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EVALUATION OF A PRACTICE GUIDELINE FOR THE MANAGEMENT OF RESPIRATORY DISTRESS SYNDROME IN PRETERM INFANTS

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DEDICATION

I dedicate this thesis to Karen Bosma, a mentor and friend of mine who encouraged me to pursue my Master of Health Studies Degree given my passion for research and my career goal of conducting my own research. This journey has taught me so much about research and has opened up many opportunities for me to pursue a new career path.

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Abstract

Background: A new practice guideline for the management of respiratory distress syndrome in preterm infants was implemented into practice as a quality improvement initiative.

Objective: To study the effects of implementing the new guideline on the use of mechanical ventilation, surfactant and the incidence of bronchopulmonary dysplasia.

Study Design: An observational one-year before and after study was conducted in preterm infants born between 26^{0} -32^{6} weeks gestation.

Results: Two hundred and seventy-two preterm infants were included in the study. Following the implementation of the guideline the number of infants treated with ongoing mechanical ventilation was reduced from 63 infants (49%) to 37 (26%) infants ($P<0.001$). There was no difference in the number of infants treated with surfactant or the incidence of bronchopulmonary dysplasia.

Conclusion: The implementation of the practice guideline helped to minimize the use of ongoing mechanical ventilation in preterm infants at high risk of respiratory distress syndrome.

Keywords: respiratory distress syndrome, preterm infants, bronchopulmonary dysplasia

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CHAPTER I

Introduction

In Canada, approximately 4000 infants are born at less than 33 weeks gestation each year and of these infants, approximately 64% of these infants have a birth weight of less than 1500 grams (Canadian Neonatal Network [CNN], 2012). Both prematurity and low birth weight places infants at risk of developing respiratory distress syndrome (RDS); a respiratory disorder that is caused by lung immaturity (Huether & McCance, 2004). RDS affects approximately 70% of infants born at less than 33 weeks gestation (CNN, 2012). The incidence and severity of RDS increases with decreasing gestational age and birth weight, affecting approximately 80% of preterm infants born between 26-28^{6} weeks and 45% of infants born between 29-32^{6} weeks gestation (CNN, 2012). Respiratory failure secondary to RDS is currently managed with one or a combination of the following therapies: mechanical ventilation, oxygen therapy, exogenous surfactant therapy and non-invasive respiratory support which includes nasal continuous positive airway pressure (CPAP) or non-invasive intermittent positive airway pressure (NIPPV). The use of supplemental oxygen and mechanical ventilation to manage RDS in preterm infants can cause lung injury which puts them at a greater risk of developing bronchopulmonary dysplasia (BPD), a form of chronic lung disease that develops later in the post-natal period as the pulmonary system matures and heals following RDS (Chess, D'Angio, Pryhuber & Maniscalco, 2006; Lopez, Rodriguez, Navarro & Sanchez-Luna, 2011). The diagnosis and severity of BPD is based on the infants need for supplemental oxygen or respiratory support at 28 days of life and 36 weeks post-menstural age (PMA) [Ehrenkranz at al., 2005]. Similar to RDS, the incidence of BPD increases with lower gestational age and birth weight (Stoll et al., 2010 & CNN, 2012). BPD is the leading cause of morbidity in preterm infants (Stoll et al., 2010) affecting

approximately 25% of surviving infants with a birth weight of less than 1500 grams and 18% of surviving infants born at less than 33 weeks gestation (CNN, 2012).

Over the last two decades, a considerable amount of research has been conducted on the use of various types of respiratory support and therapies to manage RDS. The introduction of exogenous surfactant for the treatment of RDS in 1990 greatly improved the management of the disease as its use was found to reduce mortality, the incidence of BPD and other adverse pulmonary outcomes in preterm infants (Seger & Soll, 2009 & Yost & Soll, 2000). Currently the delivery of surfactant requires endotracheal intubation and a period of positive pressure ventilation so that it can be administered directly into the lungs using using endotracheal tube.

Despite the established benefits, the use of prophylactic surfactant to manage RDS in preterm infants has declined in the past decade (Stoll et al., 2010). Instead more preterm infants are being initially managed at birth with non-invasive respiratory support with later surfactant therapy only if non-invasive respiratory support is insufficient to manage RDS (Stoll et al., 2010). Consequently, over the last decade, a non-invasive approach to RDS management has resulted in a greater proportion of preterm infants who never required intubation, surfactant therapy and mechanical ventilation (Stoll et al., 2010). Unfortunately, these changes to RDS management have not resulted in an overall reduction in the incidence of BPD (Stoll et al., 2010). However, preterm infants diagnosed with BPD today, tend to have a "new" milder form of BPD, characterized by a diffuse reduction in alveolar development which differs significantly from the "old" form of BPD which was characterized by severe airway injury, inflammation and fibrosis (Mosca, Colnaghi & Fumagalli, 2011). This decrease in the severity of BPD over the years is likely a result of fewer infants being exposed to mechanical ventilation, which reduces

the amount of lung injury that occurs during the management of RDS (Mosca, Colnaghi & Fumagalli, 2011).

Prior to release of the updated 2013 European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants (Sweet et al., 2013), the major challenge involved with using non-invasive respiratory support as a primary approach to RDS management was the lack of a consensus as to what criteria should be used to deliver surfactant therapy to preterm infants who do not require intubation at birth. Some preterm infants initially managed with non-invasive respiratory support do not receive surfactant until RDS is well established, which has been found to increase the risk for air leaks and BPD (Stevens, Harrington, Blennow & Soll, 2007; Yost & Soll, 2000). Prior to 2013, Stevens et al. (2007) recommended a fraction of inspired oxygen ($FiO_{2)}$ threshold of < 0 .45 for preterm infants at high risk of RDS, however this criterion was likely not specific enough to ensure a consistent approach to RDS management and likely led to variations in practice. Conflicting evidence also exists as to whether or not preterm infants with RDS benefit from early intubation, surfactant therapy and immediate extubation to non-invasive respiratory support, known as the INSURE (Intubate, Surfactant, Extubate) Method which aims to avoid the routine use of mechanical ventilation following surfactant delivery to help minimize the potential for lung injury (Dani et al., 2004, Dunn et al., 2011; Escobedo et al., 2004; Kandraju et al, 2013; Reininger et al., 2005, Rojas et al. 2009; Sandri et al., 2010; Tooley & Dyke, 2003; Verder et al., 1994; Verder et al., 1999). Furthermore, there is also a lack of specific recommendations for RDS management based on the preterm infant's clinical presentation at birth, which can lead to additional variations in practice. Consequently, there is a need to establish a set of clear and comprehensive guidelines that can be used to facilitate a consistent approach to RDS management that takes into

consideration the preterm infant's clinical presentation at birth. Fortunately, the updated European guideline for 2013 now provides specific FiO_2 thresholds for surfactant delivery based on gestational age which helps to guide decision making in this population.

Prior to 2012, the level III Neonatal Intensive Care Unit (NICU) at London Health Sciences Centre (LHSC) did not utilize any specific guidelines for managing RDS in the preterm population. However, in practice a large proportion of preterm infants at risk of developing RDS were being treated prophylactically with surfactant at birth and would receive ongoing mechanical ventilated afterwards. Consequently, the INSURE method was not being routinely utilized in practice. Furthermore, while non-invasive respiratory support was being utilized in older preterm infants with RDS, it was being underutilized in the lower gestation and lower birth weight infants with RDS. Given this approach to RDS management, it was not surprising that the incidence of BPD in surviving infants < 33 weeks gestation at the NICU at LHSC in 2011 was one of the highest across Canada at 32% and substantially higher than the Canadian national average of 18% (CNN, 2011).

Recognizing that this area of practice required improvement, the local NICU Evidence-Based Practice for Improving Quality (EPIQ) committee decided to focus their efforts in this area. EPIQ is a national multi-disciplinary collaboration that was developed by Dr. Shoo Lee, Director of the Neonatal Network and other members to facilitate the implementation of practice changes based on evidence, in response to the large variations in practices and outcomes that exist in Canadian NICU's (EPIQ, 2007). EPIQ is a systematic approach whose goal is to use evidence from published literature and site data to target interventions based on variations in outcomes. It utilizes a collaborative approach by involving the expertise/experience of a national network of clinicians and experts to promote continuous quality improvement in Canadian

NICU's (EPIQ, 2007). There are currently 30 NICU's across Canada involved in the national EPIQ collaboration and each NICU has a local EPIQ committee. At LHSC, the local EPIQ committee currently includes 2 neonatologists, 2 nurse practitioners, 3 respiratory therapists, 1 physiotherapist, 1 registered dietitian and 2 registered nurses, all of whose membership is voluntary. The local EPIQ committee meets once a month to discuss and plan quality improvement initiatives in the NICU.

To target a reduction in the incidence of BPD, the local EPIQ committee choose to develop and implement a new evidence based practice guideline for RDS management in preterm infants. The goal was to facilitate a consistent approach to RDS management that minimized the use of mechanical ventilation. The guideline was called the "INSURE Method Practice Guideline" and was implemented into practice by the local EPIQ committee on February 1, 2012. The INSURE Method Practice Guideline incorporates a variety of treatment approaches to RDS management by utilizing a flowchart to determine whether respiratory support and surfactant therapy is needed based on the infant's clinical presentation at birth. This guideline represents one interpretation of the current evidence to date and was developed specifically for use in the NICU at LHSC based on the current culture and available resources and therefore may differ slightly from the practices of other NICU's. In order to determine its appropriateness and effectiveness for managing RDS in preterm infants, formal evaluation of the guideline was necessary.

Purpose of the Study

The purpose of this study is to evaluate the effects of implementing the INSURE Method Practice Guideline for the management of RDS in preterm infants in the NICU at LHSC. Results

of this study will add further evidence to the discourse related to how to best manage RDS in preterm infants.

Research Questions

The research questions that guided this study were:

1. For preterm infants at high risk of RDS, does the implementation of the INSURE Method Practice Guideline:

    Reduce the use of ongoing mechanical ventilation within the first 7 days of life?

    Reduce the number of infants treated with surfactant?

    Reduce the incidence of bronchopulmonary dysplasia?

    Increase the proportion of infants treated initially with non-invasive respiratory support after birth?

    Increase the proportion of infants treated with the INSURE method after birth?

    Decrease the proportion of infants who reached treatment failure criteria after being treated with non-invasive or the INSURE method after birth?

2. For preterm infants who met criteria to be treated with the new guideline, what proportion was treated in compliance with the new guideline?

CHAPTER II

Review of the Literature

The review of the literature will begin with an overview of both RDS and BPD. This will be followed by a review of the evidence regarding each of the current therapies used to treat and/or prevent RDS which will include mechanical ventilation, surfactant therapy, CPAP, NIPPV and the INSURE method. This section will conclude with a summary of the literature review.

Respiratory Distress Syndrome (RDS)

RDS is the result of lung immaturity in the preterm infant that causes a primary deficiency of surfactant and a reduced alveolar surface area available for gas exchange (Huether & McCance, 2004). Surfactant is a substance produced in the lungs which lines the alveoli and prevents them from collapsing. It is not normally secreted in sufficient quantities until approximately the 29-30th week of gestation and as a result most preterm infants born before this gestation will be surfactant deficient (Huether & McCance, 2004). RDS usually manifests at birth or shortly after and increases in severity over the course of 2 days of life (Sweet et al., 2010). Surfactant deficiency increases the surface tension in the alveoli causing alveolar collapse, decreased lung compliance and impaired gas exchange which can cause hypercapnia, hypoxemia and increased work of breathing in the preterm infant. In severe cases, this can rapidly progress to respiratory failure and death, if left untreated (Huether & McCance, 2004). RDS can also cause major pulmonary complications including pneumothorax and pulmonary interstitial emphysema due to low lung compliance which can further compromise the functioning of the respiratory system. Diagnosis of RDS is based on the clinical symptoms of respiratory distress including nasal flaring, grunting, tachypnea, intercostal and subcostal retractions and increased oxygen requirements in an infant who is premature and can be confirmed by a chest x-ray that demonstrates lung fields with a "ground glass" appearance, reduced lung volumes and air bronchograms (Sweet et al., 2010). The management of RDS involves using non-invasive respiratory support such as CPAP or NIPPV or invasive therapies such as mechanical ventilation to keep the lungs inflated so that they can participate in gas exchange. Due to the potential for adverse effects involved with invasive therapies the goal is to use the least invasive therapy required to adequately support preterm infants with RDS. Preterm

infants who develop moderate or severe RDS and require prolonged invasive respiratory support are at a higher risk of developing respiratory complications such as BPD which manifest later in the post-natal period.

Bronchopulmonary Dysplasia (BPD)

BPD is a form of chronic lung disease which develops almost exclusively in preterm infants and is characterized by abnormal lung function and abnormal chest x-rays during the postnatal course (Jobe & Ikegami, 1998). Several different definitions exist for BPD; for the purposes of this paper, the need for supplemental oxygen and/or respiratory support at 36 weeks PMA will be used to define BPD (Jobe & Bancalari, 2001). A severity based definition of BPD has also been proposed and validated in the literature (Jobe & Bancalari, 2001; Ehrenkranz et al., 2005). Using this definition, mild BPD is classified as the need for supplemental oxygen at 28 days or more but not at 36 weeks PMA, moderate BPD is classified as the need for supplemental oxygen at 28 days in addition to the need for < .30 supplemental oxygen at 36 weeks PMA and severe BPD is classified as the need for oxygen at 28 days or more in addition to the need for > .30 supplemental oxygen and/or positive pressure at 36 weeks PMA (Jobe & Bancalari, 2001; Ehrenkranz et al., 2005). Similar to RDS, the strongest predictors of BPD are low gestational age and low birth weight (Jobe, 2011; Stoll et al, 2010 & CNN, 2012). Due to the advances in neonatal care and respiratory management practices over the past two decades, including the use of surfactant therapy, antenatal steroids, the introduction of newer modes of ventilation and additional forms of non-invasive respiratory support for the management of RDS, the pathology of BPD has changed significantly over the years. The “old” and more severe form of BPD characterized by airway injury, inflammation and fibrosis and seen in moderately preterm infants with RDS who were exposed to prolonged mechanical ventilation and supplemental oxygen has

changed to a “new” and milder form of BPD characterized by a diffuse reduction in alveolar development, a dysmorphic capillary configuration and less fibrosis (Coalson, 2006; Mosca, Colnaghi & Fumagalli, 2011; Trembath & Laughon, 2011). It has been hypothesized that the “new” milder form of BPD seen more frequently in very low birth weight infants is the result of inflammatory mediators disrupting the signalling required for normal development of the alveoli (Jobe & Ikegami, 1999). Pro-inflammatory mediators are released in the lung in response to oxygen exposure, lung infection and lung injury that can occur with mechanical ventilation and positive pressure ventilation and therefore are likely to play a role in the development of BPD (Jobe & Ikegami, 1999). Consequently, it is not surprising that the use of mechanical ventilation at day 7 of life has been found to be a major predictor of BPD (Lopez et al., 2011). Nonetheless, many other pre-natal and post-natal factors such as antenatal steroids, preeclampsia, chorioamnionitis, fetal growth restriction, maternal diabetes, severity of respiratory disease at birth, post-natal steroids, nutrition, patent ductus arteriosus, infection, sepsis, caffeine use, vitamin A use and oxygen exposure have been all been identified as factors that may affect either fetal lung development and the risk developing BPD (Eriksson et al., 2013; Jobe, 2011; Trembath & Laughon, 2012). Investigators agree that the development of BPD is multi-factorial and is likely the result of many different pre-natal and post-natal risk factors (Trembath & Laughon, 2012).

Overall the improvements to neonatal care have lead to an increased survival rate of extremely preterm infants. Since these infants are at the greatest risk of developing respiratory morbidities improved survival has resulted in an increase in the incidence of BPD (Horbar et al., 2002; Mosca et al., 2011), which is currently the most common cause of morbidity in surviving very preterm infants (Stoll et al., 2010). This is particularly important because BPD has been

associated with neurodevelopmental impairments (Anderson & Doyle, 2006), cognitive impairments (Natarjan et al., 2012) and significant pulmonary sequelae during childhood (Bhandari & Panitch, 2006). These issues can cause difficulties for the infant and family that persist into childhood and adult life. The economic impact of BPD to the healthcare system is also considerable, as it is the single most costly complication of preterm birth with an average cost of $116 000 at discharge in the US for a preterm infant with a diagnosis of BPD (Russell et al., 2007). Consequently, the development of BPD continues to be a significant issue of preterm birth which has both economic and long term health consequences. Therefore further efforts to target a reduction in the incidence of BPD are needed.

Mechanical Ventilation

Mechanical ventilation generates positive pressure which creates a pressure gradient and forces air into the lung through an endotracheal tube or mask. Mechanical ventilation is indicated for respiratory failure; a point in time when the infant is unable to adequately remove carbon dioxide and maintain adequate oxygen in the arterial blood. This mode of respiratory support has been used as a standard of therapy for respiratory failure secondary to RDS since its introduction in the 1960's and its use as a treatment for severe RDS has been found to reduce mortality in this population (Henderson-Smart, Wilkenson & Raynes-Greenow, 2002). Unfortunately, preterm infants, predisposed to lung injury due to surfactant deficiency and the structural immaturity of the lung, are at risk for developing ventilator induced lung injury (Jobe & Ikegami, 1998; Parker et al., 1993). Lung injury in preterm infants is primarily due to volutrauma and oxygen toxicity which can lead to lung injury and can initiate a pulmonary and systemic inflammatory response that can cause surfactant inactivation, alveolar damage and further pulmonary dysfunction (Clark et al., 2001). A study by Bjorklung et al. (1997) using preterm lambs demonstrated the harmful

effects of positive pressure ventilation; as few as six inflations with large volumes delivered to a surfactant deficient lung caused widespread lung injury and reduced the subsequent effectiveness of rescue surfactant treatment. It has also been suggested that ventilator-induced lung injury may also interfere with normal lung development that occurs after birth, resulting in abnormal septation of the alveoli which may increase the risk of developing BPD (Jobe & Ikegami 1999). The initiation and ongoing use of mechanical ventilation to treat RDS puts the infant at risk of further lung injury which can further compromise the immature respiratory system of preterm infants.

Several studies (Laughon et al., 2009; Lopez et al., 2011; Thomas, Meinzen-Derr, Hoath & Narendran, 2012; Van Marter et al., 2000) have found that the use of mechanical ventilation in preterm infants has been associated with the development of bronchopulmonary dysplasia. However it is unclear as to whether this association is secondary to the severity of RDS, since more severe cases of RDS are more likely to require mechanical ventilation than mild cases and are also more at risk for developing BPD. Regardless, due to the potential for lung injury in preterm infants when using mechanical ventilation, it follows that routine use of mechanical ventilation to treat RDS should be avoided if at all possible, and if required to treat respiratory failure its duration should be minimized.

Continuous Positive Airway Pressure (CPAP)

Due to the harmful effects of mechanical ventilation, continuous positive airway pressure (CPAP), a non-invasive mode of respiratory support delivered through a nasal mask or prongs, has been used to treat RDS (Diblasi, 2011). This form of respiratory support helps to prevent lung collapse by enabling infants to breathe spontaneously while receiving a baseline level of continuous pressure. Its use in preterm infants with RDS has been found to help prevent

respiratory failure and reduce the need for mechanical ventilation (De Klerk A.M & De Klerk R.K., 2001; Gitterman, Fusch, Gitterman, Regazzoni & Moessinger, 1997; Ho, Subramanian, Henderson-Smart, & Davis, 2002). CPAP has also been found to be effective at reducing extubation failure in preterm infants following a period of mechanical ventilation (Davis & Henderson-Smart, 2003). Because of the reduction in the need for and duration of mechanical ventilation, CPAP has the potential to reduce the incidence of BPD by preventing lung injury resulting from mechanical ventilation (Ramanathan, 2010; Bhandari, 2013). Avery et al. (1987) demonstrated support for this theory, when they found that neonatal centers that primarily used CPAP to treat preterm infants after birth had significantly lower rates of BPD when compared to centers that never used CPAP or used it infrequently.

Since then several studies that have evaluated the use of CPAP at birth for very preterm infants and have found that between 20-60 % of very preterm infants (24-31 weeks gestation) can be treated successfully with CPAP alone (Aly et al., 2005; Dunn et al, 2011; Lopez et al., 2011; Morley et al., 2008; Sandri et al., 2010; SUPPORT Study Group, 2010). These findings are important because a number of studies have found that preterm infants who are treated successfully with CPAP have fewer complication and morbidities compared to infants who required mechanical ventilation (Ammari et al., 2005; Aly et al., 2005; Lopez et al., 2011). Nonetheless with a CPAP success rate of between 20-60%, ultimately the remaining proportion of infants will fail CPAP and require intubation and ongoing mechanical ventilation. For this population of preterm infants the administration of surfactant is delayed and consequently may be too late to benefit infants with established RDS (Verder et al., 1994). Nasal CPAP has also been associated with other adverse events. One study found that after adjusting for severe RDS and gestational age, the rates of mortality and premature morbidities were higher in the CPAP

failure group than the CPAP success group (Ammari et al., 2005). Another study also found that the rate of necrotizing enterocolitis was significantly higher in the CPAP failure group compared to infants who received mechanical ventilation since birth (Aly et al., 2005). Controversy remains as to which preterm infants should be treated with CPAP at birth and which preterm infants should be intubated, given surfactant and mechanically ventilated.

Three large multi-center RCTs specifically evaluated the use two different respiratory management strategies for the treatment of RDS by randomizing preterm infants to either CPAP at birth with selective surfactant if intubation was required or intubation at birth, mechanical ventilation and surfactant therapy (Dunn et al., 2011; Morley et al., 2008; SUPPORT Study Group, 2010). All three studies included very preterm infants; Dunn et al. (2011) enrolled infants born between 26- $29^{6/7}$ weeks gestation; Morley et al. (2008) enrolled infants born between 25-$28^{6/7}$ weeks gestation; and the SUPPORT Study Group (2010) enrolled infants born between 24-$27^{6/7}$ weeks gestation. All three studies found no significant difference in the combined outcome of all causes of mortality or survival with BPD (Dunn et al., 2011; Morley et al., 2008; SUPPORT Study Group, 2010). However, when the results of all three studies are combined, infants randomised to the CPAP groups had a 5% lower rate in the composite outcome of mortality or survival with BPD (Carlo, 2012). Furthermore, since the studies found that between 20-55% of infants in the CPAP and selective surfactant group could be managed without surfactant and mechanical ventilation, all three studies recommended the use of early CPAP and selective surfactant as an alternative to prophylactic surfactant and mechanical ventilation. In terms of secondary outcomes, no differences were found between the two groups in the Dunn et al. (2011) and the SUPPORT Study Group (2010) studies; however, in the Morley et al. (2008) study, the incidence of pneumothorax was significantly higher in the CPAP group

(9% versus 3%, p <0.001). The increased risk of pneumothorax in the Morley et al. (2008) study can likely be attributed to the higher FiO_2 threshold (>0.60) used to deliver surfactant therapy when compared to the studies by Dunn et al. (2010) and the SUPPORT Study Group (2010) who utilized lower thresholds for surfactant delivery and did not find any difference in the outcome of pneumothorax. Nonetheless, the increased risk of pneumothorax is very concerning because the risk of mortality is significantly increased when a pneumothorax occurs (Fidanovski et al., 2005). It is important for NICUs which utilize CPAP as a primary mode of support for preterm infants at birth to incorporate a strategy of early surfactant administration for infants with established RDS to help decrease the severity of RDS and to minimize the risk for adverse events that can occur when surfactant administration is delayed (Pfister & Soll, 2012; Verder, Bohlin, Kamper, Lindwall & Jonsson, 2009).

Overall, the use of CPAP has its advantages and disadvantages. When used in preterm infants with RDS it can reduce the need of mechanical ventilation and surfactant therapy; however, in cases where CPAP is not successful, the administration of surfactant is delayed, and the delay may predispose the preterm infant to lung injury from mechanical ventilation and may increase the risk of other adverse outcomes such as pneumothoraces. This suggests that it is important to establish other treatment approaches which can reduce the number of infants who fail CPAP and require mechanical ventilation.

Nasal Intermittent Positive Pressure Ventilation (NIPPV)

Nasal intermittent positive pressure ventilation (NIPPV) is a form of non-invasive respiratory support that provides a continuous positive airway pressure as well as intermittent positive pressure inflations through the nasal interface to help augment the effectiveness of CPAP (Davis, Lemyre & de Paoli, 2001). There are many different devices and ventilators used

to deliver NIPPV and many of them vary considerably in terms of the interface used for delivery, whether it be nasal prongs, nasal mask or via a shortened endotracheal tube as well as the amount of positive pressure that can be effectively delivered to the infant. There are also several different modes of non-invasive support available for use in the preterm population, including NIPPV that is either synchronized or not synchronized with the infant's respirations as well as bi-level positive airway pressure, which allows the infants to breathe spontaneously at both levels of pressure. Recently it has been used as another non-invasive option to support preterm infants with RDS. Preterm infants managed on CPAP can experience frequent apneas due to the immaturity of the central nervous system and subsequently may require endotracheal intubation and mechanical ventilation due to poor respiratory drive (Davis, Lemyre & de Paoli, 2001). With NIPPV, the intermittent ventilator inflation can help to augment the infant's respiratory effort and reduce the frequency of apneas more effectively than CPAP and may also help to reduce the need for mechanical ventilation (Davis, Lemyre & de Paoli, 2001). NIPPV has also been found to reduce work of breathing when compared to CPAP (Aghai et al., 2006). This may be explained by the use of higher intermittent airway pressures during NIPPV, which creates a higher mean airway pressure in the lungs and may help to improve lung inflation in preterm infants with RDS. The use of NIPPV has been studied as a primary mode of support in preterm infants and also following extubation after a period of mechanical ventilation. As a primary mode of support, two RCT's (Kugelman et al., 2007; Shi, Tang, Zhao & Shen, 2013) and a recent meta-analysis (Meneses, Bhandari & Alves, 2012) found that the use of NIPPV significantly reduced the need for mechanical ventilation in moderately preterm infants with RDS. When comparing CPAP to NIPPV at reducing the need for subsequent ventilation in preterm infants following extubation, the findings are relatively consistent. One observational

study (Ancora et al., 2010), two small recent RCT's (Ramanthan, Sekar, Rasmussen, Bhatia & Soll, 2012; Kahramaner et al., 2013), and two systematic review (Davis, Lemyre, & de Paoli, 2001; Tang et al., 2013) found that NIPPV significantly reduced the need for subsequent mechanical ventilation when compared to CPAP, whereas another small RCT (O'Brien et al, 2012) did not find any difference between the two groups. Nonetheless, the effect of NIPPV on the outcome of BPD is not consistent between studies, with some studies finding a significant reduction in BPD with the use of NIPPV following mechanical ventilation, whereas others have not (Bhandari et al., 2009; Davis et al, 2001; Kahramaner et al., 2013; O'Brien et al., 2012; Ramanthan et al., 2012; Tang et al., 2013). However, the largest multi-center RCT to date which compared the use of NIPPV to CPAP at the time of first use, and included 1009 preterm infants with a birth weight of less 1000 grams and a gestational age less than 30 weeks found no significant differences between the two groups on the need for mechanical ventilation following randomization and the incidence of BPD (Kirpalani et al., 2013). In comparison to the other RCT's, the study by Kirpalani et al. (2013) included both infants who had been exposed to a period of mechanical ventilation and those who were utilizing non-invasive as a primary mode of support and it also utilized both synchronized and non-synchronized forms of NIPPV for infants randomized to the NIPPV group. Furthermore, this study also enrolled infants of much lower gestation and lower birth weight than the other studies which may help to explain the differences in findings as this study population is at a greater risk of requiring mechanical ventilation and developing BPD. Given the conflicting evidence to date, it remains unclear as to whether or not preterm infants with RDS benefit from the use of NIPPV over CPAP. Available evidence suggests that NIPPV is at least as effective as CPAP and does not increase the risk of potential adverse effects, such as airleaks, necrotizing enteorcolitis or nasal trauma (Kirpalani et al., 2013).

Some of these variations in findings can likely be attributed to the timing of NIPPV use, the type of non-invasive mode used, and the patient population studied, as these varied considerably among studies. Overall, given that there is some evidence to suggest that NIPPV in preterm infants may reduce the need for mechanical ventilation and the risk of developing BPD in some preterm infants, many would likely recommend its use as another option to CPAP before mechanical ventilation is utilized.

Surfactant Therapy

RDS is caused by a primary surfactant deficiency in the lungs, which inhibits lung expansion and leads to alveoli collapse (Huether & McCance, 2004). Exogenous surfactant administered to surfactant deficient lungs helps to reduce the surface tension in the lungs and improves the lungs' ability to expand and remain inflated. This causes a rapid improvement in oxygenation and ventilation and helps to restore the lungs ability to function normally. The introduction of surfactant in 1980 represented a major breakthrough in neonatal care which changed the clinical course of RDS by reducing the level of respiratory support needed by preterm infants at birth and decreased the mortality rate of preterm infants due to respiratory failure (Jobe, 1993). A Cochrane Review of thirteen randomized controlled trials found that the use of animal surfactant to treat preterm infants with established RDS significantly reduced the risk of pneumothorax, pulmonary interstitial emphysema, mortality and BPD when compared to controls (Seger & Soll, 2009).

A number of studies have been conducted to establish whether prophylactic (delivery room administration) surfactant is superior to selective surfactant (once RDS has been established) for preterm infants (less than 30-32 weeks gestation) at high risk for developing RDS. The problem with treating all infants at high risk of RDS with prophylactic surfactant is

that some infants who receive treatment would have not required treatment. Consequently this approach would put some preterm infants at an unnecessary risk of harm as the delivery of surfactant requires endotracheal intubation and positive pressure ventilation, can cause transient periods of bradycardia and hypoxia during administration, and increases the risk of pulmonary haemorrhage and a blocked endotracheal tube (BLES Product Monograph, 2007). The 2010 European Consensus Guidelines on the management of RDS specifically recommended surfactant prophylaxis (within 15 minutes of birth) to almost all infants < 26 week as this population is at a very high risk of RDS (Sweet et al., 2010). However, these recommendations were revised in 2013 to reflect an approach that utilizes early surfactant delivery rather than prophylactic surfactant treatment for all extremely preterm infants (Sweet et al., 2013).

In a meta-analysis, Soll & Morley (2001) compared prophylactic to selective use of surfactant in preterm infants and found that infants who received prophylactic surfactant had a decreased risk of pneumothorax, pulmonary interstitial emphysema and a decreased risk for mortality. However, a more recent meta-analysis (Rojas-Reyes, Morley & Soll, 2012) found that more recent studies which utilized routine CPAP following delivery and selective surfactant were at a lower risk for chronic lung disease or death, when compared to intubation and prophylactic surfactant. When all the studies were evaluated together, the prophylactic surfactant group was no longer superior to the selective surfactant group (Rojas-Reyes et al., 2012). The differences in the findings between these two time periods are likely a result of the role of CPAP at preventing the need for surfactant and mechanical ventilation in the selective surfactant group as earlier studies which compared prophylactic to selective surfactant did not routinely use CPAP following delivery. Another meta-analysis initially conducted in 2000 by Yost & Soll and then updated in 2012 by Bahadue & Soll evaluated whether early (first two hours of life)

surfactant administration given to preterm infants who were intubated for respiratory distress was superior to delayed surfactant delivery once RDS was established. Both meta-analysis found that the early administration of surfactant lead to a decreased risk of pneumothorax, pulmonary interstitial emphysema, chronic lung disease and neonatal mortality (Bahadue & Soll, 2012; Yost & Soll, 2000). These authors concluded that all preterm infants at high risk for RDS who require intubation for stabilization in the delivery room or early in the post-natal period for respiratory distress should be given surfactant as early as possible in order to minimize the risk of adverse outcomes (Bahadue & Soll, 2012; Yost & Soll, 2000). A meta-analysis by Stevens et al., (2007) found that using a low FiO_{2of} threshold of <0.45 to treat with surfactant for preterm infants who were not intubated at birth helped to reduce the rates of air leaks, BPD and patent ductus arteriosus when compared to using a higher treatment threshold of $FiO_2 > 0.45$. Another study by Fuchs, Linder, Leiprecht, Mendler & Hummler (2011) evaluated various threshold criteria for intubation and surfactant and found that using a threshold of $FiO_2 \geq 0$ .35-0.45 compared to 0.6 would shorten the time to surfactant delivery, without a significant increase in the intubation rate. These findings appear to indicate that treating preterm infants with RDS earlier rather than later with surfactant results in a lower risk of adverse pulmonary outcomes (Stevens et al, 2007; Fuchs et al, 2011).

Most preterm infants thought to have RDS demonstrate a favourable response to surfactant therapy that causes a rapid decrease in the oxygen requirements of the preterm infant (Jobe, 1993.) However it is estimated that approximately 10-20% of preterm infants have little or no response to surfactant (Jobe, 1993; Fujiwara, Chida & Konishi, 1991). It is suggested that these infants may also have pneumonia, pulmonary hypoplasia or congenital heart disease which is further compromising the function of the respiratory system (Jobe, 1993). Birth asphyxia can

also decrease the response to surfactant as it compromises the function of the cardiovascular system (Jobe, 1993). One study has shown that preterm infants who require early supplemental oxygen are at the greatest risk of requiring mechanical ventilation and developing BPD (Laughon et al., 2009). Therefore the initial response to surfactant is likely a good predictor to help determine whether mechanical ventilation is needed to prevent respiratory failure in preterm infants with RDS.

Surfactant Therapy and Non-Invasive Respiratory Support

Recognizing that the use of surfactant and CPAP used together may be synergistic, recently several studies have evaluated whether RDS in premature infants could be better managed by electively intubating with an endotracheal tube early in the postnatal period, followed by a brief period of ventilation to facilitate surfactant administration and immediate extubation (removal of the endotracheal tube) to non-invasive respiratory support (Dani et al., 2004, Dunn et al., 2011; Escobedo et al., 2004; Kandraju et al, 2013; Reininger et al., 2005, Rojas et al. 2009; Sandri et al., 2010; Soll, Conner & Howard, 2003; Tooley & Dyke, 2003; Verder et al., 1994; Verder et al., 1999). Since the majority of preterm infants with RDS have a good spontaneous drive early in the post-natal period, many do not require ongoing mechanical ventilation following surfactant administration. This strategy to manage RDS has been referred to the INSURE method (INtubate, SURfactant, Extubate).

The INSURE method was first described by Victorin, Deverajan, Curstedt & Robertson in 1990 without the use of CPAP for the treatment of RDS. In 1994, Verder et al. conducted a study on the INSURE method used in conjunction with CPAP for moderate to severe RDS and found that the INSURE method reduced to the need for mechanical ventilation when compared to CPAP alone. A Cochrane Review (Stevens et al., 2007) found that the INSURE method was

superior to later selective surfactant administration and continued mechanical ventilation at reducing the need for mechanical ventilation and the incidence of chronic lung disease. In a randomized controlled trial (RCT), Dani et al. (2004) compared the INSURE method to surfactant therapy and mechanical ventilation in preterm infants < 30 weeks gestation and found that the INSURE method significantly reduced the need for a second dose of surfactant and the need for mechanical ventilation at 7 days of life. Reininger et al. (2005) also found the need for additional doses of surfactant was reduced when comparing the INSURE method to CPAP and selective surfactant in preterm infants with early respiratory distress. Additionally, an observational study which implemented the INSURE method to treat preterm infants with RDS, found a significant reduction in the use of mechanical ventilation and the incidence and severity of BPD (Geary, Caskey, Fonseca & Malloy, 2008). Another similar observational study by Bohlin, Gudmundsdottir, Katz-Salamon, Jonsson & Blennow (2007) found that implementing the INSURE method significantly reduced the use of mechanical ventilation and the need for additional doses of surfactant. This study, as well as another observational study by Leone et al. (2013) also found that infants treated with the INSURE method had a more rapid and sustained improvement in oxygenation when compared to infants who received surfactant and mechanical ventilation, which may help to explain the reduction in the need for additional doses of surfactant. These findings are supported by a study conducted on rabbits which found an increase in surfactant inactivation when comparing surfactant and mechanical ventilation to surfactant and spontaneous breathing (Bohlin et al., 2005). Based on these findings Verder, Bohlin, Kamper, Lindwall & Jonsson (2009) concluded that the INSURE strategy may increase the effectiveness of surfactant therapy in addition to reducing the need for mechanical ventilation when used to manage RDS.

Prophylactic INSURE versus CPAP and Selective Surfactant

Since the INSURE approach necessitates intubation and a brief period of ventilation it remains unclear as to whether or not all preterm infants at high risk of RDS should be treated with prophylactic INSURE at birth regardless of whether signs of RDS are present or whether all preterm infants should be started on CPAP when feasible and only given surfactant when signs of RDS have developed (Dunn et al., 2011; Sandri et al., 2010). One large RCT that included infants 25-28$^{6/7}$ weeks (Sandri et al., 2010), compared prophylactic INSURE at birth followed by CPAP to CPAP at birth with early treatment with the INSURE method if signs of moderate RDS developed. This study found that the need for mechanical ventilation within the first 5 days of life was almost identical between the two groups; 31.4% for the prophylactic surfactant group and 33% for the CPAP and selective INSURE group and the incidence of death and BPD were also very similar (Sandri et al., 2010). A study conducted by Dunn et al. (2011) randomized 648 infant 26-29$^{6/7}$ and compared prophylactic INSURE at birth to CPAP with selective surfactant and discretionary use of mechanical ventilation if signs of moderate to severe RDS developed. Similar to the study by Sandri et al. (2010), Dunn and colleagues found no difference between the two groups in terms of the need for mechanical ventilation in the first week of life and the incidence of death and BPD. Both studies recommended the use of CPAP with early selective surfactant if CPAP failure criteria were reached as an alternative to prophylactic surfactant and CPAP because it resulted in a reduction in the number of infants who were intubated and given surfactant (Dunn et al., 2011; Sandri et al., 2010). Although, the outcomes for the prophylactic INSURE group were similar to the CPAP and selective surfactant group, many would agree that the use of surfactant should be limited to preterm infants with signs of RDS. Nonetheless, since both of these studies used prophylactic surfactant, the decision for surfactant treatment did not

take into account whether or not signs of RDS were present and as a result, the study found that not all preterm infants needed surfactant therapy to avoid mechanical ventilation and that approximately 45% could be treated with CPAP only (Dunn et al., 2011; Sandri et al., 2010)

Early INSURE versus CPAP and Selective Surfactant

Several studies have also evaluated the use of the INSURE method compared to CPAP with selective surfactant and ongoing mechanical ventilation in preterm infants with signs of respiratory distress (Escobedo et al., 2004; Reininger et al., 2005; Rojas et al., 2009; Soll et al., 2003; Verder et al., 1994). These studies varied considerably in terms of the gestational age range included, the timing of enrolment and the criteria for intubation and mechanical ventilation. One study (Rojas et al., 2009), randomized 279 preterm infants between the gestational age of 27-$31^{6/7}$ who had signs of increased work of breathing and required supplemental oxygen in the delivery room within one hour of birth to either INSURE or CPAP and selective surfactant and mechanical ventilation if intubation was required. The study found that the need for mechanical ventilation was significantly lower in the INSURE group (26%) when compared to the control group (39%). The incidence of air leak syndromes (pneumothorax or pulmonary interstitial emphysema) were also significantly lower in the INSURE group (2%) compared to the control group (9%). The incidence of BPD was also lower in the INSURE group at 49% compared to 59% in the control group, although this did not reach statistical significance. The other four studies (Escobedo et al., 2004; Reininger et al., 2005; Verder et al., 1994; Soll et al., 2003) randomized preterm infants later in the postnatal period (30 minutes-72 hours) once RDS was evident on chest x-ray and at varying FiO_2 requirements (.30-.60). All four studies found that the need for subsequent mechanical ventilation was lower in the INSURE group. Another study by Verder et al. (1999) randomized preterm infants less than 30 weeks gestation

with RDS on CPAP to either early INSURE (FiO_2 requirements 0.37-0.55) or later INSURE (if FiO_2 requirements increased to 0.57-0.77) and found that the need for mechanical ventilation was significantly reduced from 63% to 21% when infants were treated with early INSURE, a finding which could not be explained by other variables. Similar to this study, Kandraju et al., 2013 randomized 153 infants between 28^0 -$33^{6/7}$ weeks gestation with evidence of RDS on CPAP to either early routine surfactant administration via the INSURE technique or late INSURE (if FiO_2 increased to >0.5) and also found a significant reduction in the need for mechanical ventilation within the first week of life in the group of infants treated early with the INSURE method. These findings suggest that the effectiveness of INSURE at preventing the need for mechanical ventilation is dependent on how early surfactant is given once signs of RDS develop. These finding can be supported by the study conducted by Dani et al. (2004) that treated preterm infants with the INSURE method early in the postnatal period (< 6 hours) and using a low FiO_2 threshold of >0.30 and found that only 9% of 75 infants required subsequent mechanical ventilation and that no infants required a second dose of surfactant. Consequently the reported number of infants treated successfully with the INSURE method (those who do not require subsequent mechanical ventilation) varies considerably from study to study and ranges from as low as 35% to as high as 91% depending on the population of preterm infants studied and the timing of surfactant delivery (Dani et al, 2004; Dani et al., 2010 Dunn et al., 2011; Escobedo et al., 2004; Reininger et al., 2005 Rojas et al., 2009; Sandri et al, 2010; Verder et al., 1994). Similar to preterm infants who fail CPAP and require subsequent mechanical ventilation, observational studies have also shown that preterm infants who fail INSURE have a higher risk of mortality and other adverse outcomes when compared to preterm infants in which the INSURE method is successful (Dani et al., 2010; Cherif, Hachani & Khrouf, 2008). To date

there is only one small observational study that specifically evaluates the use of NIPPV in comparison to CPAP after infants have been treated with the INSURE method (Gizzi et al., 2012). This study found that using synchronized NIPPV significantly reduced the number of infants who failed the INSURE method and required MV when compared to infants treated with CPAP (Gizzi et al., 2012). This suggests that the use of NIPPV following the INSURE method may make this strategy even more successful at reducing the need for mechanical ventilation.

Summary

Over the past two decades there has been a considerable amount of research conducted to determine the optimal strategy for managing RDS in preterm infants. Based on the review of the literature, it is apparent that controversy remains as to what approach should be used to treat RDS. The evidence clearly supports the avoidance of mechanical ventilation in the treatment of RDS if at all possible. Inevitably some preterm infants will require mechanical ventilation for the management of respiratory failure secondary to RDS. In these situations, the evidence clearly indicates that surfactant should be given shortly after the initiation of mechanical ventilation to help reduce the risk of adverse pulmonary outcomes.

Non-invasive respiratory support should be used as a first line of support to manage infants at high risk with RDS who are spontaneously breathing at birth. The use of NIPPV may be more effective than CPAP at preventing the need for subsequent mechanical ventilation and therefore should be utilized as an additional option to CPAP to prevent the use of mechanical ventilation. In situations where treatment with surfactant is required, the evidence supports the use of the INSURE method over surfactant administration and ongoing mechanical ventilation for preterm infants who are breathing spontaneously. Furthermore, there is sufficient evidence to suggest that preterm infants who have established RDS have fewer adverse pulmonary outcomes

and are less likely to require subsequent mechanical ventilation when treated earlier with surfactant as opposed to later. Therefore, it is important to clearly establish a low FiO_2 threshold for surfactant therapy to facilitate early administration to preterm infants with RDS. Nonetheless, for infants presenting with mild to moderate RDS, non-invasive respiratory support without surfactant therapy should be used first, and surfactant only given if RDS progresses and reaches the FiO_2 threshold. In clinical practice, there is a need to establish a fine balance between minimizing the number of infants treated with early surfactant who do not require it, with the number of infants who receive delayed surfactant after failing non-invasive respiratory support. Ultimately, delivering surfactant very early in the post-natal period will result in some infants receiving surfactant who otherwise would not have required it. However, due to the potential for adverse pulmonary outcomes with delayed surfactant therapy, many would agree that benefits of early treatment outweigh the risks imposed by treatment.

In the clinical setting, RDS affects a large age range of preterm infants and its severity and progression is dependent on a number of different factors which makes it difficult to predict with certainty the acuity level at which RDS will present in preterm infants. While lower gestational age and birth weight increases the likelihood of developing RDS, it does not necessarily predict the severity of the disease. Consequently, the need for surfactant therapy and the level of respiratory support required varies considerably among preterm infants. Therefore, it is necessary to develop an approach to the early management of RDS that incorporates individualized treatment approaches based on the clinical presentation of each infant. An effective way to do this is to develop a clinical practice guideline that utilizes specific criteria to help determine whether respiratory support and or surfactant therapy is required. Since the symptoms of RDS can begin within minutes of delivery and generally increases in severity over

the first two days of life, a guideline that begins in the delivery room and provides ongoing management strategies for RDS in the post-natal period would be ideal for the clinical setting. Facilitating this type of approach would help to improve the quality of care delivered to these infants.

CHAPTER III

Conceptual Framework-Quality Improvement

Quality improvement as it applies to the healthcare setting, involves making changes that will help to improve the health and needs of its patients (Committee on Quality Health Care in America, 2001). One specific aim of quality improvement is to deliver care that is effective and efficient. This involves providing care to patients that is based on the latest scientific knowledge. Evidence based decision-making tools, such as clinical practice guidelines (CPG) help to achieve this goal. CPG are developed by synthesizing clinically relevant research findings in a specific area of practice to assist healthcare professionals in making decisions regarding the most appropriate course of treatment for that patient (Miller & Kearney, 2004). They help to improve the process and quality of care, by bridging the gap between research findings and clinical practice to ensure patient care is based on the best available evidence (Davis, Goldman & Palda, 2007; Lugtenberg, Burgers & Westert, 2009). In order for clinical practice guidelines to be effective they need to be designed for a specific patient population and circumstance and be based on the latest evidence (Davis, Goldman & Palda, 2007). Therefore it is important to assess the quality of the practice guideline before adopting the recommendations into practice and to ensure the CPG is updated regularly to ensure is reflects the most recent evidence. The Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument is a tool that that is used internationally to assess the methodological rigour in which the guideline was developed which

helps to establish the value of the recommendations (Brouwers et al., 2010). The evaluation of CPG involves measuring the degree to which the desired outcomes are achieved in clinical practice (Gray, 2009). When implementing a new CPG the goals of its use need to be clearly established in order to help determine the outcomes measures that will be used evaluate the guideline and how they will be measured. Should the guideline lead to an improvement, this would be reflected in the outcomes over time (National Health Service [NHS] Institute, 2008). Therefore, one efficient and practical way to evaluate a guideline is to compare the outcomes over a period of time before and after its implementation to determine whether or not a difference or trend in the outcomes exists. This type of approach is appropriate for assessing the effect of a guideline that is implemented on a large scale, as randomization would not be feasible (Gray, 2009).

CHAPTER IV

METHODS

Setting

The NICU at Children's Hospital, LHSC is a forty-two bed, level III, combined medical/surgical NICU serving Southwestern Ontario. A level III NICU is defined as a center that has the necessary equipment and specialized personnel needed to provide complex critical care and ongoing life support to extremely low birth weight infants (birth weight of less than 1000 grams and 28 or less weeks' gestation) and those with complex critical illnesses (American Academy of Pediatrics Committee of Fetus and Newborn, 2012). The birthing centre at LHSC is the region’s only high risk maternity care centre and each year delivers approximately 6200 babies. The NICU cares for approximately 800 newborns each year with the population ranging from extremely preterm infants to sick term or at risk newborns. The majority of infants cared

for in the NICU are inborn, and approximately 10-15% of infants admitted to the NICU are outborn (CNN, 2012). The NICU is staffed by fifteen to eighteen registered nurses, three respiratory therapists and by two neonatologists during the week, one neonatologist on weekends and one on-call afterhours. In-house coverage after hours is provided by either a nurse practitioner or a neonatal fellow. All preterm deliveries (< 34 weeks gestation) are attended by the neonatal resuscitation team which at minimum includes a registered nurse, a registered respiratory therapist and a neonatal fellow or nurse practitioner.

Planning the Intervention

The INSURE Method Practice Guideline for management of RDS in preterm infants was developed by a respiratory therapist on the EPIQ committee. The development of the guideline was based on an extensive literature review conducted on the topic of "initial RDS management strategies" and "strategies to reduce the incidence of bronchopulmonary dysplasia in preterm infants" using the Pub-Med database. The search was limited to articles published in the English language and those published between the years 1980 until the end of 2011. The search terms "respiratory distress syndrome", "preterm infants", "surfactant", "mechanical ventilation", "continuous positive airway pressure", "INSURE", "bronchopulmonary dysplasia", "non-invasive respiratory support" were used to find relevant articles on the topic. This evidence was then synthesized and developed into a "draft" practice guideline that could be used in the NICU to guide initial respiratory management strategies. The focus of the guideline was to establish an approach that would minimize the number of infants who fail non-invasive respiratory support or the INSURE Method. Taking this type of approach was deemed necessary to facilitate acceptance of the new guideline within the neonatal staff group. The primary purpose of the

guideline was to reduce the use of mechanical ventilation, specifically following surfactant therapy.

The initial draft of the guideline was first presented to the local NICU EPIQ committee as a potential practice change. Once revisions and feedback from the EPIQ committee were incorporated into the guideline, it was presented to the Neonatal Care Council, a multidisciplinary teams that oversees all practices in the NICU, and then to the Neonatologists of the NICU for review. Based on the feedback received from the Neonatal Care Council and the Neonatologists, additional minor revisions were made to the guideline before final approval was received to implement the guideline into practice in December, 2011. Education and training sessions took place over the month of January 2012 for all NICU staff (Registered Nurses, Registered Respiratory Therapists, Fellows, Residents and Neonatologists) and on February 1, 2012 the "INSURE Method Practice Guideline" was officially implemented into practice in the NICU at LHSC.

The INSURE Method Practice Guideline

The guideline was developed for use with all inborn preterm infants born between the gestational ages of $26^{0/7}$ -$32^{6/7}$ weeks; as this population are at a greater risk of developing RDS compared to infants born at > 33 weeks gestation (CNN, 2012). Infants with a birth weight of < 750 grams or those born at less than 26 weeks gestation were excluded from this guideline as previous studies had shown this population were at high risk of requiring mechanical ventilation and therefore were at high risk of failing the INSURE method or NCPAP and selective surfactant (Ammari et al, 2005; Dani et al, 2010, Sandri et al, 2010). Preterm infants with major congenital anomalies were also excluded from being treated with the guideline as these infant's respiratory management may need to be individualized based on the type of congenital anomaly present.

Each infant who met criteria to be treated according to the guideline were resuscitated at birth according to Neonatal Resuscitation Program guideline. The Neopuff™ Infant T-piece resuscitator (Fisher & Paykel Healthcare, Auckland, New Zealand) was used at delivery to provide positive pressure ventilation (PPV) and CPAP via a facemask. If clinically indicated, PPV was initiated at a peak inspiratory pressure of 20cm$H_2$0 and a positive end expiratory pressure of 5cmH20 and is increased or decreased as clinically indicated. If CPAP was indicated, this was delivered targeting a pressure of 5 to 7 cmH20 using the Neopuff™ Infant T-piece resuscitator and mask. Following the initial steps of resuscitation, the neonatal resuscitation team referred to the guideline to determine which respiratory management strategy was the most appropriate. The guideline incorporated four different approaches to RDS management by utilizing a flowchart/algorithm, shown in Figure 1. Options included:

1. **No respiratory support**: If the infant did not require any supplemental oxygen or show any signs of increased work of breathing (tachypnea, intercostal retractions, nasal flaring, or grunting) post resuscitation, the infant was to be admitted to the NICU and would not be placed on any respiratory support. The infant was then monitored, and if signs of respiratory distress developed, the infant was placed on non-invasive respiratory support and monitored for the need for surfactant.
2. **Non-invasive respiratory support only**: If the infant showed signs of increased work of breathing (tachypnea, intercostal retractions, nasal flaring, or grunting) following resuscitation, the infant was given CPAP using Neopuff™ Infant T-piece resuscitator and mask. If the infant did not require a FiO_2 > .30, the infant was admitted to the NICU and placed on non-invasive respiratory support using the Infant Flow® Sipap System (Care Fusion, San Diego, California). The choice of mode used (CPAP or Biphasic) to deliver

non-invasive respiratory support was at the discretion of the respiratory therapist and physician. If the infant's FiO_2 requirements increased to > .40 on non-invasive respiratory support, the infant was to be considered for surfactant therapy utilizing the INSURE method.

3. **INSURE Method**: If the infant showed signs of increased work of breathing (tachypnea, intercostal retractions, nasal flaring, or grunting) and required a FiO_2 of > .30 on CPAP post resuscitation, the infant was eligible for the INSURE method. The infant was electively intubated without premedication and given surfactant and then was assessed for immediate extubation. All infants who required intubation at birth for resuscitation were also given surfactant regardless of the FiO_2 requirements and were also assessed for immediate extubation. Infants were required to have a good respiratory drive, FiO_2 requirements ≤. 30 and be considered clinically stable in order to be immediately extubated following surfactant delivery. If these criteria are met, upon being admitted to the NICU, the infant was extubated to a Biphasic rate of 20, I time 1.0 sec, Pressures 8-9cmH20 on 5cmH20, utilizing the Infant Flow ® Sipap System. If an Infant Flow ® Sipap System unit was not available, the infant was extubated to CPAP utilizing the Infant Flow ® nCPAP System. Infant's extubated to Biphasic were weaned to CPAP as clinically tolerated as per standard NICU practice. The guideline recommended that all infants treated with the INSURE Method be placed on transcutaneous CO_2 monitor following extubation and be given a loading dose of caffeine at time of extubation and started on a maintenance dose of caffeine until it was no longer clinically indicated.
4. **Mechanical Ventilation**: Any infant who did not have a good respiratory drive, whose FiO_2 requirements were > .30 following surfactant delivery or who was clinically

unstable following resuscitation were to be admitted to the NICU and placed on mechanical ventilation.

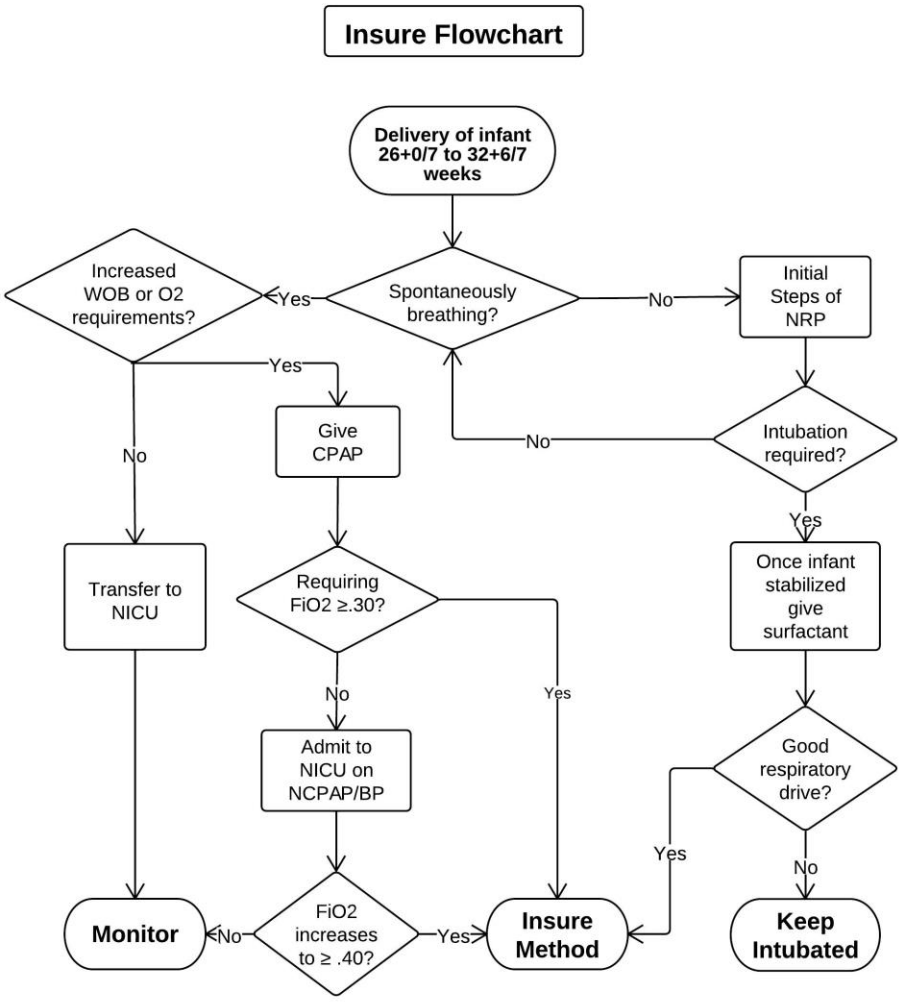
The respiratory therapist(s) were primarily responsible for driving adherence to the guideline. Their role was to assist with the resuscitation of the infant and to inform the neonatal resuscitation team of which respiratory management strategy should be utilized in accordance with the guideline. However the attending physician and/or the nurse practitioner responsible for the care of the preterm infant ultimately made the final decision based on discussion with the rest of the medical team as to whether or not the respiratory management should be in accordance with the guideline. Infants managed in accordance with the guideline were to be intubated or re-intubated within the first week of life if any one of the following criteria were met:

1. $FiO_2 > 0.40$ for at least 30 minutes
2. pH< 7.20 and CO_2 >60
3. Frequent apnea requiring stimulation (>4/Hr.)
4. Requirement for Bag Mask Ventilation (>1/Hr.)

These indications were only valid if the delivery of CPAP/Biphasic had been assessed as adequate. If the infant required ongoing mechanical ventilation to treat RDS, the endpoint of the guideline was reached and the ongoing respiratory management was determined by the attending physician based on discussions with the rest of the medical team.

Figure 1.

The INSURE Method Flowchart



Study Design

To evaluate the INSURE Method Practice Guideline, a historical cohort of preterm infants who were born at the NICU in London, Ontario during the one-year period (January 1-December 31, 2011) before the implementation of the guideline (pre-guideline cohort) were compared to a similar cohort of preterm infants who were born at the same NICU in the one-year period (February 1, 2012-January 31, 2013) following the implementation of the guideline (post-guideline cohort). The study was approved by the Athabasca University Research Ethics Board (Appendix A) and the University of Western Ontario Research Ethics Board (Appendix B). Institutional support was also obtained from the Lawson Health Research Institute (Appendix C).

Prior to the implementation of the guideline, the initial respiratory management strategy used for preterm infants at birth, as well as the post-natal respiratory management was at the attending physician or nurse practitioners discretion based on discussions with the rest of the medical team. During that time various thresholds were utilized to determine what respiratory management strategy should be used at birth. There was also no pre-defined criteria utilized to determine the need for intubation or re-intubation, mechanical ventilation or surfactant therapy, these decisions were also at the attending physicians or nurse practitioners discretion based on discussions with the medical team.

Primary and Secondary Outcomes

The primary outcome for the study was the use of ongoing mechanical ventilation (> 2 hours) during the first week of life. The secondary outcomes were the number of infants treated with surfactant therapy and the incidence of BPD. BPD was defined as the need for supplemental oxygen or respiratory support at 36 weeks PMA (Jobe & Bancalari, 2001). For infants who were transferred to another facility prior to 36 weeks PMA who could not be

properly assessed for the diagnosis of BPD, these infants were labelled as having BPD if they were on supplemental oxygen or positive pressure (CPAP, NIPPV or mechanical ventilation) at the time of transfer. To further assess the guideline's impact on clinical practice, the proportion of infants treated with each respiratory management strategy at birth (no respiratory support versus non-invasive respiratory support versus INSURE method versus surfactant and ongoing mechanical ventilation) was evaluated as well as the rate of compliance with the guideline and the number of treatment failures in each study group. Treatment failure was defined as either one of the following: the need for surfactant therapy or intubation for those infants treated with non-invasive respiratory support at birth or the need for re-intubation for infants treated with the INSURE method. Infants treated with surfactant and ongoing mechanical ventilation at birth were excluded from the treatment failure analysis as there was no feasible way to define treatment failure in this group of infants.

Inclusion and Exclusion Criteria

The inclusion criteria for the study was all infants with a gestational age between 26^0 weeks to 32^6 weeks born at the Neonatal Intensive Care Unit (NICU) in London, Ontario, within the one-year period before and after the implementation of the guideline. Infants born between January 1, 2011 and December 31, 2011 were included in the pre-guideline cohort and infants born between February 1, 2012 and January 31, 2013 were included in the post-guideline cohort. Infants born in the one month period (January 1-31, 2012) prior to guideline implementation were excluded to generate a washout period, as staff education for the new guideline took place during this time period. Infants with a birth weight of less than 750 grams or with a major congenital anomalies, including any chromosomal abnormalities, congenital heart defects (not including patent ductus arteriosus and patent foramen ovale) structural birth defects and hydrops

fetalis were excluded from the study as this group of infants did not meet criteria to be treated with the guideline.

Data Collection

All study data except for the Score for Neonatal Acute Physiology Perinatal Extension II (SNAPPE-II) was retrieved retrospectively by one data abstractor from the local administrative database for the NICU in London, Ontario. The SNAPPE-II was retrieved from the Canadian Neonatal Network (CNN) database as these scores were not collected by the local NICU database. The local NICU database contains information on all infants admitted to the NICU and the CNN database contains information on all preterm infants born at less than 33 weeks gestation admitted to a level III NICU in Canada. The information in both databases is abstracted from the patient's medical chart after discharge or after transfer to another NICU or nursery. Data on compliance was retrieved retrospectively from the INSURE Method Data Collection Tool. (Appendix D). This data collection tool was completed by the respiratory therapist for all infants in the post-guideline cohort and provided data on whether the respiratory management was in accordance with the guideline.

Data Analysis

The data for the study was analyzed using the Statistical Package for the Social Sciences (SPSS) version 19, software [International Business Machines, Armonk, New York]. Simple descriptive statistics were used to compare the two study cohorts. The baseline characteristics and the study outcomes of the two study cohorts were analyzed using a Chi Square (X^2) for categorical variables and a Mann-Whitney U- test for continuous variables as these data were not normally distributed. A post-hoc sub-group analysis of the study outcomes was also conducted in two gestational age stratums (26^0-28^6 weeks gestation or 29^0-32^6 weeks gestation). No

adjustments were made for multiple comparisons. Mean imputation was used to replace missing data to facilitate analysis with a full dataset.

CHAPTER V

Results

Study Cohorts

Figure 2 shows the number of infants who were assessed for inclusion in the study and the number of infants who were included in the pre-guideline cohort and the post-guideline cohort. A total of 304 infants met the inclusion criteria for the study during the study period; 10 of these infants were born during the washout period and were not included in the study and an additional 22 infants meet the exclusion criteria for the study. Overall, a total of 272 infants were included in the study; 129 in the pre-guideline cohort and 143 in the post-guideline cohort. The baseline demographic and clinical characteristics of the two study cohorts are shown in Table 1. The number of infants from multiple births and the number infants exposed to antepartum haemorrhages were higher in the post-guideline cohort versus the pre-guideline cohort, 50% versus 35%, $p=0.01$ and 32% vs. 17%, $p< 0.01$, respectively. The median cord venous pH was lower in the post-guideline cohort, 7.29 (6.93-7.19) versus the pre-guideline cohorts, 7.32 (6.95-7.50), $p <0.01$. All other baseline characteristics were similar between the two study cohorts.

Figure 2.

Flow Diagram of Study Participants

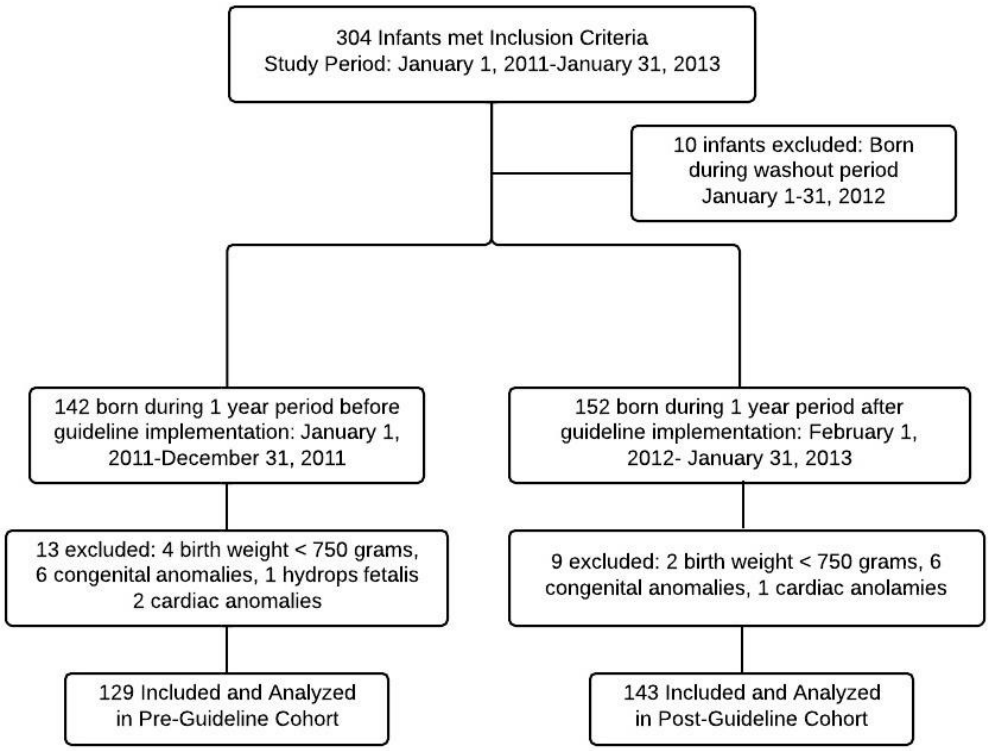


Table 1.

Baseline Characteristics of Study Cohorts

Neonatal Characteristics	Pre-Guideline n=129	Post- Guideline n=143	P-Value
Gestational age at birth, median (range)	30.14 (26-32.86)	30.86 (26-32.86)	0.51
Gestational age 26-28^{6} weeks, n (%)	39 (30)	45 (31)	0.83
Gestational age 29-32^{6} weeks, n (%)	90 (70)	98 (69)	0.83
Birth Weight, median (range)	1380 (750-2305)	1430 (780-2420)	0.56
Birth Weight %, median (range)	40 (3-95)	45 (1-95)	0.23
Apgar Score at 1 min, median (range)	6 (1-9)	5 (1-9)	0.08
Apgar Score at 5 min, median (range)	8 (2-9)	8 (1-9)	0.36
Cord arterial pH, median (range)	7.25 (6.91-7.45)	7.23 (6.88-7.38)	0.12
Cord venous pH, median (range)	7.32 (6.95-7.50)	7.29 (6.93-7.49)	<0.01
Multiple Birth, n (%)	45 (35)	72 (50)	0.01
Male Gender, n (%)	72 (56)	82 (57)	0.80
Cardiac Compressions at Birth, n (%)	2 (2)	6 (4)	0.20
SNAPPE- II, median (range)	21 (5-55)	21 (7-84)	0.86
Maternal Characteristics, n (%)			
C-section Delivery	72 (56)	80 (56)	0.98
Any Antenatal Steroids	122 (95)	131 (92)	0.34
Clinical Chorioamnionitis	6 (5)	2 (1.4)	0.11
Antepartum Haemorrhage	22 (17)	45 (32)	<0.01
Pregnancy Induced Hypertension	18 (14)	19 (13)	0.87

ROM >24 hrs	27 (21)	25 (18)	0.47
Diabetes (Type 2 or Gestational)	10 (8)	18 (13)	0.19
Oligo or Polyhydramnios	14 (11)	13(10)	0.63

Note. SNAPPE-II: Score for Neonatal Acute Physiology Perinatal Extension II, PIH: Pregnancy Induced Hypertension, ROM: Rupture of Membranes, Statistical Analysis Used: Chi (X^2) Square for categorical variables, Mann- Whitney U test for continuous variables.

Compliance with the Guideline

Data on compliance was available for 141 of 143 infants treated with the INSURE Method practice guideline. Based on the data collection tool completed by the respiratory therapists, it was estimated 124 (88%) of infants were treated in compliance with the guideline, however it should be noted that the data collection tool was not detailed enough to discern all possible deviations from the guideline. The most common deviation from the guideline; accounting for 71 % (12/17) of the all deviations, was infants who meet criteria to be extubated following surfactant delivery (INSURE method) but instead was kept mechanically ventilated. Other deviations from the guideline were: 1 infant was electively intubated for surfactant delivery but did not meet criteria to receive surfactant, 1 infant was intubated but did not meet criteria for intubation, 1 infant was re-intubated but did not meet criteria for re-intubation, 1 infant was intubated but did not receive surfactant and 1 infant was intubated but surfactant delivery was delayed.

Primary and Secondary Outcomes

The primary and secondary outcomes are shown in Table 2. Sixty-three (49%) infants in the pre-guideline cohort were treated with ongoing mechanical ventilation within the first 7 days of life compared with thirty-seven (26%) infants in the post-guideline cohort ($p < 0.001$). The number of infants treated with surfactant was similar between the two study cohorts. Seventy

infants (54%) in the pre-guideline cohort were treated with surfactant compared to seventy infants (50%) in the post-guideline cohort (p=0.45). Thirty-four (27%) infants in the pre-guideline cohort met the criteria for a diagnosis of BPD at 36 weeks compared to twenty-five (18%) infants in the post-guideline cohort (p=0.07). The number of infants who died prior to discharge was similar (4%) between the two study cohorts.

The post-hoc stratified analysis of the primary and secondary outcomes for the 26-28^6 week stratum and 29-32^6 week stratum are shown in Table 3 and 4. Similar to primary analysis, the use of ongoing mechanical ventilation within the first 7 days of life remained significantly lower in the post-guideline cohort when compared to the pre-guideline cohort when the two gestational age stratums were compared. In contrast to the primary analysis, the number of infants born between 29-32^6 weeks gestation who met the criteria for a diagnosis of BPD at 36 weeks was significantly lower in the post-guideline cohort when compared to the pre-guideline cohort (p=0.049) as was the combined outcome of BPD at 36 weeks or death (p=0.03). There was no statistically significant difference in the number of infants born between 26-28^6 weeks gestation who met criteria for a diagnosis of BPD or the combined outcome of BPD at 36 weeks or death when the two study cohorts were compared.

Table 2.

Primary and Secondary Outcomes

Outcome	Pre-Guideline (n=129) n (%)	Post-Guideline (n=143) n %)	P-value
MV in first 7 days	63 (49)	37 (26)	< 0.001
Treatment with surfactant	70 (54)	71 (50)	0.45
BPD in survivors at 36 weeks	34 (27)	25 (18)	0.07
Death prior to discharge	5 (4)	6 (4)	0.89
BPD at 36 weeks or death	39 (30)	30 (21)	0.08

Note. BPD: Bronchopulmonary Dysplasia; MV: Mechanical Ventilation. Statistical Analysis Used: Chi (X^2) Square.

Table 3.

Primary and Secondary Outcomes for 26-28^6 week Stratum

Outcome	Pre-Guideline (n=39) n (%)	Post-Guideline (n=45) n (%)	P-value
MV in first 7 days	34 (87)	20 (44)	< 0.001
Treatment with surfactant	37 (95)	42 (93)	0.77
BPD in survivors at 36 weeks	25 (71)	22 (55)	0.14
Death prior to discharge	4 (10)	6 (13)	0.66
BPD at 36 weeks or death	29 (74)	27 (60)	0.16

Note. BPD: Bronchopulmonary Dysplasia; MV: Mechanical Ventilation. Statistical Analysis Used: Chi (X^2) Square.

Table 4.

Primary and Secondary Outcomes for 29-32^6 week Stratum

Outcome	Pre-Guideline (n=90) n (%)	Post-Guideline (n=98) n %)	P-value
MV in first 7 days	29 (32)	17 (17)	0.02
Treatment with surfactant	33 (37)	29 (30)	0.30
BPD in survivors at 36 weeks	9 (10)	3 (3)	0.049
Death prior to discharge	1 (1)	0 (0)	0.30
BPD at 36 weeks or death	10 (11)	3 (3)	0.03

Note. BPD: Bronchopulmonary Dysplasia; MV: Mechanical Ventilation. Statistical Analysis Used: Chi (X^2) Square.

Table 5 compares the initial respiratory management strategy used after birth between the two study cohorts. The number of infants who did not require any respiratory support after birth, and the number of infants who were treated with non-invasive respiratory after birth, were similar between the two study cohorts. The number of infants treated with the INSURE method

increased by over 400% after the implementation of the guideline. A total of 9 (6.9%) infants in the pre-guideline cohort were treated with the INSURE method, which included 7 infants at birth and an additional 2 infants after failing non-invasive respiratory support, compared to 43 (30%) infants in the post-guideline cohort, 36 infants who were treated with the INSURE method at birth and an additional 7 infants after failing non-invasive respiratory support. Subsequently, the number of infants treated with ongoing mechanical ventilation immediately after birth decreased from 54 (42%) infants in the pre-guideline cohort to 25 (18%) infants in the post-guideline cohort.

The treatment failure rate for infants treated with non-invasive respiratory support in the pre-guideline cohort was 25% (11/44) compared to 21% (11/52) in the post-guideline cohort. The treatment failure rate for infants treated with the INSURE method was 0% (0/9) in the pre-guideline cohort compared to 16% (7/43) in the post-guideline cohort.

Table 5.

Initial Respiratory Management Strategy Used After Birth

Respiratory Management Strategy	Pre-Guideline (n=129) N (%)	Post-Guideline (n=143) n (%)	% Change from Pre-Guideline
No Respiratory Support	24 (19)	30 (21)	10 % increase
Non-invasive Respiratory Support	44 (34)	52 (36)	6% increase
INSURE Method	7 (5)	36 (25)	400% increase
Surfactant and Mechanical Ventilation	54 (42)	24 (17)	60% decrease
Mechanical Ventilation Only	0 (0)	1 (0.7)	N/A

Note: X^2 (4, N=272) =32.80, p<0.001)

Missing Data

The amount of missing data in the entire data set was relatively small. Overall, 15% percent of infants (42/272) were missing arterial cord gas pH values, 7% (19/272) were missing venous cord gas pH values and 37% (100/272) were missing Score for Neonatal Acute Physiology Perinatal Extension II (SNAPPE-II). The amount of missing data was relatively similar between the two study cohorts. In the pre-guideline cohort, 18% of infants were missing arterial cord gas pH values, 5% were missing venous cord pH values and 33% were missing SNAPPE-II values compared to 24%, 8% and 41% of infants in the post-guideline cohort, respectively. The large proportion of infants missing the SNAPPE-II was a result of infants missing one or more of the 9 items required to compute the SNAPPE-II value. The most common missing value was the arterial partial pressure of oxygen (PaO_2)/ FiO_2 ratio, as arterial blood is required to compute this value and this was not always drawn routinely in practice. The group of infants missing SNAPPE-II values had a median gestational age of 31.57 (range 26.14-32.86) weeks and median birth weight of 1600 (range 1020-2305) grams which was slightly higher than the median gestational age and birth weight of the study population at 30.71 (range 26-32.38) weeks and 1405 (range 750-2420) grams respectively. Data on the primary and secondary outcomes were complete for all infants and only 2 infants (1.4%) were missing data on compliance in the post-guideline cohort.

CHAPTER V1

Discussion

Summary

The purpose of this study was to evaluate the effects of implementing the INSURE Method Practice Guideline for the management of RDS in preterm infants born between the gestational age of 26^0 -32^6 weeks. The goal in implementing the guideline was to target a

reduction in the incidence of BPD by facilitating a consistent approach to RDS management that minimized the use of ongoing mechanical ventilation by utilizing the INSURE method and non-invasive respiratory support as less invasive respiratory management strategies. Following the implementation of the guideline, a 400% increase in the use of the INSURE method at birth was observed in practice when compared to a similar cohort born in the year prior to guideline implementation. Since the INSURE method is used as a strategy to reduce the use of ongoing mechanical ventilation in preterm infants with RDS which may lower the risk of developing BPD, it is likely that the increased use of this management strategy contributed to the observed 47% reduction in the use of ongoing mechanical ventilation and the 34% reduction in the incidence of BPD seen in the study cohort treated with the guideline.

The data on compliance demonstrates that a high proportion (88%) of infants were treated in accordance with the guideline. Nonetheless, a large proportion (71%) of the infants who were not treated in compliance with the guideline were infants who meet criteria for treatment with the INSURE method but instead were treated with ongoing mechanical ventilation. This type of protocol deviation is important because it could potentially have a negative impact on reducing the use of ongoing mechanical ventilation in preterm infants which has been associated with the development of BPD (Laughon et al., 2009; Lopez et al., 2011; Thomas, Meinzen-Derr, Hoath & Narendran, 2012; Van Marter et al., 2000). Therefore it is possible that the use of ongoing mechanical ventilation and the incidence of BPD could have been further reduced if higher compliance with the guideline was achieved. Deviations from the guideline likely reflect the tendencies of some staff to revert to previous practices when new initiatives are implemented and demonstrates the time it takes for health care professionals to accept and fully adopt the use of new guidelines into their practice. This finding is supported by

Everett Roger's Diffusion of Innovation Theory which explains how multiple factors as well as individual characteristics play a role in the length of time it takes for individuals to adopt a new practice or innovation (Kaminski, 2011).

The implementation of the guideline had little clinical impact of the overall use of surfactant therapy or on the reported use of non-invasive respiratory support only at birth. These findings were not completely unexpected since the guideline was not specifically designed to reduce surfactant use; rather the focus was on changing the way surfactant was delivered. Nonetheless, the implementation of the guideline was designed to established specific criteria to determine whether surfactant and/ or respiratory support was clinically indicated and therefore was intended to minimize the number of infants treated with prophylactic surfactant by targeting the least invasive approach needed to safely manage RDS. Consequently, it was expected that the use of the guideline would help to increase the use of non-invasive respiratory support at birth prior to being considered for treatment with the INSURE method however this was not supported by the study findings. This is likely because the education provided to staff on the new guideline focused more on increasing the use of the INSURE method in practice rather than increasing the use of non-invasive respiratory support as an initial management strategy for infants at high risk of RDS. Therefore further education focused on increasing the use of non-invasive respiratory support prior to elective intubation to facilitate surfactant delivery is likely needed improve the guideline further.

The treatment failure rate of infants treated with non-invasive respiratory support and the INSURE method remained relatively low after guideline implementation at 21% and 16%, respectively. This demonstrates the high rate of success of utilizing non-invasive respiratory support and the INSURE method as management strategies for RDS in preterm infants and also

confirm the appropriateness of this guideline for use in this patient population. Infants in the study who were treated with ongoing mechanical ventilation from birth were excluded from this analysis and therefore the treatment failure rates reflected in this study underestimate the overall number of infants who would not be successfully managed with the INSURE method or non-invasive respiratory support. When the entire cohort of infants treated with the guideline was included, this study found that 26% of infants required mechanical ventilation. This is comparable to other studies that have evaluated the use of the INSURE method or CPAP in preterm infants and have reported rates of mechanical ventilation varying between 9-65% for preterm infants treated with the INSURE method and 40-83% for preterm infants treated with the CPAP, depending on the inclusion criteria and intubation criteria used for each study (Dani et al, 2004; Dani et al., 2010; Dunn et al., 2011; Escobedo et al., 2004; Morley et al., 2008; Reininger et al., 2005 Rojas et al., 2009; Sandri et al, 2010; SUPPORT Study Group, 2010, Verder et al., 1994). This study did not find a statistically significant difference in the incidence of BPD between the two study groups, however there was a trend towards a reduction in the incidence of BPD in the group of infants treated with the guideline which suggests that use of the guideline may provide some benefit in reducing the risk of developing BPD in preterm infants with RDS.

Overall the evaluation of the INSURE Method Practice Guideline demonstrated that many preterm infants can be safely managed without the use of ongoing mechanical ventilation from birth. This type of approach to manage preterm infants at high risk of RDS may be superior to other approaches that attempt to utilize one respiratory management strategy for all preterm infants. Providing each infant with an appropriate respiratory management strategy at birth is important because it may help to minimize the potential for adverse pulmonary outcomes resulting from delayed treatment for RDS. Use of this guideline may also help to minimize the

number of infants treated with early surfactant who do not require it and the number of infants who receive delayed surfactant after failing non-invasive respiratory support. Ultimately, utilizing this type of comprehensive approach is likely to minimize the number of infants who fail treatment and require ongoing mechanical ventilation to prevent respiratory failure secondary to RDS.

Relation to other Evidence

The evaluation of the INSURE Method Practice Guideline demonstrated that both non-invasive respiratory support and the INSURE method reduced the use of mechanical ventilation for preterm infants with RDS. These findings are consistent with previous studies that have evaluated similar management strategies for the treatment of RDS in preterm infants (Bohlin et al 2007; Dani et al, 2004; De Klerk A.M & De Klerk R.K., 2001; Gitterman, Fusch, Gitterman, Regazzoni & Moessinger, 1997; Ho, Subramanian, Henderson-Smart, & Davis, 2002; Rojas et al., 2009; Sandri et al., 2010; Steven et al., 2007; Verder et al., 1994). This study also found that relatively few infants (16%) treated with the INSURE Method reached treatment failure criteria and required re-intubation. These findings are similar to other studies who have utilized the INSURE method in preterm infants at a low FiO_2 threshold, reporting failures rates between 9-33% (Dani et al., 2010; Kandraju et al., 2013; Sandri et al., 2007; Verder et al., 1999). These findings help to support the hypothesis that that the INSURE method has a higher success rate when implemented earlier in the course of RDS as opposed to later when the clinical signs and symptoms of RDS are more severe. This also suggests that the use of the INSURE method as a complement to the use of non-invasive respiratory support at birth is likely an ideal approach to help reduce the use of mechanical ventilation in the preterm population.

Overall, the use of surfactant did not decrease following the implementation of the guideline. We found that over a one year period prior to the implementation of the guidelines 54% of infants were treated with surfactant versus 50% after the guideline was implemented. Previous RCT's that have compared the use of CPAP in extremely low birth weight infants have reported that between 40-60% of infants were successfully managed with CPAP alone and did not require surfactant therapy (Dunn et al., 2011; Sandri et al., 2010; Morley et al., 2008). Compared to our study population, these studies included infants of lower gestation ($25\text{-}29^{6/7}$) who were at a higher risk of developing RDS and are more likely to require surfactant than our study population. This suggests that use of the guideline may have resulted in some infants being treated with surfactant at birth who would not have required it. This is an important finding because the delivery of surfactant via the INSURE method requires intubation as well as a brief period of positive pressure ventilation which both pose risks to preterm infants. Therefore these findings could indicate a need to tighten the criteria for initiating the INSURE method at birth. These modifications would likely help to increase the use of non-invasive respiratory support at birth and would minimize the risks associated with the delivery of surfactant therapy to infants who do not require it. Nonetheless, increasing the use of non-invasive surfactant support at birth will increase the number of infants who fail non-invasive respiratory support and receive delayed surfactant. Therefore when utilizing non-invasive support at birth as a primary mode of support for preterm infants at high risk of RDS it becomes important to incorporate an approach that utilizes early surfactant delivery to those infants who require it in order to minimize the risks of delaying surfactant therapy.

When comparing the recommendations of the recently updated 2013 European Consensus Guidelines for the Management of Neonatal Respiratory Distress Syndrome in

Preterm Infants (Sweet el al, 2013) to those of the INSURE Method Practice Guideline it is encouraging to see that the latest recommendations align very closely with the approach utilized by the INSURE Method Practice Guideline. This helps to further support the use of this guideline in this patient population and also confirms that the guideline is evidence-based.

The implementation of the guideline did not reduce the incidence of BPD in survivors at 36 weeks relative to a similar cohort one year prior to guideline implementation (p=0.07). The observed 34% reduction in the incidence of BPD in the study group treated with the guideline can be considered clinically significant. It is also possible that if the sample size had been larger, a significant reduction would have been found. This finding is similar to those reported in a meta-analysis by Stevens et al (2007) which compared early INSURE to later selective surfactant and mechanical ventilation and found a significant reduction in the incidence of BPD (typical RR 0.51, 95% CI 0.26-.99) in the INSURE group. However, more recent RCT's that have compared CPAP and selective surfactant to either INSURE or surfactant and ongoing mechanical ventilation for the management of RDS have not demonstrated any differences in the incidence of BPD when comparing the different approaches (Dunn et al., 2011; SUPPORT Study Group, 2010; Sandri et al., 2010; Morley et al., 2008). The failure of these studies to identify a single superior approach to RDS management that significantly reduces the incidence of BPD suggests that many other pre-natal and post-natal factors are likely to play a role in the development of BPD making it difficult to determine what effect the initial respiratory management strategy has on this outcome.

Limitations

The use of an uncontrolled, observational, before and after study design to evaluate the effects of implementing the INSURE guideline into practice has many weaknesses. The use of a

historical cohort as a comparator limits the ability to establish equivalence of the study cohorts and therefore conclude that the difference in outcomes were the result of the INSURE Method Practice Guideline rather than a difference between the study cohorts. Nonetheless, the baseline characteristics of the two study cohorts were relatively similar aside from the higher number of multiple births and antepartum haemorrhages in the post-guideline cohort. Although the SNAPPE-II scores were similar between the two study cohorts, a large proportion of infants were missing this data making it difficult to determine if the illness severity of the two study cohorts were similar.

Due to the observational nature of the study and the study's reliance on self-reported data to monitor compliance, it is also difficult to determine with certainty whether or not the INSURE Method Practice Guideline was followed and used as intended. This type of study design limits the study's ability to control for confounding variables such as secular changes, improvements in technology or other quality improvement initiatives which again, makes it difficult to determine with certainty whether or not changes in practice were due to the implementation of the guideline or due to some other factor. Consequently, it is important to note that midway through the control period in June 2011, the NICU moved from its location at St. Joseph's Healthcare to a new NICU, neonatal resuscitation area and delivery suite at London Health Sciences Centre. The relocation significantly increased the amount of space in the NICU, led to changes in the way the NICU was staffed and included the purchase of new monitors, new ventilators with more advanced modes of ventilation and other equipment which may have had an influence of the study outcomes. Furthermore, throughout both study periods there were other ongoing quality improvement initiatives aimed at reducing central line infections, the incidence of retinopathy of the premature and necrotizing entercolits which may have impacted the

outcome of BPD as one study has found that quality improvements interventions targeted to improve one outcome may affect other outcomes in the neonatal population (Lee et al., 2009).

The relatively small sample size of the study and the small number of infants in each gestational age stratum were likely underpowered to establish a difference in the outcome of BPD, however a power analysis to determine an appropriate sample size for the study was not calculated. Due to the multi-factorial nature of BPD, a much larger sample size is needed to establish the guidelines impact on the incidence of BPD. This study also did not control for or adjust for other any pre-natal and post-natal variables such as antenatal steroids, preeclampsia, chorioamnionitis, fetal growth restriction, maternal diabetes, severity of respiratory disease at birth, post-natal steroids, nutrition, patent ductus arteriosus, infection, sepsis, caffeine use, and oxygen exposure which have been identified as factors that may affect the risk of developing BPD (Eriksson et al., 2013; Jobe, 2011; Trembath & Laughon, 2012) and therefore further limits the ability of the study to make conclusions about the guidelines effect of the incidence of BPD.

Another limitation is that the data utilized for the study was collected retrospectively and therefore relies on the accuracy of information in the databases. The data on the incidence of BPD for 98 infants (36%) that were transferred to another NICU or nursery prior to 36 weeks corrected gestational age was based on the need for supplemental oxygen or respiratory support at the time of transfer. Using this criterion to diagnose BPD in infants transferred prior to 36 weeks overestimates the incidence of BPD in the study population and therefore should be interpreted with caution. Nonetheless, the number or infants transferred prior to 36 weeks and the mean corrected gestational age at transfer was similar between the two study groups which reduces the bias that could have resulted from diagnosing BPD in these infants.

Implications

This study suggests improvements in care resulted from the implementation of the INSURE Method Practice Guideline in an NICU that did not previously utilize any guidelines for the management of RDS. Most notable was the reduction in the use of mechanical ventilation. This has important consequences since the use of mechanical ventilation can cause lung injury in preterm infants, increasing their risk of developing BPD (Lopez et al., 2011). Any strategies that are successful at reducing the use of mechanical ventilation in preterm infants should be utilized in practice. However due to the multi-factorial nature of BPD, the use of this guideline in isolation is unlikely to reduce the incidence of BPD. The use of less invasive respiratory management strategies in addition to other interventions that aim to avoid excessive oxygen use, improve nutrition and reduce nosocomial infections have been identified as possible strategies that may reduce in the incidence or severity of BPD (Jobe, 2011).

It is important to note that the high use of mechanical ventilation and the high incidence of BPD in this population prior to the implementation of the guideline made it more likely that a difference in outcomes would be found. These findings may be specific to the NICU at the LHSC and not necessarily be applicable to other NICUs that already utilize the INSURE method or non-invasive respiratory support and selective surfactant as an alternative to surfactant and mechanical ventilation at birth. Nonetheless, this guideline provides a possible framework for other NICUs to utilize for the management of preterm infants at high risk of RDS and therefore may be useful in NICUs that do not currently utilize any practice guidelines for RDS management. In our NICU, the guideline was implemented as a quality improvement initiative designed to provide healthcare professionals with an evidence-based decision making tool for RDS management. This helped to enable health care professionals to deliver the most appropriate treatment based on the infant's clinical presentation at birth. The study included all

inborn infants born between 26-32^6 weeks gestation without any major congenital anomalies, regardless of their clinical presentation at birth therefore it is likely that the study sample is a relatively good representation of this patient population. The implementation of the guideline did not require any additional staff or the purchase of new equipment therefore it is likely that other level III NICUs with similar resources would be able to utilize this guideline for preterm infants at high risk of RDS to minimize the use of ongoing mechanical ventilation. The guideline may also help to improve the management of preterm infants presenting with RDS in level II NICU's or nurseries as staff may not have as much experience treating this type of patient population. This guideline may also have important implications in practice settings where access to mechanical ventilation is limited or transfer to another facility is necessary to provide ongoing mechanical ventilation (Bohlin et al., 2007).

Revisions to the Guideline

Following the completion of the study and upon review of the study data it was evident that the use of non-invasive respiratory support only at birth and the overall use of surfactant were relatively unchanged following the implementation of the guideline. This suggested that it was likely that a small number of infants treated under the guideline were still receiving surfactant at birth but did not require it. This prompted a re-evaluation of the criteria used by the guideline to deliver surfactant at birth. The guideline utilizes a FiO_2 of $\geq$.30 on Neopuff™ (Fisher and Paykel Healthcare, New Zealand) CPAP delivered via a mask in the resuscitation room to determine whether or not the infant should receive surfactant. Upon review of the INSURE Method Practice Guideline it was recognized that the guideline failed to specify how long the infant should be assessed on CPAP before deciding whether or not the infant meet criteria to receive surfactant. This prompted a review of the resuscitation record of a select few

infants treated with the INSURE method at birth which determined that many spontaneously breathing infants were being intubated within the first 10 minutes of life to facilitate surfactant administration which lead us to believe that many infants were not being given an adequate trial on CPAP prior to being intubated for surfactant. The other potential problem that was noted with this approach was that it is difficult to maintain a consistent seal with the Neopuff™ and facemask, and as a result infants were likely not receiving consistent CPAP. Additionally, one study has shown that the expiratory resistance of the Neopuff™ CPAP system is 5 - 10 times higher than the expiratory resistance of the infant flow CPAP system, resulting in a significant increase in the work of breathing (Wald, Kribs, Jeitler, Lirsch, Pollak & Kirchner, 2010). All of these factors led us to conclude that the CPAP system being used was likely causing the FiO_2 requirements to be overestimated and that as a result infants were likely being intubated to deliver surfactant who did not require it. To solve this problem, the guideline was revised to include a trial of CPAP on the Infant Flow™ CPAP System (Carefusion, USA) in the resuscitation room for a minimum of 10 minutes for all infants not requiring immediate intubation. This approach was thought to provide a more accurate assessment of the infants FiO_2 requirements of CPAP, which would help to better predict which infants required surfactant. This change was also intended to help increase our use of non-invasive respiratory support in this population, therefore potentially reducing the number of infants requiring endotracheal intubation to facilitate surfactant administration. The name of the guideline was also changed from “The INSURE Method Practice Guideline” to “The Practice Guideline for the Management of RDS” to better reflect the guideline in its entirety, rather than on only one aspect of it. These revisions to the guideline were officially implemented into practice on July 1, 2013. On December 1, 2013, the Practice Guideline for the Management of RDS was further revised to

include infants born at 24 and 25 weeks gestation and with a birth weight of less than 750 grams. The evidence has demonstrated that these extremely low birth weight and low gestation infants are at a higher risk of failing non-invasive respiratory support and the INSURE Method than more mature infants. Consequently this population was initially excluded from the guideline as a high failure rate was deemed likely to have a negative influence the NICU staff's initial reception to the new guideline and on adherence. Following the evaluation of the guideline and the success demonstrated in the first year of its implementation, it was deemed appropriate to expand the guideline to include lower gestation and lower birth weight infants. These revisions to the guideline were also supported by the EPIQ reports and 2012 Annual CNN report which demonstrated a decrease in the incidence of BPD at the LHSC site for infants born between 26^{0}-32^{6} after the implementation of the guideline, but showed no improvement in the infants born at less than 26 weeks gestation who were still being managed with prophylactic surfactant and ongoing mechanical ventilation. The 2013 Update of the European Consensus Guidelines of the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants also supported these revisions as they no longer recommended surfactant prophylaxis to all infants < 26 weeks gestation (Sweet et al, 2013).

Next Steps

A follow-up evaluation of the revised guideline is required to determine its effects on the use of surfactant, non-invasive respiratory support, treatment failure, mechanical ventilation, and the incidence of BPD. The changes to the guideline should result in more infants being treated initially with non-invasive respiratory support at birth and may lead to a reduction in the number of infants who are treated with surfactant and therefore are exposed to endotracheal intubation. This however may also increase the number of infants who fail non-invasive respiratory support

and receive delayed surfactant which may increase the need for ongoing mechanical ventilation. Follow-up is needed to determine whether these revisions have the desired outcomes. It will also be important to specifically evaluate the use of this guideline in the 24 and 25 week gestation infants. These infants are at a very high risk of failing treatment with either non-invasive respiratory support or the INSURE method at birth and therefore may be at higher risk of experiencing adverse events related prematurity such as air leaks, necrotizing enterocolitis, patent ductus arteriosus and severe intraventricular hemorrhage and therefore need to be studied to determine whether the use of the guideline is both safe and beneficial to this patient population. A randomized controlled trial comparing the use of this guideline to other respiratory management strategies may be warranted to help determine which approach is superior.

Further efforts are also needed to achieve ongoing compliance with the guideline so that the full potential of the guideline can be realized. Previous research into the adoption of clinical practice guidelines demonstrate that several variables including the quality and complexity of the guidelines, the characteristics of the healthcare professional and the practice setting can all have a significant impact on the adherence and utilization of practice guidelines and therefore need to be considered when addressing compliance issues in practice (Davis & Taylor-Vaisey, 1997). Research into the perspectives of healthcare professional regarding practice changes specifically in the NICU setting, found that healthcare professionals identified staffing issues, consistency in practice, the approval process, a multidisciplinary approach to care, frequency and consistency of communication, rationale for change and the feedback process as important factors influencing practice change (Stevens et al., 2007). Inadequate staffing during staff education, inconsistent practices among neonatologist and the long approval process required to implement practice changes were all identified as barriers to practice change in the NICU (Stevens et al, 2007).

Whereas identifying the rationale for change, involving healthcare professionals in the process of obtaining feedback regarding practice changes, utilizing a multi-disciplinary approach for implementing practice changes, effectively communicating practice changes to staff through various methods of communication, obtaining support for practice changes from leadership and utilizing front-line staff as "change champions" were all identified as facilitators to practice change in the NICU (Stevens et al, 2007). These findings are similar to previous research on implementation strategies which have found that multifaceted interventions, interactive education, clinical reminder systems, audit and feedback and the use of opinion leaders are effective ways to promote the use of practice changes and therefore should also be utilized in practice as potential strategies to improve and maintain guideline adherence (Davis & Taylor-Vaisey, 1997; Prior, Guerin & Grimmer-Somers, 2008).

CHAPTER VII

Conclusions

This study demonstrated that the implementation of the INSURE Method Practice Guideline in a level III NICU that did not previously utilize any practice guidelines for the management of RDS in preterm infants was an effective way to minimize the use of ongoing mechanical ventilation in this patient population. The guideline incorporated the use of non-invasive respiratory support and the INSURE method as alternatives to mechanical ventilation at birth by utilizing specific criteria based on the infants clinical presentation at birth to target the least invasive approach required to safely manage infants at high risk of RDS. In closing, the implementation of the guideline in our NICU helped to facilitate healthcare professionals to take a consistent approach to the management of preterm infants at high risk of RDS and provides other NICUs with a possible framework to help minimize the use of mechanical ventilation in a

similar patient population. Due to the risk of lung injury that can occur with mechanical ventilation in the preterm population and its association with the development of BPD, utilizing this type of approach to manage RDS may play a role in reducing the severity or overall risk of developing BPD.

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Appendix A

Athabasca University Ethics Approval Notice

MEMORANDUM

DATE: January 5, 2013

TO: Brooke Read

COPY: Debbie Fraser
Janice Green, Secretary, Athabasca University Research Ethics Board
Dr. Simon Nuttgens, Chair, Athabasca University Research Ethics Board
Eileen Paluck, Ass't to Dean, CNHS

FROM: Dr. Sharon Moore, Chair, CNHS Research Ethics Review Committee

SUBJECT: **Ethics Proposal #CNHS-12-06** *Evaluation of a Practice Guideline for the Management of Respiratory Distress Syndrome in Preterm Infants*

Thank you for providing the additional information requested by the Centre for Nursing & Health Studies (CNHS) Research Ethics Review Committee.

I am pleased to advise that the above-noted project has now been awarded **APPROVAL TO PROCEED**. **You may begin your research immediately once you have your relevant health regions' ethics approvals in place. Please forward those approvals for file purposes only, once you have received it.**

This approval of your application will be reported to the Athabasca University Research Ethics Board (REB) at their next monthly meeting. The REB retains the right to request further information, or to revoke the interim approval, at any time.

As implementation of the proposal progresses, if you need to make any significant changes or modifications prior to receipt of a final approval memo from the AU Research Ethics Board, please forward this information immediately to the CNHS Research Ethics Review Committee via Dr. Sharon Moore sharon.moore@athabascau.ca for further review.

If you have any questions, please do not hesitate to contact sharon.moore@athabascau.ca .

We wish you all the best with your project.

Appendix B

University of Western Ontario Ethics Approval Notice

Western

Research Ethics

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. David Lee
File Number: 103287
Review Level: Delegated
Approved Local Adult Participants: 270
Approved Local Minor Participants: 0
Protocol Title: Evaluation of a practice guideline for the management of respiratory distress syndrome in preterm infants
Department & Institution: Schulich School of Medicine and Dentistry\Paediatrics,Children's Hospital of Western Ontario
Sponsor:
Ethics Approval Date: January 22, 2013 **Expiry Date:** January 21, 2014
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Other	Data Collection Guideline indicating what information will be collected for the study and where the information will be collected from	2012/11/17
Other	Questionnaire used for the study to monitor compliance with the practice guideline.	2012/02/01
Western University Protocol		
Instruments	Revised Questionnaire	2012/12/10
Amendment	Ethics Revisions	2013/01/18
Instruments	Data Collection Guideline Revised	2013/01/18

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Signature

Ethics Officer to Contact for Further Information

Janice Sutherland (sutherj@uwo.ca)	Grace Kelly (grace.kelly@uwo.ca)	Stacey Wilcox (swilcox@uwo.ca)

This is an official document. Please retain the original in your files.

Appendix C

Lawson Ethics Approval Notice

LAWSON
HEALTH RESEARCH INSTITUTE

LAWSON FINAL APPROVAL NOTICE

RESEARCH OFFICE REVIEW NO.: R-12-567

PROJECT TITLE: Evaluation of a practice guideline for the management of respiratory distress syndrome in preterm infants

PRINCIPAL INVESTIGATOR: Dr. David Lee

LAWSON APPROVAL DATE: January 24, 2013

Health Sciences REB#: 103267

Please be advised that the above project was reviewed by the Clinical Research Impact Committee and the project:

Was Approved

PLEASE INFORM THE APPROPRIATE NURSING UNITS, LABORATORIES, ETC. BEFORE STARTING THIS PROTOCOL. THE RESEARCH OFFICE NUMBER MUST BE USED WHEN COMMUNICATING WITH THESE AREAS.

Dr. David Hill
V.P. Research
Lawson Health Research Institute

All future correspondence concerning this study should include the Research Office Review Number and should be directed to Sherry Paiva, CRIC Liaison, Lawson Health Research Institute, 750 Baseline Road, East, Suite 300.

cc: Administration

Appendix D

INSURE Method Data Collection Sheet

Draft INSURE Method: Data Collection *** To be filled out for all infants between the gestational of 26 $^{0/7}$- 32$^{6/7}$ even if no respiratory support is required during resuscitation***	Addressograph

Date: _____ Time of birth: _____ Gestational Age: _____ Birth weight: _____ Gender: ____
APGARS: 1 min____ 5 min ____ 10 min ____15 min ____ Antenatal Steroids? □ Yes □ No

Intubation

Was intubation performed during resuscitation? □ Yes □ No If no, proceed to patient outcome section.
Reasons for intubation: Required for resuscitation □, FiO2 ≥ 30% on CPAP □, Elective □
Surfactant given? □ Yes □ No
Did FiO_2 decrease to < 30 % post surfactant administration? □ Yes □ No
Was infant breathing spontaneously post surfactant? □ Yes □ No

Patient Outcome (Choose One Only)

1. No respiratory support required □
2. Only required NCPAP/Biphasic (No Surfactant or Intubation): □
   Did patient require intubation within 48 hours? □ Yes □ No If yes, was surfactant given? □ Yes □ No
3. INSURE method □
   Extubated to □ NCPAP □ Biphasic What time? _____
   Did patient require re-intubation? □ Yes □ No
   - within 48 hours of being extubated? □ Yes □ No
   If yes: State reason(s) _____
4. Patient remained intubated and ventilated □
   If remaining intubated and ventilated, why? (Check all that apply)
   Poor respiratory drive □ $FiO_2 \geq 30$ % post surfactant □ Signs of sepsis □
   Weight < 750grams □ Major congenital anomalies □ Clinically unstable post resuscitation □
   Other (Please specify)_____

Pneumothorax? □ Yes □ No If yes, date and time of first Xray showing pneumothorax_____
RRT Initials_____