.5)	30 (46.1)	29 (48.3)	231 (51.8)
IVH Grade 1, *n* (%)	12 (13.2)	7 (10.4)	12 (16.0)	17 (19.3)	15 (23.1)	11 (18.3)	74 (16.6)
IVH Grade 2, *n* (%)	9 (9.9)	8 (11.9)	13 (17.3)	5 (5.7)	7 (10.8)	6 (10.0)	48 (10.8)
IVH Grade 3, *n* (%)	5 (5.5)	1 (1.5)	1 (1.3)	5 (5.7)	3 (4.6)	6 (10.0)	21 (4.7)
IVH Grade 4 *n* (%)	5 (5.5)	5 (7.5)	6 (8.0)	9 (10.2)	3 (4.6)	7 (11.7)	35 (7.8)
IVH Not Evaluated, *n* (%)	4 (4.4)	4 (6.0)	9 (12.0)	12 (13.6)	7 (10.8)	1 (1.7)	37 (8.3)
Totals, n (%)	91 (20.4)	67 (15.0)	75 (16.8)	88 (19.7)	65 (14.6)	60 (13.5)	446