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Study description

1. Study Purpose and Rationale

Pneumothorax leak is a common and potentially life-threatening complication in very low birth weight (VLBW) infants. The overall incidence of pneumothorax has been estimated at approximately 5-9% in VLBW infants¹ and has been associated with the development of adverse outcomes, including bronchopulmonary dysplasia², intraventricular hemorrhage^{3,4}, and death⁵.

At this institution (MS-CHONY), while the incidence of pneumothorax has varied considerably over the years, it has consistently remained higher than the overall median of other centers in the Vermont Oxford Network (VON), a database collating patient information for VLBW infants from over 850 neonatal intensive care units (NICU) worldwide. The VON is a non-profit collaborative effort among these NICUs to gather data over 50 variables on infants with birth weights of 401-1500g in a systematic and controlled fashion. This data may then be used for a variety of purposes including quality improvement and clinical research. The data contained within the VON is confidential, but collated in such a manner that data is available yearly from the network at a population level. In addition, more detailed center data is analyzed and available to each participating unit, including de-identified individual patient data that may be used for studies such as this one.

There are a number of characteristics, including low gestational age, low birth weight, and cesarean section, that are thought to be associated with pneumothorax⁶⁻⁸. In addition, specific interventions such as the use of bag-mask ventilation during resuscitation, aggressive suctioning, and mechanical ventilation, have also been associated with pneumothorax^{6,7}. However, few of these factors (other than gestational age and low birth weight) have consistently been shown over multiple studies to be associated with the development of pneumothorax, suggesting that variation in the use of the practices, a combination of population attributes and specific interventions, or some other unknown variable may play a role. The presence of respiratory distress syndrome, inflammatory states (such as chorioamnionitis and sepsis), and the lack of antenatal steroids are also potential risk factors for pneumothorax. The administration of surfactant has been shown to be protective against pneumothorax in most studies⁹. According to VON's report from 2008, of these potential risk factors, the MS-CHONY NICU utilizes surfactant (32% v. 64%), early ETT ventilation (21% v. 53%), and bag-mask ventilation (43% v. 61%) at lower rates than the entire network; the use of early CPAP (73% v. 25%) and presence of multiple births (45% v. 28%) are higher.

The use of nasal continuous positive airway pressure (nCPAP) has previously been suggested as a risk factor for developing pneumothorax at other hospitals, but several studies have evaluated this association with varying results¹⁰⁻¹⁴. The use of early CPAP in VLBW infants has been standard practice at this institution for many years and may represent a factor in the elevated incidence of pneumothorax, but has also been considered by many to be the basis of MS-CHONY's extremely low rate of bronchopulmonary dysplasia compared to other centers¹⁵. However, the ubiquitous use of CPAP in our NICU for virtually all VLBW infants does not allow for a case-control retrospective evaluation of the potential association of CPAP use and the development of pneumothorax in our population. Comparison with NICUs employing different respiratory support strategies (namely, utilizing CPAP at much lower rates) would be a possible way to evaluate this association. To approach this question, logistic regression models based on data at NICUs utilizing different treatment modalities and applied to data at MS-CHONY will be used to evaluate this potential association (as described below in section 2). The VON database does not allow the release of individual data from other centers. However, the New York State database provides a potential source for adequate data for regression models.

Therefore, this study proposes a retrospective chart review including data from the Vermont Oxford Network and the New York State database (SPDS NICU module) to evaluate a variety of patient characteristics as well as medical interventions used in our NICU for association with the development of pneumothorax.

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2. Study design and statistical procedures

This is a retrospective, minimal risk, case-control observational study of VLBW infants in the neonatal intensive care unit between January 2005-June 2008 who were born at less than or equal to 28 weeks gestation. Data will be collected from patients admitted to this institution from the Vermont Oxford Network, as well as from individual patients' medical records. This chart review will include information on gestational age, gender, birth weight, mode of delivery, presence of multiple births, diagnosis of chorioamnionitis, and a variety of exposures including antenatal steroids, surfactant, bag-mask ventilation during resuscitation, conventional ventilation, and CPAP. These factors were selected based on a review of the literature as well as physiological plausibility. The primary outcome will be the presence of pneumothorax.

Infants will be separated into two groups based on the development of pneumothorax (defined as the presence of pulmonary air leak identified by either clinical symptoms, chest transillumination, and/or chest x-ray) at any time during hospitalization. Analysis of categorical variables for effect size is shown in Table 1, using the Chi-square test for proportions, assuming power of 80%, $\alpha_i=0.05$ (corrected 0.005), and ratio of cases to controls of 1:7. Association of risk factors with pneumothorax will be analyzed by univariate comparisons initially (utilizing Chi square test for independent proportions), followed by multivariable logistic regression. The use of more advanced statistical techniques, including the Kaplan-Meier estimator and the Cox proportional hazards model, among others, will likely be required to account for changes in variables and patients over time.

	2008 Proportion	Estimated Proportions in Pneumothorax Group	
Sex (male)	0.51	0.27	0.75
Multiples	0.45	0.22	0.7
Mode of delivery (C/S)	0.77	0.51	0.93
Chorioamnionitis	0.03	N/A	0.076
Antenatal steroids	0.79	0.53	0.94
Initial bag-mask ventilation	0.43	0.21	0.68
Initial intubation	0.21	0.063	0.47
Surfactant	0.32	0.13	0.58
Ventilation via ETT	0.53	0.29	0.76

Table 1. Power estimation. Each variable was considered separately for the purposes of determining effect size. Proportions for the controls were calculated using data from the MS-CHONY NICU throughout 2008. Estimated proportions for the cases were calculated using $\alpha=0.005$ and power of 80%. Estimates for both the upper and lower effects are included here.

As described above, the near-universal use of CPAP in MS-CHONY NICU does not allow for analysis in this manner. For this potential risk factor, a logistic regression model extrapolated from data at outside NICUs employing different practices (primarily for respiratory support), will be applied to data collected during this study to estimate changes in risk that may be associated with CPAP.

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3. Study procedures-N/A

4. Study drugs or Devices-N/A

5. Study Questionnaires – N/A

6. Study Subjects

All preterm neonates between 23 and 28 weeks gestation born between 1 January 2005 and 31 December 2008 will be included. All other neonates admitted to the NICU during this time period will be excluded. Subjects who were transferred to the NICU for the sole purpose of a procedure and were quickly transferred back to the referring hospital will also be excluded. Study subjects will be divided into two groups: infants who developed pneumothorax during the course of hospitalization and those who did not.

7. Recruitment

All infants meeting the above gestational age requirements and whose data was submitted to the Vermont Oxford Network will be included. Infants will be identified from the master list of admissions in the neonatal intensive care unit from 1 January 2005 and 31 December 2008.

8. Confidentiality of Study Data

Each infant will be de-identified and assigned a unique study number for data analysis. Identifying information (name, birth date, admission date, discharge date, and MRN) will be removed from the working data files once data collection is complete for analysis. Patient identifiers will be stored in a password protected database and key files will be kept in a locked office under the supervision of the principal investigator.

9. Potential Risks.

This is a minimal risk, retrospective chart review evaluating potential risk factors for the development of air leak at MS-CHONY. All decisions regarding patient care including specific interventions have already been made by the attending physician and have been completed prior to the initiation of this study.

10. Potential Benefits.

Identifying factors that increase risk or confer a protective benefit to developing air leak syndrome may lead to quality improvement practices to reduce the incidence of air leak at this institution. There will be no individual benefit to study subjects.

11. Alternatives.

This study is a retrospective chart review evaluating current practice in this institution's neonatal intensive care unit. The alternatives would be to not conduct the study or evaluate the evidence of investigations undertaken at other institutions employing different practices.

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12. References

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