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Cover Letter of Changes

This revised version of the California Perinatal Quality Care Collaborative (CPQCC) Toolkit Improving Initial Lung Function: Surfactant and Other Means has been updated with newer studies and relevant literature on surfactant and continuous positive airway pressure (CPAP). The rationale for both of these interventions is that they both have the potential to reduce chronic lung disease, which we will refer to as bronchopulmonary dysplasia (BPD) or chronic lung disease interchangeably throughout. We have included the NIH consensus definition of BPD and the physiologic definition of BPD, as there has been information that increasing severity of BPD is associated with increased NDI

For the use of Surfactant one of the best evidence based interventions utilized in Neonatology, the additions and updates are not substantive in that surfactant remains a very beneficial therapy for the preterm infant with respiratory distress and/or immature lungs. It is perhaps surprising and not well appreciated that the following have been noted:

- Most studies of the use of surfactant have not reported a significant reduction in BPD, and that such findings have only recently been suggested in secondary analyses of the meta analyses for the most immature infants.
- Surfactant has not been found to significantly reduce subsequent neurodevelopmental impairment (NDI), but has reduced death and not been associated with increased NDI in such survivors.
- There are now many more types of surfactant available, some natural, some artificial and there is little evidence to choose between any of the newer products. Artificial products devoid of animal protein offer the theoretical advantage of avoidance of sensitization for the infant or the transmission any disorders carried in such material. In this review we have not compared natural and artificial surfactants.

We have added information regarding surfactant administration followed by rapid extubation and the use of subsequent CPAP as this approach is being adopted by many centers. There are no significant prospective trials comparing prophylactic versus early versus later rescue surfactant, and thus no good rationale for the immediate intubation of the very preterm infant exclusively for the purpose of surfactant administration. Surfactant within the first 30 to 60 minutes of life is associated with good outcomes. In the very tiniest and fragile of infant's airway obstruction secondary to surfactant administration may be problematic. We have utilized the most recent meta analyses for the use of surfactant in the premature infant.

The other major intervention discussed in this Toolkit is the use of early CPAP. While there has been a great deal written about this intervention, there were previously no prospective randomized trials comparing early CPAP to surfactant or other interventions. This revision includes information from the recently completed and published trials, which include SUPPORT, the largest prospective study to compare early CPAP with early Surfactant for the ELBW infant, and the COIN, CURPAP and VON DR trials. In summary, these individual studies showed no difference in the primary outcome of Death or BPD between the CPAP and intubation groups but did show a decrease in other short term respiratory outcomes including the need for intubation, days of mechanical ventilation, mechanical ventilation at 7days, and steroids for BPD. The

COIN trial showed an increase in the pneumothorax in the CPAP group; however this was not seen in the other 3 studies. The overall meta analysis confirmed that the trend seen in all trials toward a decrease in death or survival with BPD, was indeed significant overall when all trials where combined.

There are a number of reasonable approaches that are described in this toolkit to potentially reduce the occurrence of BPD at neonatal discharge and hopefully NDI at 2 years of age. As further evidence becomes available in the next few years, we will endeavor to keep this toolkit relevant and evidence based.

Improving Initial Lung Function: Early CPAP, Surfactant and Other Means

Reducing Chronic Lung Disease

Quality Improvement Toolkit

California Perinatal Quality Care Collaborative

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CPQCC Quality Improvement Toolkit

Improving Initial Lung Function: Early CPAP, Surfactant and Other Means

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- Walsh MC, Yao Q, Gettner PA, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics. 2004;114 :1305 –1311
  Bassler, D.; Stoll, B. J.; Schmidt, B.; Asztalos, E. V.; Roberts, R. S.; Robertson, C. M. T., and Sauve, R. S Using a Count of Neonatal Morbidities to Predict Poor Outcome in Extremely Low Birth Weight Infants: Added Role of Neonatal Infection. *Pediatrics*. 2009; 123(1):313-318
- Lavoie, P. M.; Pham, C., and Jang, K. L. Heritability of bronchopulmonary dysplasia, defined according to the consensus statement of the National Institutes of Health. *Pediatrics*. 2008; 122(3):479-485
- TP Stevens, M Blennow, EW Myers, R Soll. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD003063. DOI: 10.1002/14651858.CD003063.pub3.
- Rojas, M. A.; Lozano, J. M.; Rojas, M. X.; Laughon, M.; Bose, C. L.; Rondon, M. A.; Charry, L.; Bastidas, J. A.; Perez, L. A.; Rojas, C.; Ovalle, O. ; Celis, L. A.; GarciaHarker, J., and Jaramillo, M. L. Very Early Surfactant Without Mandatory Ventilation in Premature Infants Treated With Early Continuous Positive Airway Pressure: A Randomized, Controlled Trial. *Pediatrics*. 2009; 123(1):137-142
- SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Early CPAP versus Surfactant in Extremely Preterm Infants. N Engl J Med. 2010 May 27;362(21):1959-69.
- Morley, C. J.; Davis, P. G.; Doyle, L. W.; Brion, L. P.; Hascoet, J. M., and Carlin, J. B. Nasal CPAP or intubation at birth for very preterm infants. New England Journal of Medicine. 2008; 358(7):700-708;

Introduction/ Background

Original Date:
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Background: Bronchopulmonary Dysplasia (BPD)

I. Definition : BPD is defined based on oxygen requirements at specific points in time. Oxygen at 28 days and 36 weeks post-conceptual age (PCA) are reported as a percentage of all infants hospitalized on day 28 and at 36 weeks, respectively. (Note: infants discharged home prior to 36 weeks PCA - whether on oxygen or not - are not included in the 36 week sample upon which the BPD rate is calculated. Thus, differing discharge practices, rather than BPD events, can affect these results).

In defining BPD experts differ as to which aspect of impaired neonatal pulmonary function to emphasize. According to VON/CPQCC, infants requiring oxygen at 36 weeks post-gestational age are considered to have BPD. In support of this definition:

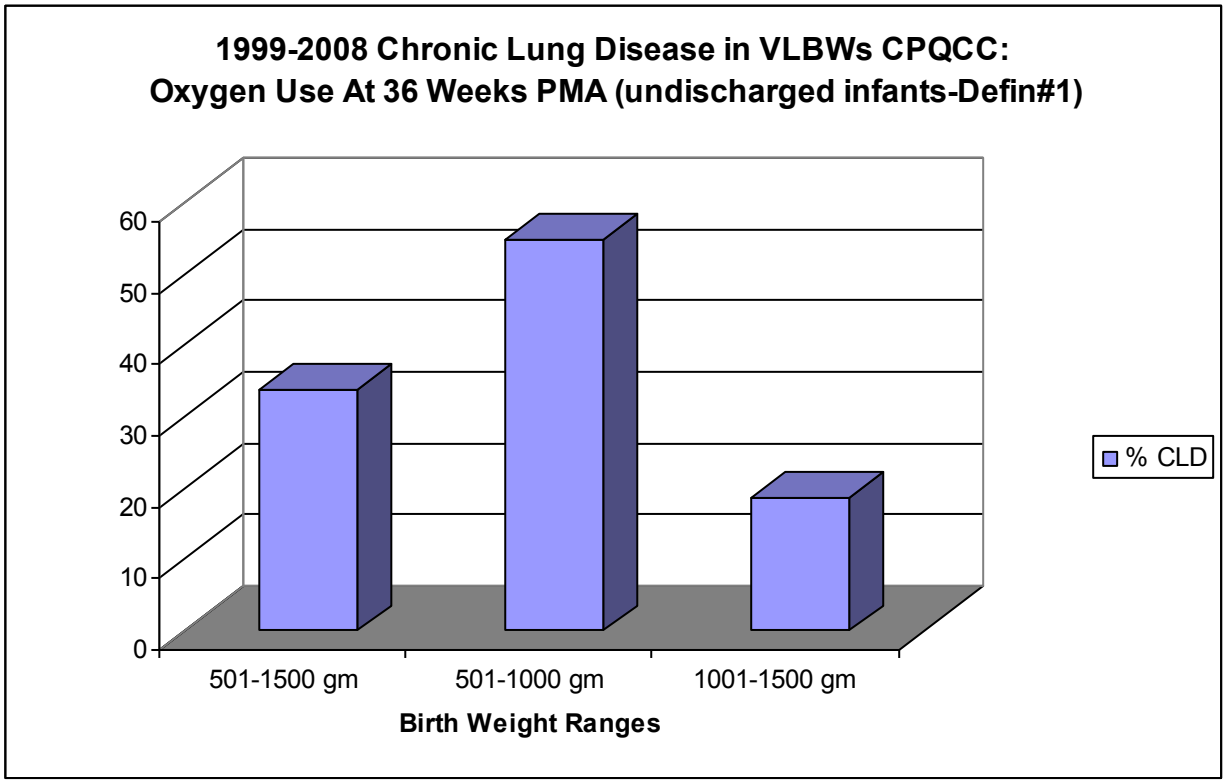
> The need for oxygen at 28 days was a good predictor of abnormal findings in infants of greater than 30 weeks gestational age but became increasingly less useful as gestational age decreased. It was found that, irrespective of gestational age at birth, the requirement for additional oxygen at 36 weeks corrected post-natal gestational age was a better predictor of abnormal outcome…[(SHN 88)]

A June 2000 National Institute of Child Health and Human Development/National Heart, Lung, and Blood Institute Workshop proposed a severity-based definition of BPD for infants less than 32 weeks' gestational age. Mild BPD was defined as a need for supplemental oxygen (O2) for ≥ 28 days but not at 36 weeks' postmenstrual age or discharge, moderate BPD as O2 for ≥ 28 days plus treatment with < 30% O2 at 36 weeks, and severe BPD as O2 for ≥ 28 days plus ≥ 30% O2 and/or positive pressure at 36 weeks' PMA.(Jobe 2001) Eherenkranz et al reported that as the severity of BPD identified by the consensus definition worsened, the incidence of selected adverse neurodevelopmental outcomes increased in the infants who were seen at follow-up.(Ehren 2005). There is also now a considered opinion that there should be a physiologic definition for BPD that demonstrates that the infant actually requires additional oxygen at 36 weeks post conceptional age to maintain adequate SpO2 levels, and the recently completed SUPPORT trial utilized this definition as part of its primary outcome. (Walsh 04)

Because so many interventions are assessed according to oxygen use at 36 weeks, CPQCC has chosen it to describe NICU performance. Data on oxygen use at 28 days is also included in the Data section of this toolkit, allowing hospitals to use this information in their quality improvement efforts as well. Many of the Figures are labeled as Chronic Lung Disease and for this document we have used these terms interchangeably.

[(SHN 88)] Shennan A, Dunn M, Ohlsson A, Lennox K, and Hoskins E. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. *Pediatrics*. 1988;8 (4).

Between 1999 and 2008, 30% of infants 501-1500 grams cared for in CPQCC member hospitals were reported to have Chronic Lung Disease. The accompanying figure displays the percentage of infants receiving oxygen at 36 weeks gestational age born at CPQCC hospitals, broken down by birth weight cohort.



Please also refer to your Hospital's most recent VON Annual Quality Management Report for a graph of BPD at your Hospital relative to the network mean and inter-quartile ranges. Chronic Lung Disease is defined based on oxygen requirements at specific points in time. Oxygen at 28 days and 36 weeks are reported as a percentage of all infants hospitalized on day 28 and 36 weeks, respectively. (Note: infants discharged home prior to 36 weeks PCA-whether on oxygen or not- are not included in the 36 week sample upon which the BPD rate is calculated. Thus, differing discharge practices, rather than BPD events, can affect these results.) Oxygen at time of discharge to home and oxygen at time of transfer to another hospital are reported as percentages of infants discharged to home and transferred, respectively. The rates are not risk-adjusted. Thus, comparing the rate at a given hospital to national or state figures without accounting for the unique patient population in that hospital can lead to inaccurate conclusions. Nonetheless, the Figure should give a general idea of performance with respect to Chronic Lung Disease.

II. Consequences of BPD

Decreasing BPD will not only reduce associated morbidities, length of stay, and associated costs, but more importantly will improve long-term neurodevelopmental outcomes. BPD is an important

precursor for significant neuromotor, developmental and behavioral sequelae[(MAJ 00)] . BPD predicts poorer motor outcome at 3 years, after controlling for other risks[(SIN 97)] and this remains true from more recent observations (Bassler, 09) Ventriculomegaly has been shown to be a predictor of poor intelligence (IQ<70) and lower verbal and performance scores at 4.5 years of age, and BPD is a significant risk factor for the development of ventriculomegaly[(MEN 99)]. In addition, infants with BPD have evidence of continuing pulmonary compromise[(JAC 98)]. Not all studies have reported that BPD is an independent risk for poorer neurodevelopmental outcome, but the preponderance of information supports an association between BPD and later motor, intellectual and pulmonary sequelae.

III. CPQCC BPD Toolkits

In view of the complexity of BPD, Perinatal Quality Improvement Panel (PQIP) is producing a series of Toolkits, each addressing a health care practice that potentially affects the incidence of BPD. Certain practices that affect BPD, including prophylactic surfactant administration, early selective surfactant administration, and early nasal CPAP, are identified in CPQCC's *Compendium of Evidence-Based Practices for the Prevention of Chronic Lung Disease,* which is located in this chapter. The Compendium serves as a map of CPQCC BPD quality improvement interventions, with each letter describing either a completed Toolkit or one in process of development.

CPQCC Toolkits are designed to promote successful quality improvement activities at the hospital level, based on hospital-specific data. The first CPQCC Toolkit focused on Antenatal Steroid (ANS) administration, and was based upon the NIH consensus statement that supports use of antenatal steroids for woman at risk of a pre-term delivery who are between 24 and 34 weeks gestational age. The *Options for Stabilization of Lung Function* Toolkit, on the other hand, encourages each NICU to develop and/or refine its own policy related to stabilization of lung function. Please refer to the "Compendium", mentioned above, for a summary of CPQCC Toolkits designed to reduce the incidence of BPD.

[(MAJ 00)] Majnemer A, Riley P, Shevell M, Birnbaum R, Greenstone H, Coates A L. Severe bronchopulmonary dysplasia increases risk for later neurological and motor sequelae in preterm survivors. *Developmental Medicine and Child Neurology*. 2000;42(1):53-60;ISSN:0012-1622.

[(SIN 97)] Singer L, Yamashita T, Lilien L, Collin M, Baley J. A longitudinal study of developmental outcome of infants with bronchopulmonary dysplasia and very low birth weight. *Pediatrics*. 1997;100(6):987-993;ISSN:0031-4005

[(MEN 99)] Ment LR, Vohr B, Allan W, Westerveld M, Katz KH, Schneider KC, Makuch, RW. The etiology and outcome of cerebral ventriculomegaly at term in very low birth weight preterm infants. *Pediatrics*. 1999;104(2): 243-248;ISSN:0031-4005.

[(JAC 98)] Jacob S V, Coates AL, Lands LC, MacNeish CF, Riley SP, Hornby L, Outerbridge EW, Davis GM. Long-term pulmonary sequelae of severe bronchopulmonary dysplasia. *Journal of Pediatrics*. 1998:133(2):193-200; ISSN: 0022-3476

(Jobe 01)Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am Rev Respir Crit Care Med. 2001;163 :1723 –1729

Ehren 2005 Ehrenkranz, R. A.; Walsh, M. C.; Vohr, B. R.; Jobe, A. H.; Wright, L. L.; Fanaroff, A. A.; Wrage, L. A., and Poole, K. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics*. 2005 Dec; 116(6):1353-60.

Walsh 04 Walsh MC, Yao Q, Gettner PA, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. *Pediatrics*. 2004;114 :1305 –1311

Outcome is affected by the inter-relation of the practices listed in the compendium. For example, early surfactant administration is likely to be particularly important for an infant who did not benefit from antenatal steroids. NICU ventilation strategy may reflect other aspects of treatment such as fluid administration. There is newer information from twin studies that suggests that the susceptibility to BPD may be in some significant part heritable, and in the future we may be able to recognize infants at increased risk apart from their level of immaturity (Lavoie 2008).
In order to adequately address the important interventions that affect BPD, and in view of a lack of clinical trials of jointly deployed practices, CPQCC is developing separate Toolkits, each focused on a particular aspect of care. However, the Toolkits should be viewed as components of a broad quality improvement effort aimed at reducing BPD. Reducing BPD in a given Hospital will require a comprehensive strategy and in some cases a close examination of a wide range of practices that impact BPD.

IV. References

Barrington, K and Finer, N. *Treatment of Bronchopulmonary Dysplasia*. Clinics in Perinatology. 25 (1) March 1998

Chronic lung disease in early infancy / edited by Richard D. Bland, Jacqueline J. Coalson. New York : M. Dekker, c2000.

Giacoia, G. P.; Venkataraman, P. S.; Westwilson, K. I., and Faulkner, M. J. (GP Giacoia/Univ Oklahoma/Coll Med/Dept Pediat/Hlth Sci Ctr/2815 S Sheridan/Tulsa, OK 74129 USA). Follow-up of school-age children with bronchopulmonary dysplasia. Journal of Pediatrics. 1997 Mar; 130(3):400-408; ISSN:0022-3476.

Gray, P. H.; Burns, Y. R.; Mohay, H. A.; Ocallaghan, M. J., and Tudehope, D. I.. Neurodevelopmental outcome of preterm infants with bronchopulmonary dysplasia. Archives of Disease in Childhood. 1995 Nov; 73(3 Sp. Iss.): F128-F134; ISSN: 0003-9888.Notes: English Article.

Jacob, S. V.; Coates, A. L.; Lands, L. C.; MacNeish, C. F.; Riley, S. P.; Hornby, L.; Outerbridge, E. W., and Davis, G. M. Long-term pulmonary sequelae of severe bronchopulmonary dysplasia. Journal of Pediatrics. 1998; 133(2): 193-200; ISSN:0022-3476.

Korhonen, P. Tammela O. Koivisto A. Laippala P, and Ikonen S. *Frequency and risk factors in BPD in a cohort of VLBW infants*. Early Human Development.54. 1999.

Majnemer, A.; Riley, P.; Shevell, M.; Birnbaum, R.; Greenstone, H., and Coates, A. L. Severe bronchopulmonary dysplasia increases risk for later neurological and motor sequelae in preterm survivors. Developmental Medicine and Child Neurology. 2000; 42(1):53-60; ISSN: 0012-1622.

Ment, L. R.; Vohr, B.; Allan, W.; Westerveld, M.; Katz, K. H.; Schneider, K. C., and Makuch, R. W. The etiology and outcome of cerebral ventriculomegaly at term in very low birth weight preterm infants. Pediatrics. 1999; 104(2):243-248; ISSN: 0031-4005.

Singer, L.; Yamashita, T.; Lilien, L.; Collin, M., and Baley, J.. A longitudinal study of developmental outcome of infants with bronchopulmonary dysplasia and very low birth weight. Pediatrics. 1997; 100(6):987-993; ISSN:0031-4005.

Van Marter L., Pagano M., Allred E., Leviton A and Kuban K. *Rate of BPD as a function of neonatal intensive care practices*. Journal of Pediatrics 120 (6) 1992.

Bassler, D.; Stoll, B. J.; Schmidt, B.; Asztalos, E. V.; Roberts, R. S.; Robertson, C. M. T., and Sauve, R. S Using a Count of Neonatal Morbidities to Predict Poor Outcome in Extremely Low Birth Weight Infants: Added Role of Neonatal Infection. Pediatrics. 2009; 123(1):313-318

Lavoie, P. M.; Pham, C., and Jang, K. L. Heritability of bronchopulmonary dysplasia, defined according to the consensus statement of the National Institutes of Health. Pediatrics. 2008; 122(3):479-485

(MAJ 00) Majnemer A, Riley P, Shevell M, Birnbaum R, Greenstone H, Coates A L. Severe bronchopulmonary dysplasia increases risk for later neurological and motor sequelae in preterm survivors. Developmental Medicine and Child Neurology. 2000;42(1):53-60;ISSN:0012-1622.

(SIN 97) Singer L, Yamashita T, Lilien L, Collin M, Baley J. A longitudinal study of developmental outcome of infants with bronchopulmonary dysplasia and very low birth weight. Pediatrics. 1997;100(6):987-993;ISSN:0031-4005

(MEN 99) Ment LR, Vohr B, Allan W, Westerveld M, Katz KH, Schneider KC, Makuch, RW. The etiology and outcome of cerebral ventriculomegaly at term in very low birth weight preterm infants. Pediatrics. 1999;104(2): 243-248;ISSN:0031-4005.

(JAC 98) Jacob S V, Coates AL, Lands LC, MacNeish CF, Riley SP, Hornby L, Outerbridge EW, Davis GM. Long-term pulmonary sequelae of severe bronchopulmonary dysplasia. Journal of Pediatrics. 1998:133(2):193-200; ISSN: 0022-3476

(Jobe 01)Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am Rev Respir Crit Care Med. 2001;163 :1723 –1729

Ehren 2005 Ehrenkranz, R. A.; Walsh, M. C.; Vohr, B. R.; Jobe, A. H.; Wright, L. L.; Fanaroff, A. A.; Wrage, L. A., and Poole, K. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005 Dec; 116(6):1353-60.

Walsh 04 Walsh MC, Yao Q, Gettner PA, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics. 2004;114 :1305 –1311

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Compendium of Practices to Prevent and/or Treat BPD

A. Antenatal Steroids (ANS)

A. Administration of ANS to women at risk of preterm delivery (G.A. 24-34 weeks) following NIH guidelines.

B. Improve initial lung function. Center may select Option B1, B2, B3 or B4 based on unit policy, randomization or other criteria

Option B1: Early CPAP with Rescue Surfactant
- Start CPAP following delivery
- If respiratory distress and > .35 - .45 FiO2 intubate + surfactant

Option B2: Prophylactic Surfactant
- Eligibles intubated in DR
- Surfactant given within 30 minutes

Option B3: Early Selective Surfactant
- Intubation for RDS
- Surfactant given within 30-120 mins
- Brief ventilation / early extubation

C. Ventilation Strategy

C1. High Frequency Ventilation
C2. Conventional Mechanical Ventilation
C3. Avoid hypocarbia
C4. Permissive hypercarbia

D. Extubation

D. Early Extubation

E. Practices applicable to all cases

E1. Avoid fluid overload
E2. Post-natal steroid use considerations
E3. Vitamin A supplementation
E4. Caffeine use

Note: arrows indicate to proceed if certain clinical criteria are met. Letters refer to applicable sections of CPQCC BPD quality improvement Toolkit(s)

Commended Practice One:

Early Nasal CPAP

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Nasal CPAP for Prophylaxis/Initial Treatment of Respiratory Distress: Summary

I. Definition and Physiologic Rationale

Prophylactic nasal CPAP describes the use of nasal CPAP commencing soon after birth in the VLBW infant, regardless of the infant's respiratory status. Prophylactic nasal CPAP differs from "standard" methods of treatment where CPAP is used for a defined respiratory conditions not requiring immediate intubation (termed "initial" treatment of respiratory distress). Four to six cm water pressure is applied usually by nasal CPAP, although a mask alternative has also been described.[(RHO 73)(LIN 99)] The rationale is that end expiratory pressure establishes and maintains an adequate functional residual capacity for gas exchange.

II. Benefits

Two Cochrane meta-analyses[(SUB 00)(HO 00)] found insufficient evidence, especially from the contemporary era of antenatal steroid administration to the mothers of delivered VLBW infants, modern methods for rendering distending pressure and the availability of surfactant, to make recommendations regarding the clinical practice. However, recently there have been 4 randomized controlled trials that compared use of nasal CPAP to intubation in extremely premature infants (SUPPORT, 24 weeks- 276/7ths, or VON, 26 – 29 6/7ths, COIN and CURPAP, 25 0/7 – 28 6/7ths weeks).
In summary, these studies showed no difference in the primary outcome of Death or BPD between the CPAP and intubation groups but did show a decrease in other short term respiratory outcomes including the need for intubation, mechanical ventilation at 7 days, steroids for BPD, and days of mechanical ventilation. The COIN trial showed an increase in the pneumothorax in the CPAP group; however this was not seen in the other 3 studies. Another multicenter study from Columbia showed that there was a decrease in the need for mechanical ventilation with early surfactant administration and extubation to CPAP compared to the CPAP only group. It should be noted that the gestational age of the enrolled infants in the Columbia trial (27 0/7 – 31 6/7ths weeks) represents a more mature population that those enrolled in the other trials (24 0/7 – 28 6/7ths weeks)

III. Risks

[(RHO 73)] Rhodes PG, Hall RT. Continuous positive airway pressure delivered by face mask in infants with the idiopathic respiratory distress syndrome: A controlled study. *Pediatrics*. 1973;52:1-5.
[(LIN 99)] Lindner W, Vossbeck S, Hummler H, Pohlandt F: Delivery room management of extremely low birth weight infants-Spontaneous breathing or intubation? *Pediatrics* 1999;103:961-967.
[(SUB 00)] Subramaniam P, Henderson-Smart DJ, Davis PG. Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants. *Cochrane Review*. In: The Cochrane Library: 2000;3. Oxford: Update Software. (Last Update 2/10/99)
[(HO 00)] Ho JJ, Subramaniam P, Henderson-Smart DJ, Davis PG. Continuous distending airway pressure for respiratory distress syndrome in preterm infants (Cochrane Review).In: The Cochrane Library: 2000;3. Oxford; Update Software (Last Update- 26/5/2000)

- Air leaks (pneumothorax, pneumopericardium and pneumoperitoneum)
- Nasal excoriation, nasal septal injury (pressure necrosis), bleeding and secondary infection
- Delay in treating while respiratory distress syndrome progresses may lessen surfactant treatment effectiveness[(VER 94)(VER 99)]
- Gastric distension may impair feeding tolerance

[(VER 94)] Verder H, Robertson B, Greisen G, Ebbesen F, Albertsen P, Lundstrom K, Jacobsen T. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. *The New England Journal of Medicine*. 1994; 331(16):1051-5.
[(VER 99)] Verder H, Albersen P, Ebbesen F, Greisen G, Robertson B, Bertelsen A, et al: Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. *Pediatrics*. 1999;103(2).

Nasal CPAP for Prophylaxis/Initial Treatment of Respiratory Distress

I. Definition and Physiologic Rationale

Prophylactic nasal CPAP describes the use of nasal CPAP commencing soon after birth in the VLBW infant, regardless of the infant's respiratory status. Prophylactic nasal CPAP differs from "standard" methods of treatment where CPAP is used for a defined respiratory conditions not requiring immediate intubation (termed "initial" treatment of respiratory distress). Four to six cm water pressure is applied usually by nasal CPAP, although a mask alternative has also been described.[(RHO 73)(LIN 99)]

The rationale for the use of nasal CPAP is that it increases the transpulmonary pressure, which results in an increased thoracic gas volume and functional residual capacity [(Verder 09)]. The increase in functional residual capacity is due to recruitment of collapsed alveoli. This increases the surface area for gas exchange and decreases intrapulmonary shunt. Maintaining adequate functional residual capacity from birth prevents atelectasis and may promote release of surfactant stores. The constant distending pressure has been shown in animal models to promote lung development. Avoiding intubation promotes normal airway mucociliary function and prevents airway damage and the significant complications associated with this procedure. This further decreases the inflammation and lung damage that results from mechanical ventilation.

Multiple different devices and pressure sources are used to deliver nasal CPAP. A recent Cochrane Review [(DePaoli 08)] concluded that short binasal prong devices are more effective than single prongs in reducing the rate of re-intubations. Although the Infant Flow Driver appears more effective than Medicorp prongs the most effective short binasal prong device remains to be determined. The two main type of pressure sources are variable flow and constant flow systems. The constant flow device can be ventilator derived or the classic underwater bubble CPAP system. The variable flow system may have the benefit of variable flow decreasing the work of breathing in the infant. Among the constant flow systems, the bubble CPAP is speculated to have better CO2 removal due to oscillations along with the advantage of being simple and inexpensive.

II. Benefits

There are now at least 4 prospective trials which have randomized premature infants to receive

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[(RHO 73)] Rhodes PG, Hall RT. Continuous positive airway pressure delivered by face mask in infants with the idiopathic respiratory distress syndrome: A controlled study. *Pediatrics*. 1973;52:1-5.

[(LIN 99)] Lindner W, Vossbeck S, Hummler H, Pohlandt F: Delivery room management of extremely low birth weight infants-Spontaneous breathing or intubation? *Pediatrics* 1999;103:961-967.

(Verder09) Henrik Verder, Kajsa Bohlin, Jens Kamper, Robert Lindwall, Baldvin Jonsson. Nasal CPAP and surfactant for treatment of respiratory distress syndrome and prevention of bronchopulmonary dysplasia. *Acta Paediatr. 2009 Sep;98(9):1400-8*

(DePaoli08) De Paoli AG, Davis PG, Faber B, Morley CJ. Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. *Cochrane Database Syst Rev. 2008 Jan 23;(1):CD002977.*

either CPAP at birth or intubation with or without surfactant (SUPPORT, 24 weeks- 276/7ths, or VON, 26 – 29 6/7ths, COIN and CURPAP, 25 0/7 – 28 6/7ths weeks). Even though these studies showed no difference in the primary outcome of Death or BPD between the CPAP and intubation groups, they did show a decrease in other short term respiratory outcomes including the need for intubation, mechanical ventilation at 7days, steroids for BPD, and days of mechanical ventilation. The COIN trial showed an increase in the pneumothorax in the CPAP group; however this was not seen in the other 3 studies. Another multicenter study from Columbia showed that there was a decrease in the need for mechanical ventilation with early surfactant administration and extubation to CPAP compared to the CPAP only group. It should be noted that the gestational age of the enrolled infants in the Columbia trial (27 0/7 – 31 6/7ths weeks) represents a more mature population that those enrolled in the other trials (24 0/7 – 28 6/7ths weeks). Overall the results of a meta analysis for all the randomized trials does show a significant reduction in death or survival with BPD, and there was no increase in any significant morbidity. The increase in air leaks seen in the COIN trial was not significant in the overall metal analysis and no such increase was seen in the Largest study (SUPPORT)
The main benefit of early CPAP is the decrease in the need and duration of mechanical ventilation without a significant increase in the adverse events. The SUPPORT trial also showed a significant decrease in mortality in the 24-25weeks gestation in the CPAP group.

The details of the individual studies are listed below.

The COIN trial enrolled 610 randomly assigned infants who were born at 25-to-28-weeks' gestation and where spontaneously breathing at 5 minutes of age to CPAP or intubation and ventilation at 5 minutes after birth. They reported that at 36 weeks' gestational age, 33.9% of 307 infants who were assigned to receive CPAP had died or had bronchopulmonary dysplasia, as compared with 38.9% of 303 infants who were assigned to receive intubation (odds ratio non-significantly favoring CPAP, 0.80; 95% confidence interval [CI], 0.58 to 1.12; P=0.19). At 28 days, there was a lower risk of death or need for oxygen therapy in the CPAP group than in the intubation group (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006). There was no difference in overall mortality. In the CPAP group, 46% of infants were intubated during the first 5 days, and the use of surfactant was halved. The incidence of pneumothorax was 9% in the CPAP group, as compared with 3% in the intubation group (P<0.001). This study used 8 cm H2O CPAP initially and this may be a factor in the increased rate of air leaks observed. The CPAP group had fewer days of ventilation. (Morley 2008)

The SUPPORT Trial enrolled 1316 infants from 24 0/7ths weeks gestation to 27 6/7ths weeks in 2 strata. These infants were randomized to receive either CPAP and a limited ventilator strategy following delivery or surfactant within the first hour of life. The rates of the primary outcome of death or survival with physiologically defined BPD were not significantly different between the CPAP and surfactant groups, when adjusted for gestational age, center and familial clustering (47.8% vs. 51.0%, Relative risk(RR) =0.95 (95% Confidence interval (CI) 0.85, 1.05) . Results were similar (rates 48.7% vs. 54.1%, respectively; RR=0.91 (CI 0.83, 1.01), when BPD was defined by any oxygen requirement at 36 weeks gestation . Fewer CPAP treated neonates required intubation or post natal steroids for BPD, (p<.001) and more were alive and off mechanical ventilation by day 7, (p=0.011). Infants in the immature strata of 24 to 25 6/7 weeks gestation randomized to CPAP had a significantly lower mortality rate while hospitalized than those randomized to surfactant 23.9% vs. 32.1%, RR=0.74, (0.57, 0.98), p=0.034, Treatment

with CPAP, versus surfactant, was not associated with increased risks for adverse neonatal outcomes.

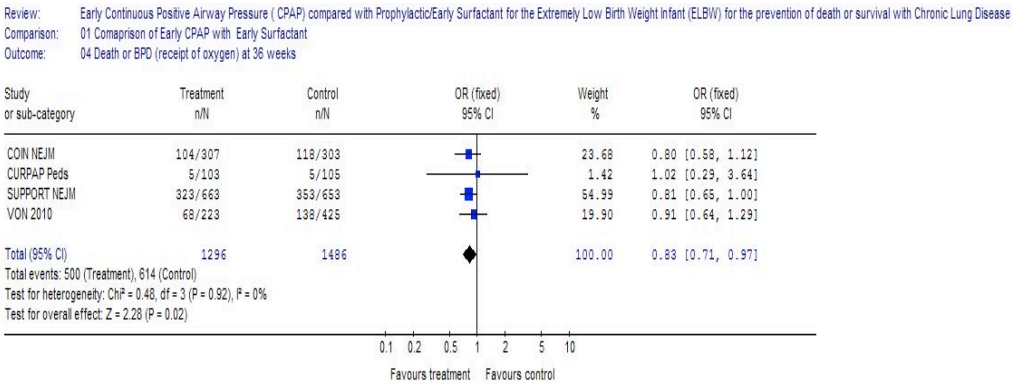
The VON trial compared prophylactic surfactant with early CPAP and with an approach that included prophylactic surfactant followed by immediate extubation. This trial enrolled 648 infants from 26 to 296/7ths weeks gestation at 27 centers. There were no differences in baseline population characteristics. Fewer infants in the NCPAP vs the prophylactic surfactant group received surfactant (46 %vs 99%) and were ventilated (45% vs 96%) during the first week of life. No differences were seen in the primary outcome of death or BPD at 36 weeks postmenstrual age. There were no statistically significant differences in mortality, other complications of prematurity or the composite outcome of death or major morbidity (severe ROP, CLD, PVL or severe IVH) between their groups. Death or BPD was lowest in their CPAP group, (40.6%) compared with the prophylactic surfactant group (53.1%), and the intubate/surfactant/extubate group (43.4%) although these differences did not reach significance.

The CURPAP (Sandri et al). study enrolled 208 newborns from 25+0–28+6 wks with spontaneous breathing were randomized after birth to two groups: Group 1-intubation, prophylactic surfactant administration within 30 minutes from birth; Group 2-early stabilization on NCPAP with early rescue surfactant administration according to defined clinical criteria. The incidence of the need for mechanical ventilation in the first 5 days was similar between the two groups (Group 1: 31.4%,Group 2: 33.0%.RR:0.95;95% CI:0.64-1.41); 21.9% and 21.4% infants respectively required oxygen treatment or respiratory support or had died at 36 weeks PMA. There was no difference in the incidence of BPD (Group 1: 23.8%, Group 2: 22.3%.RR:1.05; 95% CI: 0.65-1.70). The incidence of pneumothorax was 6.7% in Group 1 (Prophylactic Surfactant) and 1% in Group 2 (RR: 6.82; 95% CI: 0.86-53.75). There were no differences in the incidence of other complications.

As previously describe above, the multicenter study from Colombia, South America prospectively evaluated 279 infants born between 27 and 31(6/7) weeks' gestation with evidence of respiratory distress and treated with supplemental oxygen in the delivery room. (Rojas et al). Infants were randomly assigned within the first hour of life to intubation, very early surfactant, extubation, and nasal continuous positive airway pressure (treatment group) or nasal continuous airway pressure alone (control group). The need for mechanical ventilation was lower in the treatment group (26%) compared with the control group (39%). Air- leak syndrome occurred less frequently in the treatment group (2%) compared with the control group (9%) as was the percentage of patients receiving surfactant after the first hour of life was also significantly less in the treatment group (12%) compared with the control group (26%). The incidence of chronic lung disease was 49% in the treatment group compared with 59% in the control group. It should be noted that this trial enrolled infants of at least 27 weeks gestation, and thus represents a more mature population that those enrolled in SUPPORT (24 weeks- 276/7ths, or VON, 26 – 29 6/7ths weeks .

The evidence for CPAP at present suggests that all infants regardless of gestational age, should be given a trial of CPAP. If they fail they should receive surfactant if they have respiratory

distress and from the meta analysis by Stevens et al such treatment appears most appropriate at an FiO2 between .35 and .45. All the trials show that CPAP infants have a reduced need for intubation, some show a lower vs higher air leak rate- not consistent, and this may be dependent on the level of CPAP. In addition for the most immature infants SUPPORT reported a decreased mortality for the CPAP assigned infants with no increases in any morbidities. All of the trials found at least equivalent rates of BPD/death for prophylactic surf vs CPAP, but most found decreases rates of these in the CPAP infants – COIN did not compare early surf to early CPAP.\ We have performed a meta- analysis on the current trials with available information and as can be seen, there is an overall reduction in death or BPD with the use of early CPAP. We have included COIN which did not compare CPAP to early surfactant



III. Risks

CPAP related side effects:

- Air leaks (pneumothorax, pneumopericardium and pneumoperitoneum)
- Nasal excoriation, nasal septal injury (pressure necrosis), bleeding and secondary infection
- Gastric distension may impair feeding tolerance – CPAP belly

Delay in intubation and use of surfactant:

- Delay in treating while respiratory distress syndrome progresses may lessen surfactant treatment effectiveness[(VER 94)(VER 99)]

Morley, C. J.; Davis, P. G.; Doyle, L. W.; Brion, L. P.; Hascoet, J. M., and Carlin, J. B. Nasal CPAP or intubation at birth for very preterm infants. New England Journal of Medicine. 2008; 358(7):700-708

[(VER 94)] Verder H, Robertson B, Greisen G, Ebbesen F, Albertsen P, Lundstrom K, Jacobsen T. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. *The New England Journal of Medicine*. 1994; 331(16):1051-5.
[(VER 99)] Verder H, Albersen P, Ebbesen F, Greisen G, Robertson B, Bertelsen A, et al: Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. *Pediatrics*. 1999;103(2).

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Early CPAP versus Surfactant in Extremely Preterm Infants. N Engl J Med. 2010 May 27;362(21):1959-69.

Dunn, M, Kaempf, J, de Klerk,, A de Klerk, R, Reilly, M, Howard, D, Ferrelli, K, Soll, R.Delivery Room Management of Preterm Infants at Risk for Respiratory Distress Syndrome (RDS). Pediatric Academic Societies, 2010 Vancouver, E-PAS20101670.2

Sandri, F, Plavka, R, Ancora,G, Simeoni, U Stranak, Z, Martinelli S et al. Prophylactic or Early Surfactant Combined with nCPAP in Very Preterm Infants . PEDIATRICS Vol. 125 No. 6 June 2010, pp. e1402-e1409

Rojas, M. A.; Lozano, J. M.; Rojas, M. X.; Laughon, M.; Bose, C. L.; Rondon, M. A.; Charry, L.; Bastidas, J. A.; Perez, L. A.; Rojas, C.; Ovalle, O. ; Celis, L. A.; GarciaHarker, J., and Jaramillo, M. L. Very Early Surfactant Without Mandatory Ventilation in Premature Infants Treated With Early Continuous Positive Airway Pressure: A Randomized, Controlled Trial. Pediatrics. 2009; 123(1):137-142

Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD003063

Rationale

Commended Practice Two:

Prophylactic Administration of Surfactant

Original Date:
Revised 11/30/11

Prophylactic Administration of Surfactant: Summary

I. Definition and Physiologic Rationale

Prophylactic surfactant administration describes the practice of giving surfactant within the first few minutes of life, and prior to establishment of respiratory distress, to a group of eligible infants, where eligibility is usually determined by gestational age. We define prophylactic surfactant administration as administration occurring less than 30 minutes after birth. Surfactant administration reduces both ventilatory pressures required to inflate the lung and lung damage from positive pressure ventilation.

II. Benefits

The 2001 Cochrane meta-analysis, Prophylactic Surfactant vs. Treatment with Surfactant,[(SOL 97)] summarizes the benefits of the practice:

> Prophylactic surfactant administration to infants judged to be at risk for developing respiratory distress syndrome has been demonstrated to improve clinical outcome. Infants who receive prophylactic surfactant have a decreased risk of pneumothorax, a decreased risk of pulmonary interstitial emphysema, and a decreased risk of mortality.

III. Risks

The risk of prophylactic surfactant follows from the need to intubate in order to administer the agent, thereby setting in motion a course of ventilation with its attendant complications, and the possibility of airway obstruction secondary to surfactant administration to very immature infants with very narrow airways.

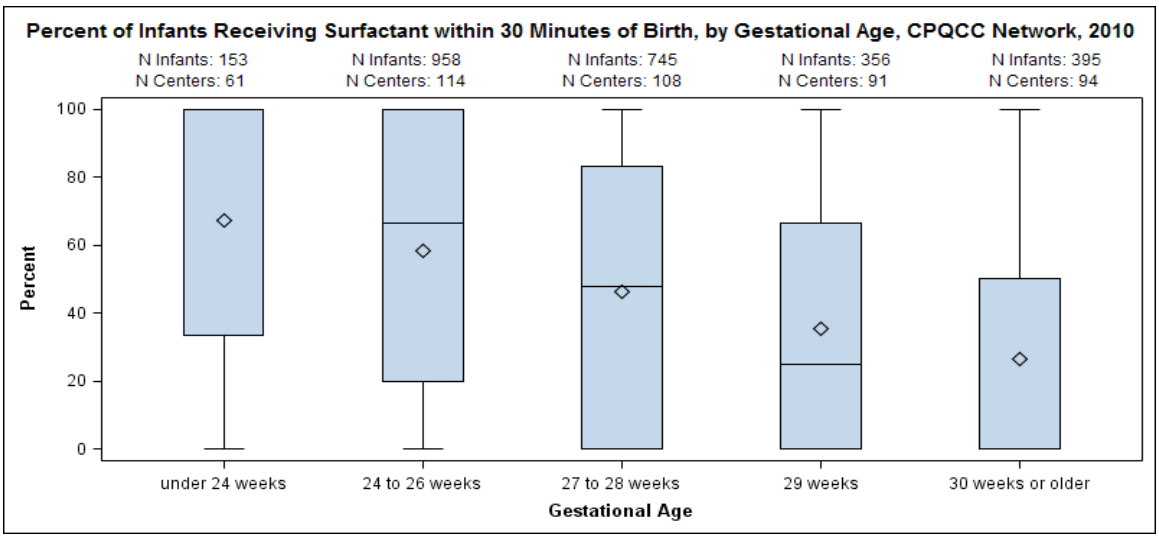
IV. Benchmarking

The below chart is based on all inborn CPQCC infants by gestational age who did not die in the delivery room and who received surfactant either in the DR or after NICU admission.

[(SOL 97)] Soll RF, Morley CJ. The Cochrane Database of Systematic Reviews. Prophylactic versus selective use of surfactant for preventing morbidity and mortality in preterm infants. *The Cochrane Library*. 1997.

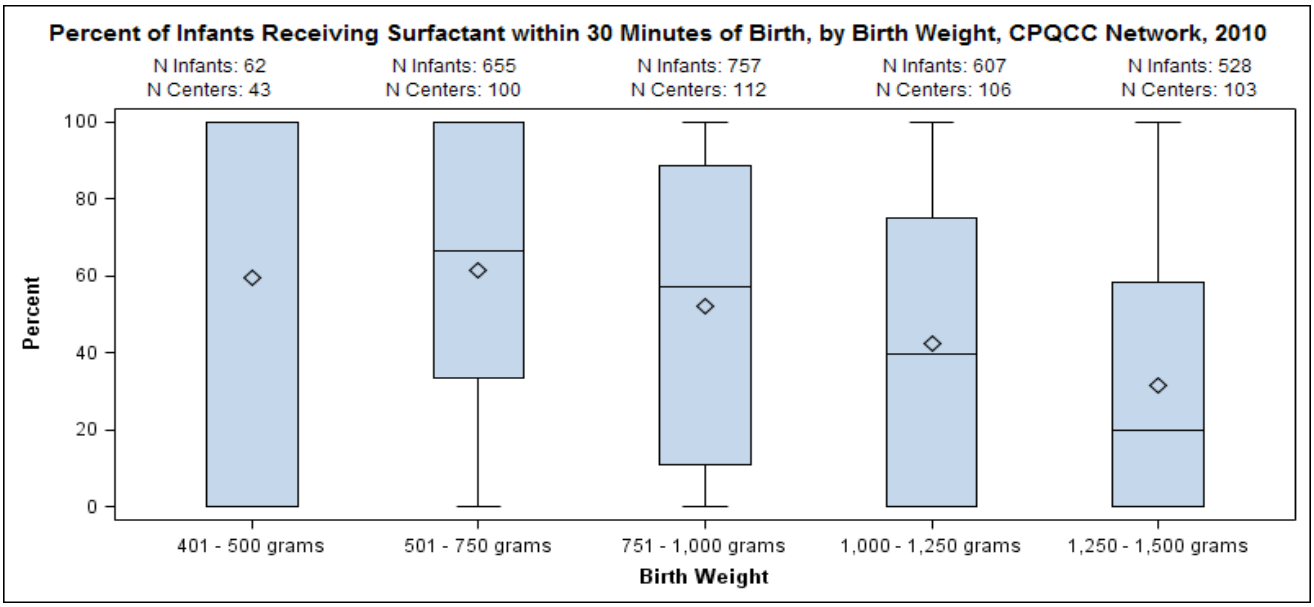
RF Soll, CJ Morley. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 2001, Issue 2. Art. No.: CD000510. DOI: 10.1002/14651858.CD000510

Original Date:
Revised 11/30/11



Infants with unknown surfactant time are excluded (N=167).

The below chart is based on all inborn CPQCC infants 401 to 1,500 grams, by birthweight, who did not die in the delivery room and who received surfactant either in the DR or after NICU admission.



Infants with unknown surfactant time are excluded (N=167).

Prophylactic Administration of Surfactant

I. Definition and Physiologic Rationale

The term *prophylactic* describes surfactant administration during the first few minutes of life to a group of *eligible* infants, with eligibility usually determined by gestational age.[(MBU 98)] Clinical trials vary in their definitions: some define prophylactic as within 5 minutes of birth, while others consider surfactant administration within 15 minutes of birth to be prophylactic. Alternatively, prophylactic administration can be defined as, "prior to initiation of respiration," or, "immediately post intubation." For our purposes, we are defining this as less than 30 minutes.

CPQCC does not promote prophylactic use of surfactant for all infants under a particular gestational age or birth weight. Rather, the Data section of this toolkit provides hospital-specific data that facilitates policy formulation at the hospital level. Units that opt to implement prophylaxis will need to determine *eligibility* by defining a gestational age and/or birth weight threshold. If an infant is eventually going to receive surfactant, it is beneficial to administer surfactant earlier rather than later. The challenge, therefore, is to identify as early as possible those infants who are likely to require surfactant.

One physiologic rationale for surfactant is provided in the book *Chronic Lung Disease in Early Infancy*[(JOB 00)]

> Surfactant has several effects on the pre-term, surfactant-deficient lung that results in improved lung function. These effects should decrease the need for mechanical ventilation and supplemental oxygen. Treatment of the surfactant-deficient lung changes the pressure-volume relations of the lung. The lung fills with more gas at a lower pressure and is more stable on deflation. Because dead space is changed very little, the increased gas volume is being accommodated by the recruitment of parenchymal gas volume with the potential for improved gas exchanges. The increased volume stability translates to an increased functional residual capacity. The primary clinical outcome of increased lung gas volume and functional residual capacity is improved arterial oxygenation.

[(MBU 98)] Mbuyamba M, Holman M, Kresch M. Gestational age can predict the need for prophylaxis with surfactant therapy. *Am Journal of Perinatology*. 1998;15(4).
[(JOB 00)] Ibid.

II. Benefits

The benefits of prophylactic surfactant are demonstrated in this meta-analysis: Soll RF, Morley CJ. The Cochrane Database of Systematic Reviews: Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants 2001. The Cochrane Library. This meta analysis of 8 studies reported the following typical overall results.

Prophylactic administration of surfactant will lead to significant reduction in the risk of pneumothorax (typical relative risk 0.62, 95% CI 0.42, 0.89; typical risk difference -0.02, 95% CI - 0.04, -0.01), a significant reduction in the risk of pulmonary interstitial emphysema (typical relative risk 0.54, 95% CI 0.36, 0.82; typical risk difference -0.03, 95% CI -0.04, -0.01), and did not support any difference in the risk of bronchopulmonary dysplasia (typical relative risk 0.96, 95% CI 0.82, 1.12; typical risk difference -0.01, 95% CI -0.03, 0.02). There was an overall decrease in the risk of both neonatal mortality and in mortality prior to hospital discharge associated with prophylactic surfactant administration with a typical relative risk of 0.61, 95% CI 0.48, 0.77 (typical risk difference -0.05, 95% CI -0.07, -0.02) and the relative risk for mortality prior to hospital discharge was 0.75, 95% CI 0.59, 0.96 (typical risk difference -0.05, 95% CI -0.09, -0.01). There was a decreased risk of bronchopulmonary dysplasia or death (typical relative risk 0.85, 95% CI 0.76, 0.95; typical risk difference -0.04 95% CI -0.07, -0.01), although significant heterogeneity was noted.

These authors also performed a secondary analysis of only infants less than 30 weeks gestation, and reported a significant decrease in neonatal mortality in this high risk group (typical relative risk 0.62, 95% CI 0.49, 078; typical risk difference -0.06, 95% CI -0.09, -0.03). Similarly this group also showed a significant decrease in the incidence of bronchopulmonary dysplasia or death in this subgroup (typical relative risk 0.87, 95% CI 0.77, 0.97; typical risk difference -0.05, 95% CI -0.09, -0.01

There were no differences for NEC, IVH or severe IVH and ROP

There are now a number of studies comparing natural surfactants containing animal protein with artificial products devoid of such animal protein. When used to prevent subsequent respiratory distress in preterm infants, ie prophylaxis, there does not appear to be any significant difference between either of these surfactants. In the recent Cochrane review the authors concluded that there were no statistically different clinical differences in death and chronic lung disease and other clinical outcomes for infants treated with either type of surfactant. (PFISTER 07)

Classifying the strength and quality of the evidence:(GRA 97)

1. Strong evidence from at least one systematic review of multiple well-designed randomized controlled trials
2. Strong evidence from at least one properly designed randomized controlled trial of appropriate size
3. Evidence from well-designed trials without randomization, including single group pre-post, cohort, time series or matched case-control studies
4. Evidence from well-designed non-experimental studies preferably from more than one center or research group
5. Opinions of respected authorities, based on clinical evidence, descriptive studies or reports of expert committees

(GRA 97) Gray Muir JA. *Evidence Based Healthcare: How to make health policy and management decisions. Churchill Livingstone*. NY; 1997:61.

Studies Included in Meta-analysis (with evidence classification):
The review constitutes Level 1 evidence; it is entirely drawn from Level 2 studies.

Bevilacqua G, Parmigiani S, Robertson B and the Italian Collaborative Multicentre Study Group. Prophylaxis of respiratory distress syndrome by treatment with modified porcine surfactant at birth: a multicentre prospective randomized trial. J Perinat Med 1996; 24:1-12. (Level 2 evidence)

Bevilacqua G, Chernev T, Parmigiani S, Iarakova N, Gaioni L, Volante E, Gambini L, Bussolati G. Use of surfactant for prophylaxis versus rescue treatment of respiratory distress syndrome: experience from an Italian-Bulgarian trial. Acta Biomed Ateneo Parmense 1997;68(Suppl 1):47-54. (Level 2 evidence)

Dunn MS, Shennan AT, Zyack D, Possmayer F. Bovine surfactant replacement therapy in neonates of less than 30 weeks' gestation: a randomized controlled trial of prophylaxis vs treatment. Pediatrics 1991; 87:377-386. (Level 2 evidence)

Egberts J, DeWinter JP, Sedin G, DeKleine MJK, Broberger U, VanBel F, Curstedt T and Robertson B. Comparison of prophylaxis and rescue treatment with Curosurf in neonates less than 30 weeks gestation: a randomized trial. Pediatrics; 1993; 92:768-774. (Level 2 evidence)

Kattwinkel J, Bloom BT, Delmore P, Davis CL, Farrell E, Friss H, Jung AL, King K and Mueller D. Prophylactic administration of calf lung surfactant extract is more effective than early treatment of respiratory distress syndrome in neonates of 29 through 32 weeks' gestation. Pediatrics 1993; 92:90-98. (Level 2 evidence)

Kendig JW, Notter RH, Cox C, Reubens LJ, Davis JM, Maniscalco WM, Sinkin RA, Bartoletti A, Dweck HS, Horgan MJ, Rosemberg H, Phelps DL, Shapiro DL. A comparison of surfactant as immediate prophylaxis and as rescue therapy in newborns of less than 30 weeks' gestation. N Engl J Med 1991; 324:865-871. (Level 2 evidence)

Merritt TA, Hallman M, Berry C, Pohjavuori M, Edwards DK, Jaaskelainen J, Grafe MR, Vaucher Y, Wozniak P, Heldt G, Rapola J. Randomized, placebo-controlled trial of human surfactant given at birth vs rescue administration in very low birthweight infants with lung immaturity. J Pediatr 1991; 118:581-594. (Level 2 evidence)

Walti H, Paris - Llado J, Breart G, Couchard M, and the French Collaborative Multicentre Study Group. Porcine surfactant replacement therapy in newborns of 25-31 weeks' gestation: a randomized multicentre trial of prophylaxis versus rescue with multiple low doses. Acta Paediatr 1995; 84(8):913-21. (Level 2 evidence)

Moya F, Gadzinowski J, Bancalari E, Salinas V, Kopelman B, Bancalari A, et al. A multicenter, randomized, masked, comparison trial of lucinactant, colfosceril palmitate, and beractant for the prevention of respiratory distress syndrome in very preterm infants. Pediatrics 2005;115:1018-29. (Level 2 evidence)

Sinha S, Lacaze-Masmonteil T, Valls i Soler A, Gadzinowski J, Hadju J, Bernstein G, et al. A multicenter, randomized, controlled trial of lucinactant versus poractant alfa in very premature infants at high risk for respiratory distress syndrome. Pediatrics 2005;115:1030-8. (Level 2 evidence)

Perinatal Quality Improvement Panel Comments on the meta-analysis: This meta-analysis includes eight studies, all of which compare incidence of BPD as determined at 28 days, and other outcomes between two groups of infants: those to whom surfactant was administered prophylactically and those receiving surfactant after demonstrating signs of RDS. Each study employs slightly different definitions of "prophylactic" treatment although all administered surfactant by 30 minutes of age. There is also variation in terms of criteria for administration of rescue therapy, ranging from, "intubation and respiratory insufficiency" to "severe RDS requiring oxygen greater than 60%". This heterogeneity appears to strengthen rather than limit the findings of the meta-analysis in the sense that, regardless of definitions employed, prophylactic use almost consistently yields lower mortality rates: The more recent analyses include a secondary comparison of the infants less than 30 weeks gestation. While none of the studies were powered to look at such a population, these trends are interesting and suggest that more immature infants may show a greater benefit from surfactant. Plerase see Section on Early CPAP and studies comparing Early CPAP to Surfactant. Level of severity of BPD is not assessed, but can be assumed to contribute to mortality[(JOB 00)]. The relationship between administration of antenatal steroids and the beneficial effects of prophylactic use of surfactant is not explored in this meta-analysis.

III. Risks

Toxicity: Surfactant administration can produce transient bradycardia or oxygen desaturation often associated with transient airway obstruction. Careful weaning of oxygen supplementation and assisted ventilation is essential to avoid hyperoxia or excessive ventilation.[(BEN 95)] Meta-analysis does not support an increase in severe intracranial hemorrhage[(SOL 97)]; reports from individual trials have shown trends of both increases and decreases in ICH rates.

Intubation: Prophylactic surfactant carries the additional risk of intubation in order to administer the agent. Complications of intubation include: local trauma, intubation of one lung, usually the right lung, cardiopulmonary compromise during the procedure, pulmonary interstitial emphysema and air leak syndromes, tube blockage, subglottic stenosis, post-extubation stridor, and bacterial colonization.[(DAS 97)], [(RIV 92)].

[(JOB 00)] Jobe A, Influence of surfactant replacement on development of BPD. From CLD in Early Infancy, edited by Bland R, Coalson J. New York, NY: Marcel Dekker, Inc.; 2000:241.
[(BEN 95)] Benitz W, Tatro D. *The Pediatric Handbook*. St. Louis, MO: Mosby; 1995:146.
[(SOL 97)] Soll RF, Morley FJ. The Cochrane Database of Systematic Reviews: Prophylactic versus selective use of surfactant for preventing morbidity and mortality. *The Cochrane Library*. 1997.
[(DAS 97)] Da Silva O, Stevens D. Complications of airway management in very-low-birth-weight infants. *Biol Neonate*. 1997;5:40-5
[(RIV 92)] Rivera R, Tibballs J. Complications of endotracheal intubation and mechanical ventilation in infants and children. *Crit Care Med*. 1992;20:193-9.

IV. Benchmarking

CPQCC centers submit standardized data forms for very low birth weight infants to the CPQCC Data Center where they are reviewed for errors and omissions. These forms contain information on nearly 50 variables. Question 34 of the Discharge form records whether an infant received oxygen at 36 weeks adjusted gestational age. Question 21 of the Discharge form records whether or not an infant received exogenous surfactant at any time. If yes, the postnatal age in hours and minutes is also entered.

CPQCC Data Center submits data to Vermont Oxford Network (VON) for analysis. CPQCC/VON aggregates data and computes indicators that reflect clinical procedures and outcomes. Each center receives its respective set of indicators as well as the national and state median and interquartile range for each indicator in the CPQCC quarterly report. Indicators are displayed in graphs to facilitate comparisons. The following tables/figures can be generated for your center using's the VON Nightingale Reporting features:

Table Respiratory outcomes and Interventions Percentages at your Hospital and Percentile Ranks Relative to all NICUs of your "type." Comparisons with the national dataset that comprise VON hospitals of a like type can be made by making the appropriate selections in the Nightingale report generator: Comparisons with the CPQCC dataset that comprise California hospitals of a like type can be made by examining the California-only version of the same Table by accessing the CPQCC Report generator and making similar selections. As a reminder, we repeat the definitions of each category.

RF Soll, CJ Morley. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 2001, Issue 2. Art. No.: CD000510. DOI: 10.1002/14651858.CD000510.

RH Pfister, RF Soll, T Wiswell. Protein containing synthetic surfactant versus animal derived surfactant extract for the prevention and treatment of respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD006069. DOI: 10.1002/14651858.CD006069.pub3.

Dunn, M, Kaempf, J, de Klerk,, A de Klerk, R, Reilly, M, Howard, D, Ferrelli, K, Soll, R.Delivery Room Management of Preterm Infants at Risk for Respiratory Distress Syndrome (RDS). Pediatric Academic Societies, 2010 Vancouver, E-PAS20101670.2

Rojas, M. A.; Lozano, J. M.; Rojas, M. X.; Laughon, M.; Bose, C. L.; Rondon, M. A.; Charry, L.; Bastidas, J. A.; Perez, L. A.; Rojas, C.; Ovalle, O. ; Celis, L. A.; GarciaHarker, J., and Jaramillo, M. L. Very Early Surfactant Without Mandatory Ventilation in Premature Infants Treated With Early Continuous Positive Airway Pressure: A Randomized, Controlled Trial. Pediatrics. 2009; 123(1):137-142

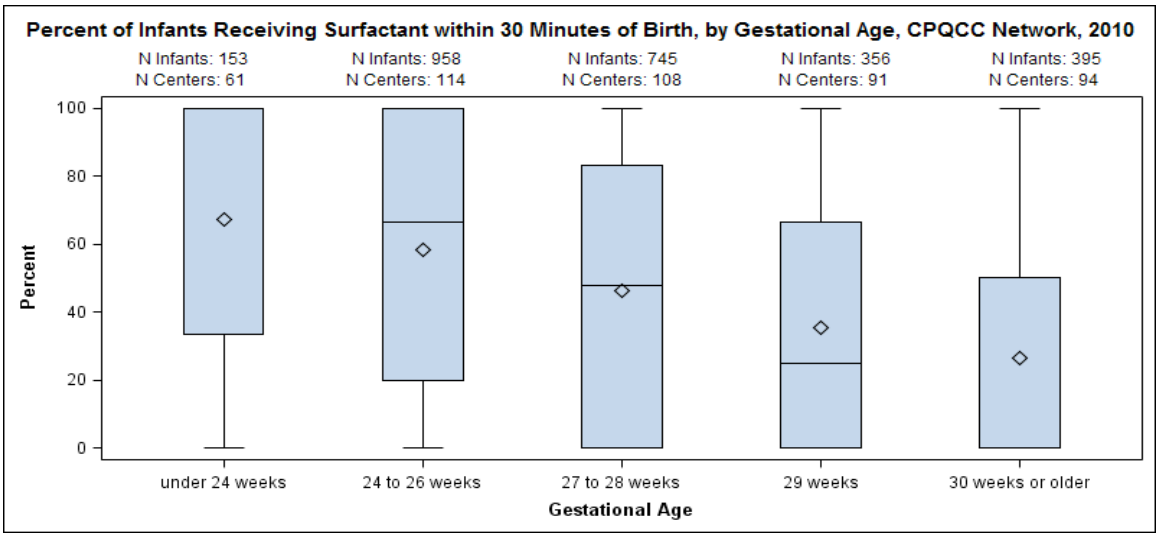
Sandri, F, Plavka, R, Ancora,G, Simeoni, U Stranak, Z, Martinelli S et al. Prophylactic or Early Surfactant Combined with nCPAP in Very Preterm Infants . PEDIATRICS Vol. 125 No. 6 June 2010, pp. e1402-e1409

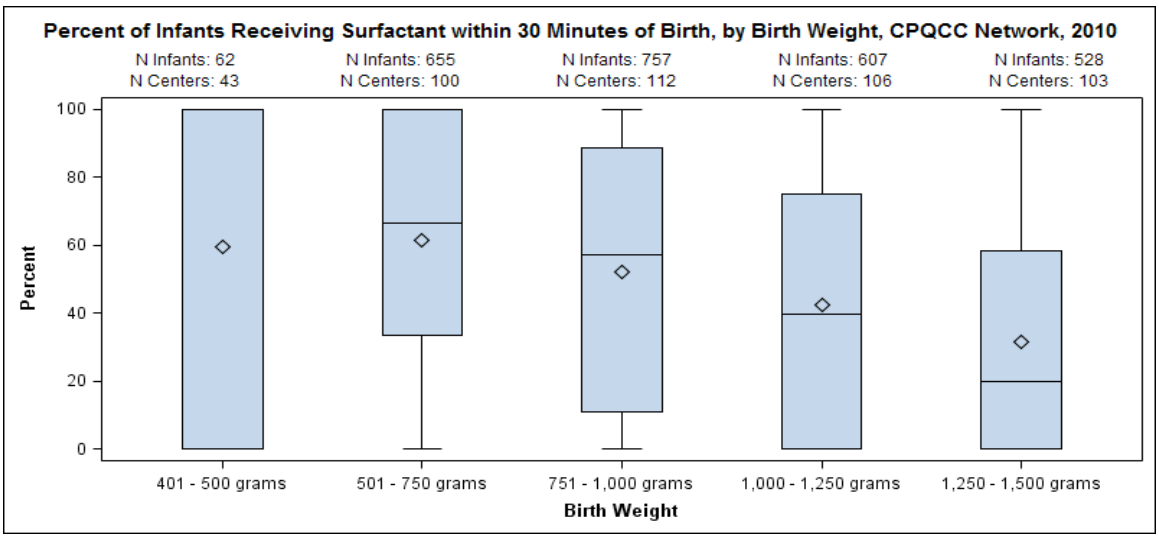
Type A NICUs are Centers that have a restriction on assisted ventilation (infants transferred to another hospital for assisted ventilation based on either patient characteristics or the duration of assisted ventilation) or that only perform minor surgery.

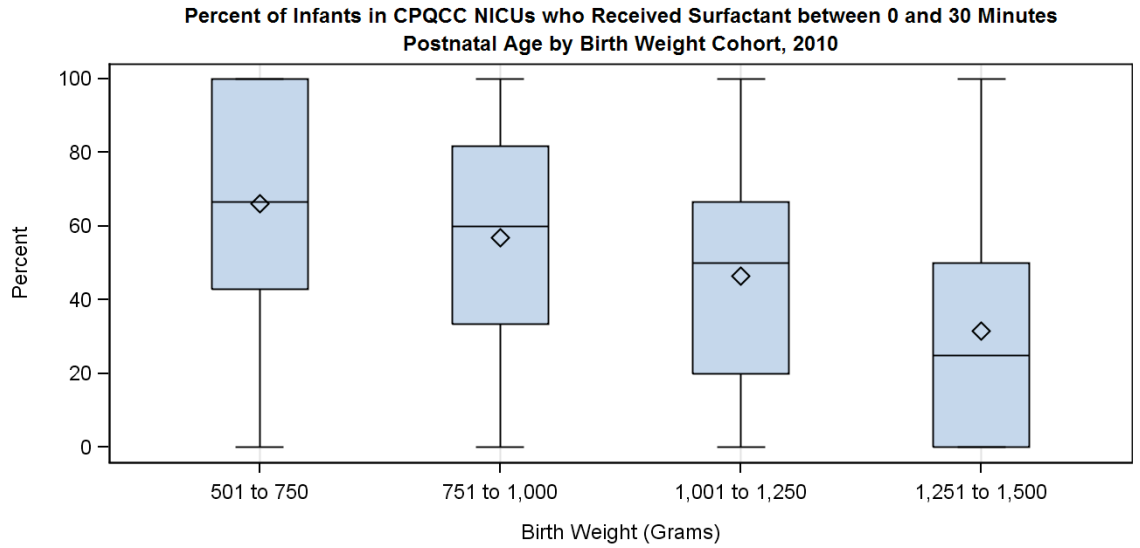
Type B NICUs are Centers with no restriction on assisted ventilation and which perform major surgery. Major surgery includes one or more the following: omphalocele repair, ventriculoperitioneal shunt, TEF/esophageal atresia repair, bowel resection/reanastomosis, meningomyelocoele repair, cardiac catherization or PDA ligation.

Type C NICUs are centers that perform cardiac surgery requiring bypass for newborn infants.

Prophylactic surfactant administration: CPQCC member use of prophylactic surfactant is presented both by gestational age and birthweight cohorts. The following charts display by gestational age and birthweight CPQCC's indicator, albeit imprecise, for implementation of the prophylactic surfactant strategy.







The boxplot shows the median, minimum, maximum, 25% and 75% percentiles for the percent for 133 NICUs.
The mean percent across all CPQCC NICUs is represented by the diamond.

Commended Practice Three:

Early Selective Surfactant Administration

Original Date:
Revised 11/30/11

Early Selective Surfactant Administration: Summary

I. Definition and Physiologic Rationale

As distinct from prophylactic, early surfactant typically describes a policy of administering surfactant within the first two hours of life to infants intubated for early signs of respiratory distress syndrome (RDS) and/or requiring ventilation for respiratory failure.

II. Benefits

The 1999 Cochrane meta-analysis, *Early versus Delayed Selective Surfactant Treatment for Neonatal Respiratory Distress Syndrome*, summarizes the benefits of the practice:[(YOS 99)]

> Early selective surfactant administration given to infants with RDS requiring assisted ventilation leads to a decreased risk of acute pulmonary injury (decreased risk of pneumothorax and pulmonary interstitial emphysema) and a decreased risk of neonatal mortality and chronic lung disease compared to delaying treatment of such infants until they develop more severe RDS.

The 2007 Cochrane meta-analysis *Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome* summarized the benefits of such early administration followed by brief ventilation as follows:

> Early surfactant replacement therapy with extubation to NCPAP compared with later selective surfactant replacement and continued mechanical ventilation with extubation from low ventilator support is associated with less need mechanical ventilation, lower incidence of BPD and fewer air leak syndromes. A lower treatment threshold (FIO2< 0.45) confers greater advantage in reducing the incidences of airleak syndromes and BPD; moreover a higher treatment threshold (FIO2 at study > 0.45) was associated with increased risk of PDA. These data suggest that treatment with surfactant by transient intubation using a low treatment threshold (FIO2< 0.45) is preferable to later, selective surfactant therapy by transient intubation using a higher threshold for study entry (FIO2 > 0.45) or at the time of respiratory failure and initiation of mechanical ventilation.

III. Risks

Some infants are likely to receive surfactant later than under a policy of prophylactic surfactant that calls for immediate intubation and surfactant administration to eligible infants.

IV. Benchmarking

The following chart displays by gestational age CPQCC's indicator, albeit imprecise, for implementation of the early surfactant strategy. If an infant received surfactant between 31 and 120 minutes postnatal age, then we classify the infant as having received early surfactant (numerator). (Note: infants who receive surfactant prior to 30 minutes are classified having been treated according to the prophylactic strategy.) The denominator consists of all those delivered in that Gestational Age cohort. The benchmark rate is established by determining the 75th percentile of the rates among hospitals for each Gestational Age cohort (2007 dataset). Hospitals with less than six infants in a cohort are excluded from the analysis. The

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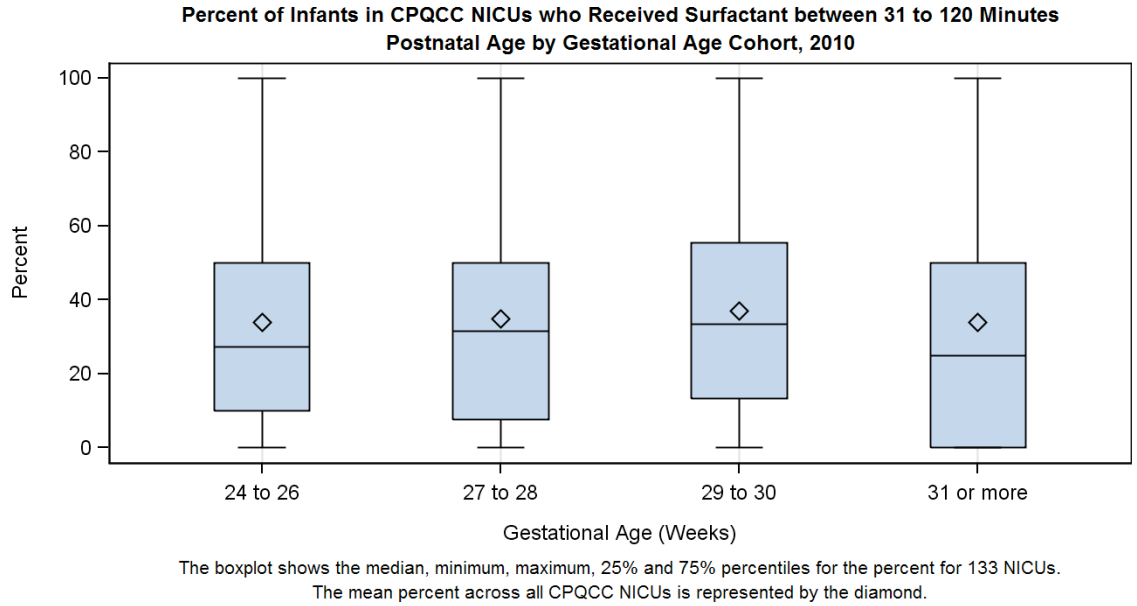
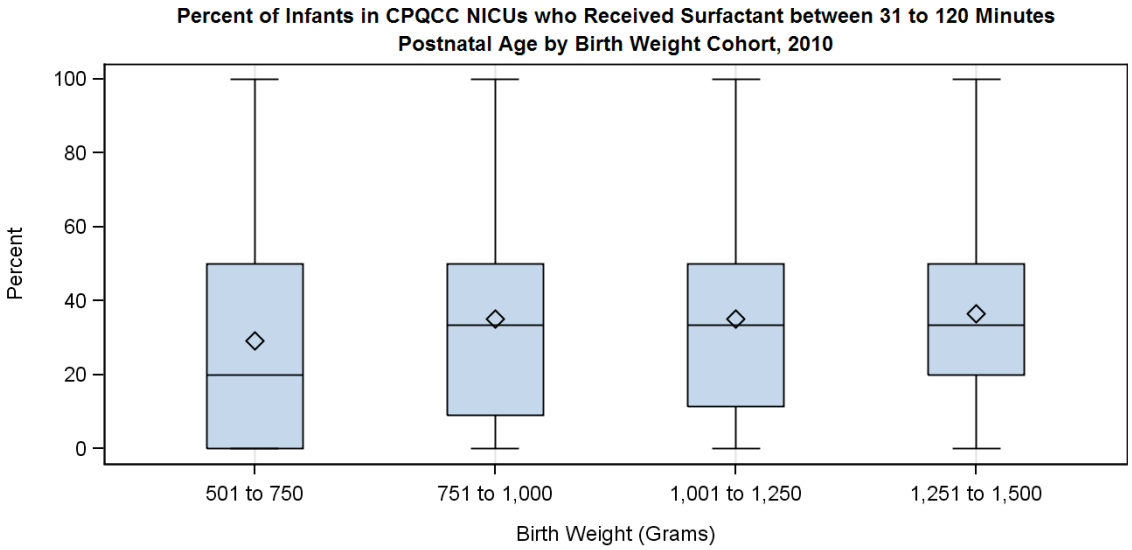
[(YOS 99)] Yost CC, Soll RF. The Cochrane Database of Systematic Reviews: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *The Cochrane Library*. 1999.

benchmark rate for each cohort is: 46% (24-26 wk); 58% (27-28 wk); 48% (29-30 wk); and 50% (31 wk or more). A birthweight cohort display follows the GA one.

Per Cent of Infants in each CPQCC NICU Who Received Surfactant Between 31-120 minutes Postnatal Age By Gestational Age Cohort. Box shows percentages for the mean, 25th & 75th percentiles of CPQCC NICUs in 2010.



The following chart displays by birthweight CPQCC's indicator, albeit imprecise, for implementation of the early surfactant strategy. If an infant received surfactant between 31 and 120 minutes postnatal age, then we classify the infant as having received early surfactant (numerator). (Note: infants who receive surfactant prior to 30 minutes are classified having been treated according to the prophylactic strategy.) The denominator consists of all those delivered in that Birth Weight cohort. The benchmark rate is established by determining the 75th percentile of the rates among hospitals for each Birth Weight cohort (2007 dataset). Hospitals with less than six infants in a cohort are excluded from the analysis. The benchmark rate for each cohort is: 49% (501-750 gm); 42% (751-1000 gm); 57% (1001-1250 gm); and 50% (1251-1500 gm).



The boxplot shows the median, minimum, maximum, 25% and 75% percentiles for the percent for 133 NICUs.
The mean percent across all CPQCC NICUs is represented by the diamond.

Original Date:
Revised 11/30/11

Early Selective Surfactant Administration

I. Definition and Physiologic Rationale

As distinct from prophylaxis, this section refers to infants intubated for respiratory distress. The term*, early surfactant*, encompasses some variation but typically describes a policy of administering surfactant within the first two hours of life to infants intubated for early signs of respiratory distress syndrome (RDS) and/or requiring ventilation for respiratory failure. Trials that have examined the practice of early surfactant administration have defined early surfactant as surfactant administration that includes the following:

- During the first 30 minutes of life (Konishi, 1992)
- Within the first hour of life (Gortner, 1998) or
- Prior to 2 hours of life (European Exosurf Trial (1992) and the OSIRIS Trial (1992))

There is also a group of studies that evaluated the early administration of surfactant followed by brief ventilation (less than 1 hour) and extubation to later selective surfactant administration. These studies gave early surfactant to infants who developed evidence of RDS, usually at less than 24 hours of age. There were no studies in this meta analysis of the use of this technique to prevent later RDS, ie a prophylactic approach.

Studies also varied in terms of the definition of "respiratory distress". Definitions specify that the infant requires:

- Intubation and mechanical ventilation (European, Gortner)
- Intubation for early signs of respiratory distress (Konisi)
- Intubation for ventilatory assistance (Osiris)

A physiologic rationale for surfactant is provided in the published book *Chronic Lung Disease in Early Infancy*:[(JOB 00)]

> Surfactant has several effects on the pre-term, surfactant-deficient lung that results in improved lung function. These effects should decrease the need for mechanical ventilation and supplemental oxygen. Treatment of the surfactant-deficient lung changes the pressure-volume relations of the lung. The lung fills with more gas at a lower pressure and is more stable on deflation. Because dead space is changed very little, the increased gas volume is being accommodated by the recruitment of parenchymal gas volume with the potential for improved gas exchanges. The increased volume stability translates to an increased functional residual capacity. The primary clinical outcome of increased lung gas volume and functional residual capacity is improved arterial oxygenation.

[(JOB 00)] Jobe A, Influence of surfactant replacement on development of BPD. From CLD in Early Infancy, edited by Bland R, Coalson J. New York, NY: Marcel Dekker, Inc.; 2000.

II. Benefits

The 2007 Cochrane meta-analysis *Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome* summarized the benefits of such early administration followed by brief ventilation as follows:

> Early surfactant replacement therapy with extubation to NCPAP compared with later selective surfactant replacement and continued mechanical ventilation with extubation from low ventilator support is associated with a lower incidence of mechanical ventilation [typical RR 0.67, 95% CI 0.57, 0.79], air leak syndromes [typical RR 0.52, 95% CI 0.28, 0.96] and BPD [typical RR 0.51, 95% CI 0.26, 0.99]. A larger proportion of infants in the early surfactant group received surfactant than in the selective surfactant group [typical RR 1.62, 95% CI 1.41, 1.86]. The number of surfactant doses per patient was significantly greater among patients randomized to the early surfactant group [WMD 0.57 doses per patient, 95% CI 0.44, 0.69]. In stratified analysis by FIO2 at study entry, a lower threshold for treatment (FIO2< 0.45) resulted in:
>
> - lower incidence of air leak [typical RR 0.46 and 95% CI 0.23, 0.93] and
> - BPD [typical RR 0.43, 95% CI 0.20, 0.92].
>
> A higher treatment threshold (FIO2 > 0.45) at study entry was associated with:
>
> - a higher incidence of patent ductus arteriosus requiring treatment [typical RR 2.15, 95% CI 1.09, 4.13]
> - less need mechanical ventilation,
> - lower incidence of BPD and
> - fewer air leak syndromes.
>
> These data suggest that treatment with surfactant by transient intubation using a low treatment threshold (FIO2< 0.45) is preferable to later, selective surfactant therapy by transient intubation using a higher threshold for study entry (FIO2 > 0.45) or at the time of respiratory failure and initiation of mechanical ventilation.

There were no studies for this review comparing prophylactic surfactant and early extubation with a selective surfactant strategy.

More recently a multicenter study from Colombia, South America prospectively evaluated 279 infants born between 27 and 31(6/7) weeks' gestation with evidence of respiratory distress and treated with supplemental oxygen in the delivery room. (Rojas et al) Infants were randomly assigned within the first hour of life to intubation, very early surfactant, extubation, and nasal continuous positive airway pressure (treatment group) or nasal continuous airway pressure alone (control

group). The need for mechanical ventilation was lower in the treatment group (26%) compared with the control group (39%). Air- leak syndrome occurred less frequently in the treatment group (2%) compared with the control group (9%) as was the percentage of patients receiving surfactant after the first hour of life was also significantly less in the treatment group (12%) compared with the control group (26%). The incidence of chronic lung disease was 49% in the treatment group compared with 59% in the control group.

While there have been no studies comparing prophylactic with early surfactant, Hentschel et al (Hen 2009) reported on the later neurodevelopmental outcomes of infants enrolled in a previous trial that compared early (31 min) with later surfactant (202 min) (GORTNER 98) and found that the early treated infants exhibited a delay in the subscale 'personal social' of the Griffiths test and in one 'milestone' of motor development (rolling over from supine to prone), and an increased rate of elevated muscle tone. These observations will require further confirmation.

The CPQCC Surfactant Toolkit was designed to convey the message that a policy of early and/or prophylactic use of Surfactant is best considered and formulated at the hospital level, to reflect each hospital's patient population. This meta-analysis supports the statement that if an infant is eventually going to receive surfactant, it is beneficial to administer surfactant earlier rather than later. The challenge, therefore, is to identify as early as possible infants who are likely to require surfactant. Hospital-specific data are provided in the Data section of this Toolkit to help Centers meet this challenge.

Studies Included in Meta-analysis (with evidence classification):
The review constitutes Level 1 evidence; it is entirely drawn from Level 2 studies.

European Exosurf Study Group. Early or selective surfactant (Colfosceril Palmitate, Exosurf) for intubated babies at 26 to 29 weeks gestation: A European double-blind trial with sequential analysis. Online J Curr Clin Trials 1992 Nov 10; 1992 (Doc No 28). (Level 2 evidence)

Gortner L, et al. Early versus late surfactant treatment in preterm infants of 27 to 32 weeks' gestational age: A multicenter controlled clinical trial. Pediatrics 1998;102:1153-1160. (Level 2 evidence)

Konishi M, et al. A prospective randomized trial of early versus late administration of a single dose of surfactant-TA. Early Human Development 1992;29:275-282. (Level 2 evidence)

The OSIRIS Collaborative Group. Early versus delayed neonatal administration of a synthetic surfactant - The judgement of OSIRIS. Lancet 1992; 340:1363-1369. (Level 2 evidence)

TP Stevens, M Blennow, EW Myers, R Soll. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD003063. DOI: 10.1002/14651858.CD003063.pub3.

Included studies from this review:

Dani C, Bertini G, Pezzati M, Cecchi A, Caviglioli C, Rubaltelli FF. Early extubation and nasal continuous positive airway pressure after surfactant treatment in preterm infants of less than 30 weeks' gestation. Pediatrics 2004;**113**:e560-3.

Haberman B, Shankaran S, Stevenson DK, Papile LA, Stark A, Korones S, et al. Does surfactant and immediate extubation to nasal continuous positive airway pressure reduce use of mechanical ventilation?. Pediatric Research 2002;**51**:349A.

Reininger A, Khalak R, Kendig JW, Ryan RM, Stevens TP, Reubens L, D'Angio CT. Surfactant administration by transient intubation in infants 29 to 35 weeks' gestation with respiratory distress syndrome decreases need of later mechanical ventilation: a randomized controlled trial. Journal of Perinatology 2005;**25**:703-8.

The Texas Neonatal Research Group, 2004. Early surfactant for neonates with mild to moderate respiratory distress syndrome: A multicenter randomized trial. Journal of Pediatrics 2004;**144**:804-8.

Verder H, Robertson B, Greisen G, Ebbesen F, Albertsen P, Lundstrom K, et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. The New England Journal of Medicine 1994;**331**:1051-5.

Soll RF, Conner JM, Howard D and the Investigators of the Early Surfactant Replacement Study. Early surfactant replacement in spontaneously breathing premature infants with RDS. Pediatric Research 2003:Late Breaker Abstract 12, PAS 2003 meeting.

Colombia Study:
Rojas, M. A.; Lozano, J. M.; Rojas, M. X.; Laughon, M.; Bose, C. L.; Rondon, M. A.; Charry, L.; Bastidas, J. A.; Perez, L. A.; Rojas, C.; Ovalle, O. ; Celis, L. A.; GarciaHarker, J., and Jaramillo, M. L. Very Early Surfactant Without Mandatory Ventilation in Premature Infants Treated With Early Continuous Positive Airway Pressure: A Randomized, Controlled Trial. Pediatrics. 2009; 123(1):137-142

Perinatal Quality Improvement Panel Comments on surfactant administration practice:

In this more recent meta-analysis of surfactant timing, ***early*** surfactant administration is compared to ***delayed*** administration. Early surfactant is given at less than 1 or 2 hours of age to patients who require ventilation for respiratory failure; delayed administration is given only to patients who develop severe RDS. Similar to the meta-analysis of prophylactic administration, systematic review of early selective administration studies shows a significant decrease in pneumothorax, PIE, mortality and the combined outcome of mortality or BPD, when compared to delayed administration. Neither prophylaxis nor early surfactant administrations decrease the incidence of BPD when analyzed by itself.

Two of the four early surfactant studies reported total number of surfactant doses, which were significantly increased in the early surfactant group compared to the delayed group. The pooled data show that it takes an estimated 8.5 doses of surfactant to prevent one case of death or BPD at 36 weeks. Although this represents a significant drug expense, the financial and societal costs associated with BPD and/or death are far greater. Thus the strategy of early surfactant administration would be both clinically prudent and cost beneficial.

Significant differences were noted between studies in the timing of the first dose. Konishi (1992) administered the early dose of surfactant within the first 30 minutes of life. The European Exosurf Trial (1992) and the OSIRIS Trial (1992) both defined early treatment as prior to 2 hours of life. Gortner (1998) used 1 hour of life as the cut-off for early treatment.
Studies varied by birth weight and GA inclusion criteria (highest 1500 gm and 32 wks) and degree of "respiratory distress".

The studies evaluating the administration of surfactant with rapid extubation suggest that this is a viable approach. Most infants in these studies and the study from Colombia (Rojas 2009) were > 25 weeks of gestation and included infants up to 35 weeks of gestation, and thus more immature infants may not demonstrate the same benefit. This approach requires further testing in such populations.

III. Risks

Toxicity: Surfactant administration can produce transient bradycardia or oxygen desaturation often associated with airway obstruction. Careful weaning of oxygen supplementation and assisted ventilation is essential to avoid hyperoxia or excessive ventilation.[(BEN 95)] Meta-analysis did not find an increase in severe intracranial hemorrhage[(SOL 97)]; reports from individual trials have shown trends for both increases and decreases in ICH rates.

Intubation: Prophylactic surfactant carries the additional risk of intubation in order to administer the agent. Complications of intubation include: local trauma, cardiopulmonary compromise during the procedure, pulmonary interstitial emphysema and air leak syndromes, tube blockage, inadvertent right mainstem intubation, subglottic stenosis, post-extubation stridor, and bacterial colonization.[(DAS 97)] [(RIV 92)]
One approach used to deliver early selective surfactant is to “Intubate, administer surfactant and extubate”. In light of the American Academy of Pediatric’s most recent statement on

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[(BEN 95)] Benitz W, Tatro D. *The Pediatric Handbook*. St. Louis, MO: Mosby; 1995:146.
[(SOL 97)] Soll RF, Morley FJ. The Cochrane Database of Systematic Reviews: Prophylactic versus selective use of surfactant for preventing morbidity and mortality in preterm infants. *The Cochrane Library*. 1997.
[(DAS 97)] Da Silva O, Stevens D. Complications of airway management in very-low-birth-weight infants. *Biol Neonate*. 1997;5:40-5
[(RIV 92)] Rivera R, Tibballs J. Complications of endotracheal intubation and mechanical ventilation in infants and children. *Crit Care Med*. 1992;20:193-9.
(Hen 2009)Hentschel, R.; Dittrich, F.; Hilgendorff, A.; Wauer, R.; Westmeier, M., and Gortner, L. (Neurodevelopmental outcome and pulmonary morbidity two years after early versus late surfactant treatment: does it really differ? Acta Paediatrica. 2009; 98(4):654-659

"Premedication for the non-emergent endoctracheal intubation", there may be a delay in extubation due to respiratory depression secondary to the medications used. This may add to the potential lung injury caused by mechanical ventilation.

IV. Benchmarking

CPQCC centers submit standardized data forms for very low birth weight infants to the CPQCC Data Center where they are reviewed for errors and omissions. These forms contain information on nearly 50 variables. Question 34 of the Discharge form records whether an infant received oxygen at 36 weeks adjusted gestational age. Question 21 of the Discharge form records whether or not an infant received exogenous surfactant at any time. If yes, the postnatal age in hours and minutes is also entered.

CPQCC Data Center submits data to Vermont Oxford Network (VON) for analysis. CPQCC/VON aggregates data and computes indicators that reflect clinical procedures and outcomes. Each Center receives its respective set of indicators as well as the national and CPQCC (state) median and interquartile range for each indicator in the CPQCC quarterly report. Indicators are displayed in graphs to facilitate comparisons. The following tables/figures can be generated for your center using's the VON Nightingale Reporting features:

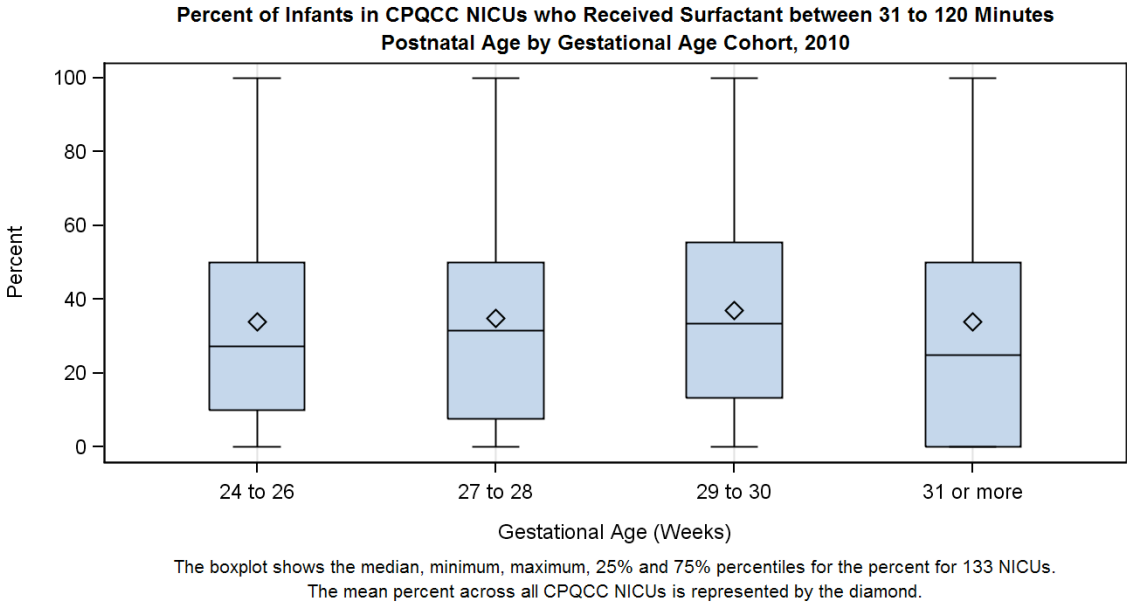
Table Respiratory outcomes and Interventions Percentages at your Hospital and Percentile Ranks Relative to all NICUs of your "type." Comparisons with the national dataset that comprise VON hospitals of a like type can be made by making the appropriate selections in the Nightingale report generator: Comparisons with the CPQCC dataset that comprise California hospitals of a like type can be made by examining the California-only version of the same Table by accessing the CPQCC Report generator and making similar selections. As a reminder, we repeat the definitions of each category.

> Type A NICUs are Centers that have a restriction on assisted ventilation (infants transferred to another hospital for assisted ventilation based on either patient characteristics or the duration of assisted ventilation) or that only perform minor surgery
>
> Type B NICUs are Centers with no restriction on assisted ventilation and which perform major surgery. Major surgery includes one or more the following: omphalocoele repair, ventriculoperitioneal shunt; TEF/esophageal atresia repair; bowel resection/reanastomosis; meningomyelocoele repair; cardiac catherization or PDA ligation.
>
> Type C NICUs are Centers that perform cardiac surgery requiring bypass for newborn infants.

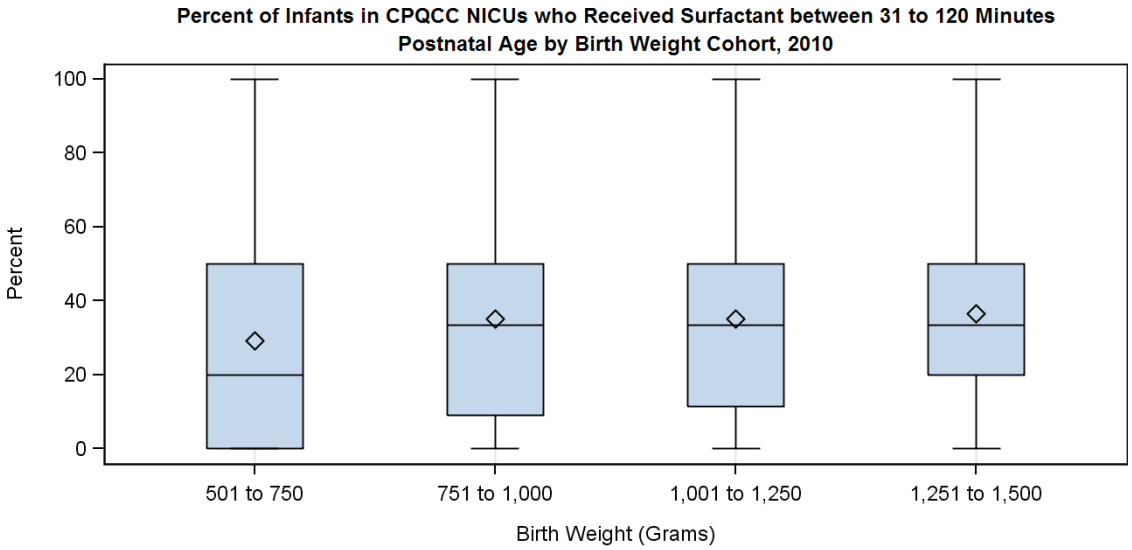
Early selective surfactant administration: CPQCC member use of early selective surfactant is presented both by gestational age and birthweight cohorts. The following charts display by gestational age and birthweight CPQCC's indicator, albeit imprecise, for implementation of the

early selective surfactant strategy. If an infant received surfactant between 31 and 120 minutes postnatal age (regardless of where intubated), then we classify the infant as having received early selective surfactant (numerator). (Note: infants who receive surfactant prior to 30 minutes are classified having been treated according to the prophylactic strategy.) The denominator consists of all those delivered in that gestational age or birth weight cohort. The benchmark rate is established by determining the 75th percentile of the rates among hospitals for each gestational age or birth weight cohort (2010 dataset). Hospitals with less than six infants in a cohort are excluded from the analysis.

Per Cent of Infants in each CPQCC NICU Who Received Surfactant Between 31-120 minutes Postnatal Age By Gestational Age Cohort. Box shows percentages for the mean, 25th and 75th percentiles of these NICUs (2010 Dataset)



Per Cent of Infants in each CPQCC NICU Who Received Surfactant Between 31-120 minutes Postnatal Age By Birthweight Cohort. Box shows percentages for the mean, 25th and 75th percentiles of these NICUs (2010 Dataset)



The boxplot shows the median, minimum, maximum, 25% and 75% percentiles for the percent for 133 NICUs.
The mean percent across all CPQCC NICUs is represented by the diamond.

Comparing the Three Options for Improving Lung Function

Treatment of RDS with Early Nasal CPAP: Delivery of nasal CPAP, commencing at 6 cms H2O pressure, during the first two hours of life and/or at the first signs of RDS. COMMENDED PRACTICE	**Prophylactic Surfactant:** The practice of giving surfactant within the first few minutes of life, and prior to establishment of respiratory distress. COMMENDED PRACTICE	**Early Selective Surfactant:** Surfactant administration to infants intubated for respiratory distress within the first two hours of life. This section also includes the use of early surfactant followed by early extubation. COMMENDED PRACTICE
Randomized Controlled Trials: **A. SUPPORT** Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Early CPAP versus Surfactant in Extremely Preterm Infants. N Engl J Med. 2010 May 27;362(21):1959-69. **Conclusions**: The rates of the primary outcome (death/BPD) did not differ significantly between the CPAP group and the surfactant group. Infants who received CPAP treatment, as compared with infants who received surfactant treatment, less frequently required intubation or postnatal corticosteroids for bronchopulmonary dysplasia, required fewer days of mechanical ventilation, and were more likely to be alive and free from the need for mechanical ventilation by day 7. The results of this study support consideration of CPAP as an alternative to intubation and surfactant in preterm infants. B. **COIN trial**: Morley, C. J.; Davis, P.	**Meta-analysis:** RF Soll, CJ Morley. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 2001, Issue 2. Art. No.: CD000510. DOI: 10.1002/14651858.CD000510. **Conclusions**: Prophylactic surfactant administration to infants judged to be at risk for developing respiratory distress syndrome has been demonstrated to improve clinical outcome. Infants who receive prophylactic surfactant have a decreased risk of pneumothorax, a decreased risk of pulmonary interstitial emphysema and a decreased risk of mortality. What is unclear from this study is exactly what criteria will be chosen to judge "risk" in these infants. Although most studies chose to study infants less than 30 weeks gestation, Kattwinkel (1993) demonstrated significant clinical improvements in infants of somewhat older gestational age (29-32 weeks). It is also unclear how aggressive physicians	**Early Surfactant with conventional ongoing ventilation:** **Meta-analysis:** Yost, CC and Soll, RF. The Cochrane Database of Systematic Reviews: Early versus Delayed Selective Surfactant Treatment for Neonatal Respiratory Distress Syndrome. 1999. The Cochrane Library. 2000 update. **Conclusions:** Early surfactant administration significantly reduces the risk of key clinical outcomes including pneumothorax, PIE, chronic lung disease, and neonatal mortality. Given the efficacy of prophylactic surfactant therapy,[(SOL 97)] this meta-analysis suggests that early selective surfactant administration to intubated infants with early signs of RDS may be part of a clinical spectrum of improved outcomes with earlier treatment. The difficulty of judging which infant is at risk for surfactant deficiency continues. The meta-analysis would suggest that neonates with early respiratory distress should be given surfactant as early as possible. Improved identification of the infant at risk for RDS will improve the selection criteria for prophylactic or early selective surfactant therapy. Given the difficulty in determining

[(SOL 97)] Soll RF, Morley CJ. The Cochrane Database of Systematic Reviews: Prophylactic surfactant vs. treatment with surfactant. *The Cochrane Library*; 2000 update. 1997.

G.; Coyle, L. W.; Brion, L. P.; Hascoet, J. M., and Carlin, J. B. Nasal CPAP or intubation at birth for very preterm infants. New England Journal of Medicine. 2008; 358(7):700-708 **Conclusions:** In infants born at 25-to-28-weeks' gestation, early nasal CPAP did not significantly reduce the rate of death or bronchopulmonary dysplasia, as compared with intubation. Even though the CPAP group had more incidences of pneumothorax, fewer infants received oxygen at 28 days, and they had fewer days of ventilation. C. **CURPAP:** Sandri, F, Plavka, R, Ancora,G, Simeoni, U Stranak, Z, Martinelli S et al. Prophylactic or Early Surfactant Combined with nCPAP in Very Preterm Infants . PEDIATRICS Vol. 125 No. 6 June 2010, pp. e1402-e1409 **Conclusions:** Prophylactic surfactant was not superior to nCPAP and early selective surfactant in decreasing the need for MV in the first 5 days of life and the incidence of main morbidities of prematurity in spontaneously breathing very preterm infants on nCPAP D. **VON DR study**: Dunn, M, Kaempf, J, de Klerk,, A de Klerk, R, Reilly, M, Howard, D, Ferrelli, K, Soll, R.Delivery Room Management of Preterm Infants at Risk for Respiratory Distress Syndrome (RDS). Pediatric Academic Societies, 2010 Vancouver, E-PAS20101670.2	should be regarding demonstrations of lung immaturity prior to surfactant treatment. **2000 Version**: Prophylactic surfactant administration to infants judged to be at risk of developing respiratory distress syndrome (intubated infants less than 30-32 weeks gestation) has been demonstrated to improve clinical outcome. Infants who receive prophylactic surfactant have a decreased incidence of pneumothorax, a decreased incidence of pulmonary interstitial emphysema and a decreased incidence of mortality. However, it remains unclear exactly which criteria should be used to judge "at risk" infants who would require prophylactic surfactant administration.	which infant is at risk for respiratory distress syndrome and the known over-treatment of some infants with prophylactic surfactant therapy, further comparison of prophylactic versus very early selective surfactant treatment might provide further insight into the optimal timing for surfactant treatment. **Early Selective Surfactant followed by Extubation** **Meta-analysis:** TP Stevens, M Blennow, EW Myers, R Soll. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003063. **Conclusions**: Early surfactant replacement therapy with extubation to NCPAP compared with later selective surfactant replacement and continued mechanical ventilation with extubation from low ventilator support is preferable to later, selective surfactant therapy by transient intubation using a higher threshold for study entry (FIO2 > 0.45) or at the time of respiratory failure and initiation of mechanical ventilation E. Columbia study: Rojas, M. A.; Lozano, J. M.; Rojas, M. X.; Laughon, M.; Bose, C. L.; Rondon, M. A.; Charry, L.; Bastidas, J. A.; Perez, L. A.; Rojas, C.; Ovalle, O. ; Celis, L. A.; GarciaHarker, J., and Jaramillo, M. L. Very Early Surfactant Without Mandatory Ventilation in Premature Infants Treated With Early Continuous Positive Airway Pressure: A Randomized, Controlled Trial. Pediatrics. 2009; 123(1):137-142 Conclusions: In premature infants treated with

Conclusions: There were no differences were seen in the primary outcome of death or BPD at 36 weeks postmenstrual age, mortality, other complications of prematurity or the composite outcome of death or major morbidity (severe ROP, CLD, PVL or severe IVH) between their groups. E. Columbia study: Rojas, M. A.; Lozano, J. M.; Rojas, M. X.; Laughon, M.; Bose, C. L.; Rondon, M. A.; Charry, L.; Bastidas, J. A.; Perez, L. A.; Rojas, C.; Ovalle, O. ; Celis, L. A.; GarciaHarker, J., and Jaramillo, M. L. Very Early Surfactant Without Mandatory Ventilation in Premature Infants Treated With Early Continuous Positive Airway Pressure: A Randomized, Controlled Trial. Pediatrics. 2009; 123(1):137-142 Conclusions: In premature infants treated with nasal continuous positive airway pressure early after birth, the addition of very early surfactant therapy without mandatory ventilation decreased the need for subsequent mechanical ventilation, decreased the incidence of air-leak syndrome, and seemed to be safe. **Conclusions:** In preterm infants with RDS the application of CDAP either as CPAP or CNDP is associated with benefit – There is a reduction in death/BPD in the overall meta analyses of all current trials, and the SUPPORT trial, the largest study and the only one to include infants of 24 weeks gestation found a significant reduction in mortality in the most immature infants		nasal continuous positive airway pressure early after birth, the addition of very early surfactant therapy without mandatory ventilation decreased the need for subsequent mechanical ventilation, decreased the incidence of air-leak syndrome, and seemed to be safe.

	Anticipated Benefits: decreased incidence of pneumothorax, (relative risk 0.62, 95% CI 0.42, 0.89), a decreased incidence of pulmonary interstitial emphysema (relative risk 0.54, 95% CI 0.36, 0.82), and a decreased incidence of mortality (relative risk 0.59, 95% CI 0.46, 0.76)	**Anticipated Benefits of Early Surfactant:** significant reductions in risk of pneumothorax (Typical RR 0.70, 95%CI 0.59, 0.82), pulmonary interstitial emphysema (Typical RR 0.63, 95%CI 0.43, 0.93), decreased risk of neonatal mortality (Typical RR 0.87, 95%CI 0.77, 0.99), chronic lung disease (Typical RR 0.70, 95%CI 0.55, 0.88), chronic lung disease or death at 36 weeks (Typical RR 0.84, 95%CI 0.75, 0.93).
	Considerations: Although prophylactic administration will increase exposure to treatment and cost of treatment (approximately twice as many infants at risk for respiratory distress will receive surfactant using the prophylactic approach), the clinical benefits appear great enough to warrant these expenses. Other than expense, no mitigating outcomes are noted in the meta-analysis to lead to concern about using the prophylactic approach. In a secondary analysis including only enrolled infants less than 30 weeks gestation, similar clinical improvements are noted……)…. The meta-analysis suggests that for every 100 infants treated prophylactically, there will be 2 fewer pneumothoraces, and 5 fewer deaths.	**Anticipated Benefits of Selective Surfactant followed by Extubation:** a lower incidence of mechanical ventilation [typical RR 0.67, 95% CI 0.57, 0.79], air leak syndromes [typical RR 0.52, 95% CI 0.28, 0.96] and BPD [typical RR 0.51, 95% CI 0.26, 0.99]. In stratified analysis by FIO2 at study entry, a lower threshold for treatment (FIO2< 0.45) resulted in lower incidence of airleak [typical RR 0.46 and 95% CI 0.23, 0.93] and BPD [typical RR 0.43, 95% CI 0.20, 0.92]. A higher treatment threshold (FIO2 > 0.45) at study entry was associated with a higher incidence of patent ductus arteriosus requiring treatment [typical RR 2.15, 95% CI 1.09, 4.13] less need mechanical ventilation, lower incidence of BPD and fewer air leak syndromes
	Reports not included in Cochrane MetaAnalysis: Not applicable	**Considerations:** It is difficult to compare the use of surfactant in these studies with prophylactic surfactant. These studies suggest that for infants of 25 weeks or greater, who have RDS and an oxygen requirement, that the administration of surfactant followed by an early attempt to extubate the infant will result in lesser morbidity. There is a need to evaluate the use of prophylactic or earlier surfactant followed by early extubation compared with rescue

		surfactant as is being done in the VON trial .
	Implementation Issues: 1. Defining gestational age/birthweight threshold for your perinatal center; 2. Organizing team effort to apply practice uniformly and safely.	**Implementation Issues:** 1. Defining RDS criteria for "early" intervention for your perinatal center; 2. Defining the criteria for surfactant administration 3. Instituting an early extubation practice following surfactant administration 4. Organizing team effort to apply practice uniformly and safely.