AARC Clinical Practice Guideline. Surfactant Replacement Therapy: 2013

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We searched the MEDLINE, CINAHL, and Cochrane Library databases for English-language randomized controlled trials, systematic reviews, and articles investigating surfactant replacement therapy published between January 1990 and July 2012. By inspection of titles, references having no relevance to the clinical practice guideline were eliminated. The update of this clinical practice guideline is based on 253 clinical trials and systematic reviews, and 12 articles investigating surfactant replacement therapy. The following recommendations are made following the Grading of Recommendations Assessment, Development, and Evaluation scoring system: 1: Administration of surfactant replacement therapy is strongly recommended in a clinical setting where properly trained personnel and equipment for intubation and resuscitation are readily available. 2: Prophylactic surfactant administration is recommended for neonatal respiratory distress syndrome (RDS) in which surfactant deficiency is suspected. 3: Rescue or therapeutic administration of surfactant after the initiation of mechanical ventilation in infants with clinically confirmed RDS is strongly recommended. 4: A multiple surfactant dose strategy is recommended over a single dose strategy. 5: Natural exogenous surfactant preparations are recommended over laboratory derived synthetic suspensions at this time. 6: We suggest that aerosolized delivery of surfactant not be utilized at this time. *Key words: exogenous surfactant administration; intratracheal administration; prematurity; neonatal respiratory distress syndrome; surfactant*. [Respir Care 2013;58(2):367–375. © 2013 Daedalus Enterprises]

SRT 1.0 PROCEDURE

Surfactant replacement therapy

SRT 2.0 DESCRIPTION/DEFINITION

Endogenous surfactant is a biochemical compound composed of phospholipids, neutral lipids, and proteins[1–3] that forms a layer between the terminal airways/alveolar surfaces and the alveolar gas. In 1961, Klaus and colleagues were the first to isolate alveolar surfactant from bovine lungs, and extracted a phospholipid fraction that displayed a surface active behavior.[4] Ten years later, Gluck et al discovered a technique that allows fetal lung maturity to be measured using the lecithin/sphingomyelin ratio in amniotic fluid.[5] Surfactant is secreted by the type-II pneumocyte and functions to reduce lung collapse during end-exhalation by decreasing surface tension within the terminal airways and alveoli.[2,6] Infants who are born prematurely are more likely to have lungs that are surfactant-deficient at birth. Surfactant deficiency is associated with onset of respiratory distress syndrome (RDS), a major cause of morbidity and mortality in premature infants.[2] Surfactant is also effective in treating infants with meconium aspiration syndrome (MAS), pulmonary hemorrhage,[7] and pneumonia, although the evidence base for their use in these disease processes is much weaker than the primary indication of RDS.[8,9] Surfactant reduces surface tension, improves lung compliance, and stabilizes lung volumes at a

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lower transpulmonary pressure.[10] Without surfactant, alveoli may never inflate or may collapse on expiration and require an inordinate amount of force to re-expand on inspiration, leading to the development of severe RDS and air leak syndromes.[2,6] Surfactant's secondary function is to enhance macrophage activity and mucociliary clearance, and to reduce inflammation.[11] The incidence of RDS is related more to lung immaturity than to gestational age.[12] However, in general, the more premature the infant, the less the surfactant production and the higher the probability for RDS.[12] Mechanical ventilation is often necessary for the treatment of RDS; however, ventilator-induced lung injury can deactivate the production of endogenous surfactant production and compromise the therapeutic effect of surfactant replacement therapy.[13] Direct tracheal instillation of surfactant has been shown to reduce mortality and morbidity in infants with RDS.[14–29]

Exogenous lung surfactant can be either natural or synthetic. Natural surfactant is extracted from animal sources such as bovine or porcine. Synthetic surfactant is manufactured from compounds that mimic natural surfactant properties. Both forms of surfactant replacement are effective at reducing the severity of RDS; however, comparative trials demonstrate greater early improvement in the requirement for ventilatory support and fewer pneumothoraces associated with natural surfactant extract treatment. On clinical grounds, natural surfactant extracts would seem to be the more desirable choice.[30]

Two basic strategies for surfactant replacement have emerged: prophylactic or preventive treatment, in which surfactant is administered at the time of birth or shortly thereafter to infants who are at high risk for developing RDS from surfactant deficiency; and rescue or therapeutic treatment, in which surfactant is administered after the initiation of mechanical ventilation in infants with clinically confirmed RDS.[3,19,25,29,31,32]

Prophylactic surfactant administration to infants at risk of developing RDS is associated with lower risk of air leak and mortality, compared to selective use of surfactant in infants with established RDS.[33] Surfactant administration with brief lung-protective ventilation (followed by extubation to nasal CPAP) for premature infants at risk for developing RDS is associated with a lower incidence of mechanical ventilation, air leak syndromes, and chronic lung disease, compared to selective surfactant and continued mechanical ventilation.[34]

Surfactant is traditionally administered by instilling through the ETT, but can also be delivered effectively by injection through the nasopharynx during delivery[35] or by using a thin catheter.[36] Experimental evidence also supports the delivery of some surfactants using a nebulizer.[37] Some early promising studies also look at using surfactant as a delivery agent for the administration of steroids directly to the lungs.[9]

SRT 3.0 SETTINGS

Surfactant is administered by trained personnel in:

3.1 Delivery room

3.2 ICU

3.3 Newborn nursery (if awaiting external transport to ICU)

3.4 Institutions that have the ability to perform neonatal resuscitation and stabilization procedures[38]

SRT 4.0 INDICATIONS

4.1 Prophylactic administration may be indicated in:

4.1.1 Premature infants at high risk of developing RDS secondary to surfactant deficiency (eg $<$ 32 weeks or low birth weight $<$ 1,300 g)[15–17,19,21,25,26,29,31,32,39,40]

4.1.2 Infants in whom there is laboratory evidence of surfactant deficiency such as lecithin/sphingomyelin ratio $<$ 2:1,[41] bubble stability test indicating lung immaturity,[42] or the absence of phosphatidylglycerol[43]

4.2 Rescue or therapeutic administration may be indicated in preterm or full-term infants who are suspected of having surfactant deficiency by inactivation and

4.2.1 who require endotracheal intubation and mechanical ventilation secondary to respiratory failure[20,44,45] and

4.2.2 who require an $F_{IO_2} \geq 0.40$,[46,47] and

4.2.2.1 Clinical and radiographic evidence of neonatal RDS or MAS,[48,49] including:

4.2.2.2 neonates with mean airway pressure $>$ 7 cm H_2O to maintain an adequate P_{aO_2}, arterial oxygen saturation, or S_{pO_2}.[19,20,26,27,29,32,45,46,50–54]

4.3 Surfactants may be used as a vehicle to deliver other drugs such as antibiotics, anti-inflammatory agents, and bronchodilators.[9]

4.4 Postoperative development of ARDS following cardiac surgery. The use of exogenous surfactant reduces time on positive-pressure ventilation and reduces the ICU and hospital stay.[55]

4.5 Treatment of severe respiratory syncytial virus-induced respiratory failure with porcine surfactant may improve gas exchange and respiratory mechanics and shorten the duration of invasive mechanical ventilation and hospital stay.[56]

SRT 5.0 CONTRAINDICATIONS

Relative contraindications to surfactant administration are:

5.1 the presence of congenital anomalies incompatible with life beyond the neonatal period[26–28,32,40,41,53,54,57]

5.2 respiratory distress in infants with laboratory evidence of lung maturity[31,40,53,54]

5.3 diagnosis of congenital diaphragmatic hernia. The congenital diaphragmatic hernia study group enrolled 2,376 patients into their registry and found that early use of surfactant (< 1 hour post birth) did not alter the odds ratio, when compared with the no surfactant group, and those with immediate distress receiving surfactant had greater odds of death than the group who did not receive surfactant.[58,59] Furthermore, it is also plausible that administration of surfactant may cause a clinical deterioration in infants with substantial pulmonary hypoplasia, although further randomized controlled trials are needed to confirm.[60]

5.4 patient hemodynamically unstable

5.5 active pulmonary hemorrhage

SRT 6.0 HAZARDS/COMPLICATIONS

6.1 Procedural complications resulting from the administration of surfactant include:

- **6.1.1** plugging of endotracheal tube (ETT) by surfactant[3]
- **6.1.2** hemoglobin desaturation and increased need for supplemental O_2[29,54]
- **6.1.3** bradycardia due to hypoxia[54,61]
- **6.1.4** tachycardia due to agitation, with reflux of surfactant into the ETT[45,54]
- **6.1.5** pharyngeal deposition of surfactant
- **6.1.6** administration of surfactant to only one lung (ie, right mainstem intubation)
- **6.1.7** administration of suboptimal dose

6.2 Physiologic complications of surfactant replacement therapy include:

- **6.2.1** apnea[24,28,49]
- **6.2.2** pulmonary hemorrhage from right to left shunting[18,19,28,42,45,47,62,63]
- **6.2.3** increased necessity for treatment for patent ductus arteriosus[18,29,39,43,64]
- **6.2.4** marginal increase in retinopathy of prematurity[29]
- **6.2.5** volutrauma resulting from increase in lung compliance following surfactant replacement and failure to change ventilator settings accordingly[43,65]
- **6.2.6** hyperventilation from 6.2.5 and hypoventilation from 6.1.1, 6.2.1, 6.2.3, both of which can alter blood flow to the brain, leading to further complications.

6.3 Early surfactant therapy strategies increase the number of infants receiving surfactant, leading to more infants exposed to potential risks of intubation, mechanical ventilation, and surfactant administration.[34,48,66]

SRT 7.0 LIMITATIONS OF METHOD

7.1 Surfactant administered prophylactically may be given to some infants in whom neonatal RDS would not have developed.[19,25,32]

7.2 When surfactant is administered prophylactically in the delivery room, ETT placement may not have been verified by chest radiograph, resulting in the inadvertent administration to only one lung or to the stomach.[32]

7.3 Prophylactic surfactant administration may delay patient stabilization.[32]

7.4 Atelectasis and lung injury may occur prior to therapeutic administration.[32]

7.5 Tracheal suctioning should be avoided immediately following surfactant administration if ventilation can be adequately maintained.[23,27,29,31,47,49,57,67] Most studies suggest a time period of 1–6 hours following surfactant delivery.[23,31,57] Therefore, we recommend using good clinical judgment and tracheal suctioning following surfactant, as needed.

7.6 Not all infants who are treated with a single dose of surfactant experience a positive response,[48] or the response may be transient.

7.7 Positioning recommended for surfactant administration may further compromise the unstable infant.[47,52]

SRT 8.0 ASSESSMENT OF NEED

Determine that valid indications are present.

8.1 Assess lung immaturity prior to prophylactic administration of surfactant by gestational age and birth weight and/or by laboratory evaluation of tracheal or gastric aspirate.

8.2 Establish the diagnosis of neonatal RDS by chest radiographic criteria and the requirement for mechanical ventilation in the presence of short gestation and/or low birth weight.

SRT 9.0 ASSESSMENT OF OUTCOME

9.1 Reduction in F_{IO_2} requirement[45,46,54]

9.2 Reduction in work of breathing[68]

9.3 Improvement in aeration, as indicated by chest radiograph[52]

9.4 Improvement in pulmonary mechanics (compliance, airways resistance) and lung volume (functional residual capacity)[51,67,69–73]

9.5 Reduction in ventilator support (peak inspiratory pressure, PEEP, airway pressure)[46,54,69]

9.6 Improvement in ratio of arterial to alveolar P_{O_2} and oxygen index[45,46,52,54]

SRT 10.0 RESOURCES

Administration procedures recommended for specific preparations of surfactant should be adhered to.

10.1 Equipment:[19,20,25,31,45,48,52,67,74]

10.1.1 Administration equipment

10.1.1.1 Syringe containing the ordered dose of surfactant, warmed to room temperature or manufacturer's recommendation[19,47,52]

10.1.1.2 Appropriate size feeding tube or catheter, ETT connector with delivery port, or closed catheter system

10.1.1.3 Mechanical ventilator with tidal volume monitoring capability[67,69]

10.1.2 Resuscitation equipment

10.1.2.1 Laryngoscope and appropriately sized ETT[19,20,25,47]

10.1.2.2 Manual resuscitator[19,25,31,52,67] that is capable of providing PEEP/CPAP, and airway manometer[75]

10.1.2.3 Blended oxygen source capable of delivering F_{IO_2} of 0.21–1.0[57]

10.1.2.4 Suction equipment (ie, catheters, sterile gloves, collecting bottle and tubing, and vacuum generator)[74]

10.1.2.5 Radiant warmer ready for use as applicable

10.1.3 Monitoring equipment

10.1.3.1 Tidal volume monitor, if available (if not within ventilator)[67]

10.1.3.2 Pulse oximeter[29,32,45,48,52,54,69]

10.1.3.3 Cardiorespiratory monitor

10.2 Personnel: Surfactant replacement therapy should be performed by healthcare providers who are proficient at administering surfactant and capable of handling adverse events.

10.2.1 Proper use, understanding, and mastery of the equipment and technical aspects of surfactant replacement therapy[9,38]

10.2.2 Comprehensive knowledge and understanding of ventilator management and pulmonary anatomy and pathophysiology

10.2.3 Patient assessment skills, including the ability to recognize and respond to adverse reactions and/or complications of the procedure

10.2.4 Knowledge and understanding of the patient's history and clinical condition

10.2.5 Knowledge and understanding of airway management

10.2.6 Ability to interpret monitored and measured blood gas variables and vital signs

10.2.7 Proper use, understanding, and mastery of emergency resuscitation equipment and procedures, including intubation

10.2.8 Ability to evaluate and document outcome (section 9.0)

10.2.9 Understanding and proper application of universal precautions

SRT 11.0 MONITORING

The following should be monitored as part of surfactant replacement therapy.

11.1 Proper placement and position of delivery device and ETT

11.2 F_{IO_2} and ventilator settings[31,47,57]

11.3 Reflux of surfactant into ETT[45,54]

11.4 Position of patient[23,29]

11.5 Chest-wall movement[76]

11.6 Oxygen saturation by pulse oximetry[29,32,45,48,52,54,69]

11.7 Vital signs[20,31,32,45,54,61,69]

11.8 Pulmonary mechanics and tidal volumes

11.9 Breath sounds[29,47]

11.10 Following administration, the below may be obtained:

11.10.1 Invasive and/or noninvasive measurements of arterial blood gases[19,20,23,26–29,31,32,39,40,47–49,54,57]

11.10.2 Chest radiograph[19,20,27–29,47,49,52,57]

SRT 12.0 FREQUENCY

In infants at high risk of respiratory distress, a policy of multiple doses of surfactant has resulted in greater improvements regarding oxygenation and ventilatory requirements, a decreased risk of necrotizing enterocolitis, and decreased mortality.[77] The ability to give multiple doses of surfactant to infants with ongoing respiratory insufficiency appears to be the most effective treatment regimen.[38] Repeat doses of surfactant are contingent upon the continued diagnosis of neonatal RDS. The frequency with which surfactant replacement is performed should depend upon the clinical status of the patient and the indication for performing the procedure. Additional doses of surfactant, given at 6–24-hour intervals, may be indicated in infants who experience increasing ventilator requirements or whose conditions fail to improve after the initial dose.[24,32,43,45,46]

SRT 13.0 CURRENTLY AVAILABLE INTRATRACHEAL SUSPENSIONS (Table)

13.1 As of March 6, 2012, Lucinactant is the first synthetic peptide-containing surfactant cleared by the FDA for use to treat neonatal RDS.

13.1.1 When compared in clinical trials, lucinactant, was found to have similar rates of mortality and morbidity as did beractant and poractant alfa.[38]

13.2 A major component of animal derived surfactants (beractant, calfactant, and poractant alfa) is sur-

Table. Currently Available Surfactants

	Trade Name	Source	Manufacturer	Dose	Surfactant Protein B
Poractant alfa	Curosurf	Porcine	Chiesi Farmaceutici	100–200 mg/kg/dose (1.25–2.5 mL/kg)	0.45
Calfactant	Infasurf	Bovine	Ony	105 mg/kg/dose (3 mL/kg)	0.26
Beractant	Survanta	Bovine	Abbott Laboratories	100 mg/kg/dose (4 mL/kg)	< 1
Lucinactant	Surfaxin	Synthetic	Discovery Labs	5.8 mL/kg	KL_4

factant protein B (SP-B). SP-B has been found to reduce surface tension to a greater extent than surfactant protein-C (SP-C). Congenital absence of SP-B at birth is lethal, while SP-C deficiency is not associated with respiratory failure.[78] Older generation synthetic surfactant preparations did not contain any peptide-chain proteins such as SP-B, which led to the universal practice of using animal derived surfactants, of which all contained variable amount of SP-B protein.[79] Lucinactant has an SP-B mimicking protein called KL_4.

13.3 Current data support the use of natural exogenous surfactant over the use of laboratory derived synthetic surfactant. Natural surfactants have shown superior surface absorption and better lowering of alveolar surface tension. In comparative randomized clinical trials, natural surfactant also showed lower oxygen requirement, lower risks of pneumothorax, bronchopulmonary dysplasia (BPD), and death.[79,80]

13.4 Synthetic preparations may have better quality control than natural surfactants, due to the batch-to-batch variations in natural surfactants. The purification procedure for natural surfactants includes extraction with organic solvents to remove hydrophilic proteins SP-A and SP-D.[79]

13.5 There is a small concern with the transmission of prion diseases from natural surfactant preparations.[81] There are some cultural and religious concerns with the use of bovine and/or porcine surfactant preparations.

SRT 14.0 INFECTION CONTROL

14.1 Universal precautions should be implemented.

14.2 Aseptic technique should be practiced and a close catheter system is preferred.

14.3 Appropriate infection control guidelines for the patient should be posted and followed.

SRT 15.0 PROPHYLACTIC VERSUS SELECTIVE TREATMENT OF RDS

15.1 Early surfactant therapy has the advantage of rapidly establishing normal surfactant levels to the lungs and improving lung mechanics, but it can expose an infant who may not develop RDS to intubation, mechanical ventilation, and expose the infant to a drug that may not be necessary.[34]

15.2 Selective treatment treats only infants with symptoms of RDS, but this technique has the potential to delay surfactant administration and allow the lung inflammation and protein-containing fluid influx to impair gas exchange.[64]

15.3 Prophylactic and early surfactant replacement therapy (within 2 hours of birth)[66] reduces mortality and pulmonary complications in mechanically ventilated infants with RDS, compared to later selective administration.[34]

15.4 A lower treatment threshold of $F_{IO_2} < 0.45$ reduces the incidence of air leak syndromes (pulmonary interstitial emphysema and pneumothorax) and BPD.[34]

15.5 A higher treatment threshold of $F_{IO_2} > 0.45$ is associated with an increased risk of patent ductus arteriosus.[34]

15.5.1 There is evidence of as much as a 22 mm Hg change in mean arterial pressure immediately (within 15 min) of administering surfactant, leading to a hemodynamically important ductus arteriosus.[64]

15.6 Early surfactant therapy followed by planned extubation at 1 hour to nasal CPAP significantly reduces the incidence of BPD, compared to selective administration of surfactant.[34,66]

16.0 DEVELOPMENTAL OUTCOMES

16.1 Early treatment of RDS (within 2 hours of birth) to infants < 30 weeks gestation was associated with fewer long-term clinical pulmonary complications than assignment to a selective administration group.[82]

16.2 Surfactant replacement therapy (early or selective methods) has been associated with reduced mortality, without any increase in neuro-developmental disability in survivors at 1–2 year follow-up examinations.[83]

17.0 DELIVERY TECHNIQUES

17.1 INSURE *(In*tubation, *Sur*factant, *E*xtubation)

17.1.1 This technique features early surfactant replacement therapy with prompt extubation to

nasal CPAP. The technique is associated with less need for mechanical ventilation, lower incidence of BPD, and fewer air leak syndromes, when compared with later, selective surfactant replacement therapy, mechanical ventilation, and extubation from lower ventilator settings.[34,84]

17.2 Selective surfactant replacement therapy with mechanical ventilation followed by extubation from lower ventilator settings

17.2.1 This technique is initiated upon clinical evidence of RDS, such as radiological findings, increased F_{IO_2} requirement, and/or increased work of breathing.

17.3 Pharyngeal instillation before first breath

17.3.1 As soon as the infant's head appears on the perineum or at operative incision, the mother stops pushing and the pharynx and stomach are suctioned with a catheter. The surfactant solution is then instilled into the posterior pharynx through a catheter, without direct laryngoscopy. The infant is then stimulated to breathe as soon as the shoulders and rest of the body are delivered. There have been no randomized controlled trials in humans to validate this technique. Animal studies have confirmed improvement of lung expansion and better survival rates.[84]

17.4 Laryngeal mask airway (LMA) administration

17.4.1 The LMA has been identified to require less skill to place than a traditional oral or nasal intubation with an ETT. In an animal study comparing ETT to LMA surfactant delivery, it was reported that surfactant delivery could be accomplished sooner in the LMA group with equivalent efficacy.[85] While far from conclusive, this method holds hope for areas in which ETT intubation skills are lacking.

17.5 Bronchoalveolar lavage

17.5.1 Bronchoalveolar lavage has shown promise in the treatment of MAS. An animal study conducted by Rey-Santano et al[86] demonstrated that surfactant lavage is a safe and effective alternative treatment for MAS. The synthetic surfactant Lucinactant was used, due to its properties to resist inactivation by plasma proteins and oxidants present in inflamed lungs.[86] A human trial conducted by Sinha et al, also using lucinactant, demonstrated that surfactant lavage seemed safe and effective in the treatment of MAS.[8,87]

17.6 Aerosolized surfactant

17.6.1 Although aerosolized surfactant has been studied in the treatment of adult ARDS, no clinical study has shown it to reduce mortality, stay on mechanical ventilation, need for oxygen supplementation, or stay in the ICU.[88]

17.6.2 Aerosolized surfactant and nasal CPAP could theoretically allow administration of surfactant without intubation, but the ideal preparation, dose, and route of delivery are still being researched for optimal alveolar delivery.[38]

17.7 In animal studies, distribution of intratracheally instilled surfactant has been largely determined by gravity, and unaffected by the position of the chest.[89] Therefore, leaving the chest in a horizontal position may result in the most even distribution of surfactant to the lungs.

18.0 RECOMMENDATIONS

The recommendations below are made following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.[90]

18.1 Administration of surfactant replacement therapy is strongly recommended in a clinical setting where properly trained personnel and equipment for intubation and resuscitation is readily available. (1A)

18.2 Prophylactic surfactant administration is recommended for neonatal RDS in which surfactant deficiency is suspected. (1B)

18.3 Rescue or therapeutic administration of surfactant after the initiation of mechanical ventilation in infants with clinically confirmed RDS is strongly recommended. (1A)

18.4 A multiple surfactant dose strategy is recommended over a single dose strategy. (1B)

18.5 Natural exogenous surfactant preparations are recommended over laboratory derived synthetic suspensions at this time. (1B)

18.6 We suggest that aerosolized delivery of surfactant not be utilized at this time. (2B)

19.0 RTS CPG IDENTIFYING INFORMATION

19.1 Adaptation

Original Publication: Respir Care 1994;39(8):824–829.

19.2 Guideline developers

American Association for Respiratory Care Clinical Practice Guidelines Steering Committee

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REFERENCES

1. Jobe A. Surfactant treatment for respiratory distress syndrome. Respir Care 1986;31(6):9.
2. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. AMA J Dis Child 1959;97(5 Pt 1):517-523.
3. Berry DD. Neonatology in the 1990's: surfactant replacement therapy becomes a reality. Clin Pediatr (Phila) 1991;30(3):167-172.
4. Klaus MH, Clements JA, Havel RJ. Composition of surface-active material isolated from beef lung. Proc Natl Acad Sci USA 1961;47: 1858-1859.
5. Gluck L, Kulovich MV, Borer RC Jr, Brenner PH, Anderson GG, Spellacy WN. Diagnosis of the respiratory distress syndrome by amniocentesis. Am J Obstet Gynecol 1971;109(3):440-445.
6. Hallman M, Teramo K, Ylikorkala O, Merritt TA. Natural surfactant substitution in respiratory distress syndrome. J Perinat Med 1987; 15(5):463-468.
7. Kaneko M, Watanabe J, Ueno E. Surfactant lavage and replacement in meconium aspiration syndrome with pulmonary hemorrhage. J Perinat Med 2001;29(4):351-356.
8. El Shahed AI, Dargaville P, Ohlsson A, Soll RF. Surfactant for meconium aspiration syndrome in full term/near term infants. Cochrane Database Syst Rev 2007;(3):CD002054.
9. Sweet DG, Halliday HL. The use of surfactants in 2009. Arch Dis Child Educ Pract Ed 2009;94(3):78-83.
10. Turell DC. Advances with surfactant. Emerg Med Clin North Am 2008;26(4):921-928.
11. Wright JR. Pulmonary surfactant: a front line of lung host defense. J Clin Invest 2003;111(10):1453-1455.
12. Stableman. Acute respiratory disorders in the newborn. Philadelphia: LB Lippincott; 1975:221-249.
13. Bjorklund LJ, Ingimarsson J, Curstedt T, John J, Robertson B, Werner O, et al. Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. Pediatr Res 1997;42(3):348-355.
14. Berry DD, Pramanik AK, Philips JB 3rd, Buchter DS, Kanarek KS, Easa D, et al. Comparison of the effect of three doses of a synthetic surfactant on the alveolar-arterial oxygen gradient in infants weighing ≥1250 grams with respiratory distress syndrome. American Exosurf Neonatal Study Group II. J Pediatr 1994;124(2):294-301.
15. Bose C, Corbet A, Bose G, Garcia-Prats J, Lombardy L, Wold D, et al. Improved outcome at 28 days of age for very low birth weight infants treated with a single dose of a synthetic surfactant. J Pediatr 1990;117(6):947-953.
16. Corbet A, Bucciarelli R, Goldman S, Mammel M, Wold D, Long W. Decreased mortality rate among small premature infants treated at birth with a single dose of synthetic surfactant: a multicenter controlled trial. American Exosurf Pediatric Study Group 1. J Pediatr 1991;118(2):277-284.
17. Corbet AJ, Long WA, Murphy DJ, Garcia-Prats JA, Lombardy LR, Wold DE. Reduced mortality in small premature infants treated at birth with a single dose of synthetic surfactant. J Paediatr Child Health 1991;27(4):245-249.
18. Couser RJ, Ferrara TB, Ebert J, Hoekstra RE, Fangman JJ. Effects of exogenous surfactant therapy on dynamic compliance during mechanical breathing in preterm infants with hyaline membrane disease. J Pediatr 1990;116(1):119-124.
19. Dunn MS, Shennan AT, Zayack D, Possmayer F. Bovine surfactant replacement therapy in neonates of less than 30 weeks' gestation: a randomized controlled trial of prophylaxis versus treatment. Pediatrics 1991;87(3):377-386.
20. Fujiwara T, Konishi M, Chida S, Okuyama K, Ogawa Y, Takeuchi Y, et al. Surfactant replacement therapy with a single postventilatory dose of a reconstituted bovine surfactant in preterm neonates with respiratory distress syndrome: final analysis of a multicenter, double-blind, randomized trial and comparison with similar trials. The Surfactant-TA Study Group. Pediatrics 1990;86(5):753-764.
21. Gortner L, Bartmann P, Pohlandt F, Bernsau U, Porz F, Hellwege HH, et al. Early treatment of respiratory distress syndrome with bovine surfactant in very preterm infants: a multicenter controlled clinical trial. Pediatr Pulmonol 1992;14(1):4-9.
22. Hallman M, Merritt TA, Jarvenpaa AL, Boynton B, Mannino F, Gluck L, et al. Exogenous human surfactant for treatment of severe respiratory distress syndrome: a randomized prospective clinical trial. J Pediatr 1985;106(6):963-969.
23. Hoekstra RE, Jackson JC, Myers TF, Frantz ID 3rd, Stern ME, Powers WF, et al. Improved neonatal survival following multiple doses of bovine surfactant in very premature neonates at risk for respiratory distress syndrome. Pediatrics 1991;88(1):10-18.
24. Horbar JD, Wright EC, Onstad L. Decreasing mortality associated with the introduction of surfactant therapy: an observational study of neonates weighing 601 to 1300 grams at birth. The Members of the National Institute of Child Health and Human Development Neonatal Research Network. Pediatrics 1993;92(2):191-196.
25. Kattwinkel J, Bloom BT, Delmore P, Davis CL, Farrell E, Friss H, et al. 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(1):90-98.
26. Lang MJ, Hall RT, Reddy NS, Kurth CG, Merritt TA. A controlled trial of human surfactant replacement therapy for severe respiratory distress syndrome in very low birth weight infants. J Pediatr 1990; 116(2):295-300.
27. Liechty EA, Donovan E, Purohit D, Gilhooly J, Feldman B, Noguchi A, et al. Reduction of neonatal mortality after multiple doses of bovine surfactant in low birth weight neonates with respiratory distress syndrome. Pediatrics 1991;88(1):19-28.
28. Long W, Corbet A, Cotton R, Courtney S, McGuiness G, Walter D, et al. A controlled trial of synthetic surfactant in infants weighing 1250 g or more with respiratory distress syndrome. The American Exosurf Neonatal Study Group I, and the Canadian Exosurf Neonatal Study Group. N Engl J Med 1991;325(24):1696-1703.
29. Merritt TA, Hallman M, Berry C, Pohjavuori M, Edwards DK 3rd, Jaaskelainen J, et al. Randomized, placebo-controlled trial of human surfactant given at birth versus rescue administration in very low birth weight infants with lung immaturity. J Pediatr 1991;118(4 Pt 1):581-594.
30. Soll RF, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. Cochrane Database Syst Rev 2001(2):CD000144.
31. Egberts J, de Winter JP, Sedin G, de Kleine MJ, Broberger U, van Bel F, et al. Comparison of prophylaxis and rescue treatment with Curosurf in neonates less than 30 weeks' gestation: a randomized trial. Pediatrics 1993;92(6):768-774.
32. Kendig JW, Notter RH, Cox C, Reubens LJ, Davis JM, Maniscalco WM, et al. 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(13):865-871.
33. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2001(2):CD000510.
34. 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(4): CD003063.
35. Kattwinkel J, Robinson M, Bloom BT, Delmore P, Ferguson JE. Technique for intrapartum administration of surfactant without requirement for an endotracheal tube. J Perinatol 2004;24(6):360-365.
36. Kribs A. Early administration of surfactant in spontaneous breathing with nCPAP through a thin endotracheal catheter: an option in the treatment of RDS in ELBW infants? J Perinatol 2009;29(3):256.
37. Donn SM, Sinha SK. Aerosolized lucinactant: a potential alternative to intratracheal surfactant replacement therapy. Expert Opin Pharmacother 2008;9(3):475-478.
38. Engle WA. Surfactant-replacement therapy for respiratory distress in the preterm and term neonate. Pediatrics 2008;121(2):419-432.
39. Heldt GP, Pesonen E, Merritt TA, Elias W, Sahn DJ. Closure of the ductus arteriosus and mechanics of breathing in preterm infants after surfactant replacement therapy. Pediatr Res 1989;25(3):305-310.
40. Soll RF, Hoekstra RE, Fangman JJ, Corbet AJ, Adams JM, James LS, et al. Multicenter trial of single-dose modified bovine surfactant extract (Survanta) for prevention of respiratory distress syndrome. Ross Collaborative Surfactant Prevention Study Group. Pediatrics 1990;85(6):1092-1102.
41. Lotze A, Knight GR, Martin GR, Bulas DI, Hull WM, O'Donnell RM, et al. Improved pulmonary outcome after exogenous surfactant therapy for respiratory failure in term infants requiring extracorporeal membrane oxygenation. J Pediatr 1993;122(2):261-268.
42. Raju TN, Langenberg P. Pulmonary hemorrhage and exogenous surfactant therapy: a meta analysis. J Pediatr 1993;123(4):603-610.
43. Hallman M, Merritt TA, Bry K, Berry C. Association between neonatal care practices and efficacy of exogenous human surfactant: results of a bicenter randomized trial. Pediatrics 1992;91(3):552-560.
44. Hazan J, Chessex P, Piedboeuf B, Bourgeois M, Bard H, Long W. Energy expenditure during synthetic surfactant replacement therapy for neonatal respiratory distress syndrome. J Pediatr 1992;120(2 Pt 2):S29-S33.
45. Horbar JD, Wright LL, Soll RF, Wright EC, Fanaroff AA, Korones SB, et al. A multicenter randomized trial comparing two surfactants for the treatment of neonatal respiratory distress syndrome. National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr 1993;123(5):757-766.
46. Khammash H, Perlman M, Wojtulewicz J, Dunn M. Surfactant therapy in full-term neonates with severe respiratory failure. Pediatrics 1993;92(1):135-139.
47. Stevenson D, Walther F, Long W, Sell M, Pauly T, Gong A, et al. Controlled trial of a single dose of synthetic surfactant at birth in premature infants weighing 500 to 699 grams. The American Exosurf Neonatal Study Group I. J Pediatr 1992;120(2 Pt 2):S3-S12.
48. Dunn MS, Shennan AT, Possmayer F. Single- versus multiple-dose surfactant replacement therapy in neonates of 30 to 36 weeks' gestation with respiratory distress syndrome. Pediatrics 1990;86(4): 564-571.
49. Long W, Thompson T, Sundell H, Schumacher R, Volberg F, Guthrie R. Effects of two rescue doses of a synthetic surfactant on mortality rate and survival without bronchopulmonary dysplasia in 700- to 1350-gram infants with respiratory distress syndrome. The American Exosurf Neonatal Study Group I. J Pediatr 1991;118(4 Pt 1): 595-605.
50. Goldman SL, Bosque E, McCann E, Lewis K. Pulmonary mechanics in premature infants one month after treatment with synthetic surfactant. J Pediatr 1992;120(2 Pt 2):S25-28.
51. Annibale DJ, Hulsey TC, Wallin LA, Engstrom PC. Clinical diagnosis and management of respiratory distress in preterm neonates: effect of participation in a controlled trial. Pediatrics 1992;90(3): 397-400.
52. Hellstrom-Westas L, Bell AH, Skov L, Greisen G, Svenningsen NW. Cerebroelectrical depression following surfactant treatment in preterm neonates. Pediatrics 1992;89(4 Pt 1):643-647.
53. Speer CP, Harms K, Herting E, Neumann N, Curstedt T, Robertson B. Early versus late surfactant replacement therapy in severe respiratory distress syndrome. Lung 1990;168(Suppl):870-876.
54. Zola EM, Gunkel JH, Chan RK, Lim MO, Knox I, Feldman BH, et al. Comparison of three dosing procedures for administration of bovine surfactant to neonates with respiratory distress syndrome. J Pediatr 1993;122(3):453-459.
55. Cai J, Su Z, Zhou Y, Shi Z, Xu Z, Liu J, et al. Beneficial effect of exogenous surfactant in infants suffering acute respiratory distress syndrome after cardiac surgery. Eur J Cardiothorac Surg 2011;40(3): 557-562.
56. Luchetti M, Ferrero F, Gallini C, Natale A, Pigna A, Tortorolo L, et al. Multicenter, randomized, controlled study of porcine surfactant in severe respiratory syncytial virus-induced respiratory failure. Pediatr Crit Care Med 2002;3(3):261-268.
57. Speer CP, Robertson B, Curstedt T, Halliday HL, Compagnone D, Gefeller O, et al. Randomized European multicenter trial of surfactant replacement therapy for severe neonatal respiratory distress syndrome: single versus multiple doses of Curosurf. Pediatrics 1992; 89(1):13-20.
58. Colby CE, Lally KP, Hintz SR, Lally PA, Tibboel D, Moya FR, et al. Surfactant replacement therapy on ECMO does not improve outcome in neonates with congenital diaphragmatic hernia. J Pediatr Surg 2004;39(11):1632-1637.
59. Lally KP, Lally PA, Langham MR, Hirschl R, Moya FR, Tibboel D, et al. Surfactant does not improve survival rate in preterm infants with congenital diaphragmatic hernia. J Pediatr Surg 2004;39(6): 829-833.
60. Van Meurs K. Is surfactant therapy beneficial in the treatment of the term newborn infant with congenital diaphragmatic hernia? J Pediatr 2004;145(3):312-316.
61. Gunkel JH, Banks PL. Surfactant therapy and intracranial hemorrhage: review of the literature and results of new analyses. Pediatrics 1993;92(6):775-786.
62. van Houten J, Long W, Mullett M, Finer N, Derleth D, McMurray B, et al. Pulmonary hemorrhage in premature infants after treatment with synthetic surfactant: an autopsy evaluation. The American Exosurf Neonatal Study Group I, and the Canadian Exosurf Neonatal Study Group. J Pediatr 1992;120(2 Pt 2):S40-44.
63. Zola EM, Overbach AM, Gunkel JH, Mitchell BR, Nagle BT, DeMarco NG, et al. Treatment investigational new drug experience with Survanta (beractant). Pediatrics 1993;91(3):546-551.
64. Kumar A, Lakkundi A, McNamara PJ, Sehgal A. Surfactant and patent ductus arteriosus. Indian J Pediatr 2010;77(1):51-55.
65. Goldsmith LS, Greenspan JS, Rubenstein SD, Wolfson MR, Shaffer TH. Immediate improvement in lung volume after exogenous surfactant: alveolar recruitment versus increased distention. J Pediatr 1991;119(3):424-428.
66. Howell EA, Holzman I, Kleinman LC, Wang J, Chassin MR. Surfactant use for premature infants with respiratory distress syndrome in three New York city hospitals: discordance of practice from a community clinician consensus standard. J Perinatol 2010;30(9):590-595.

67. Bhutani VK, Abbasi S, Long WA, Gerdes JS. Pulmonary mechanics and energetics in preterm infants who had respiratory distress syndrome treated with synthetic surfactant. J Pediatr 1992;120(2 Pt 2):S18-S24.
68. Bhat R, Dziedzic K, Bhutani VK, Vidyasagar D. Effect of single dose surfactant on pulmonary function. Crit Care Med 1990;18(6): 590-595.
69. Abbasi S, Bhutani VK, Gerdes JS. Long-term pulmonary consequences of respiratory distress syndrome in preterm infants treated with exogenous surfactant. J Pediatr 1993;122(3):446-452.
70. Armsby DH, Bellon G, Carlisle K, Rector D, Baldwin R, Long W, et al. Delayed compliance increase in infants with respiratory distress syndrome following synthetic surfactant. Pediatr Pulmonol 1992; 14(4):206-213.
71. Kelly E, Bryan H, Possmayer F, Frndova H, Bryan C. Compliance of the respiratory system in newborn infants pre- and postsurfactant replacement therapy. Pediatr Pulmonol 1993;15(4):225-230.
72. Pfenninger J, Aebi C, Bachmann D, Wagner BP. Lung mechanics and gas exchange in ventilated preterm infants during treatment of hyaline membrane disease with multiple doses of artificial surfactant (Exosurf). Pediatr Pulmonol 1992;14(1):10-15.
73. Yuksel B, Greenough A, Gamsu HR. Respiratory function at follow-up after neonatal surfactant replacement therapy. Respir Med 1993;87(3):217-221.
74. Kaapa P, Seppanen M, Kero P, Saraste M. Pulmonary hemodynamics after synthetic surfactant replacement in neonatal respiratory distress syndrome. J Pediatr 1993;123(1):115-119.
75. Hillman NH, Nitsos I, Berry C, Pillow JJ, Kallapur SG, Jobe AH. Positive end-expiratory pressure and surfactant decrease lung injury during initiation of ventilation in fetal sheep. Am J Physiol Lung Cell Mol Physiol 2011;301(5):L712-L720.
76. Sitler CG, Turnage CS, McFadden BE, Smith EO, Adams JM. Pump administration of exogenous surfactant: effects on oxygenation, heart rate, and chest wall movement of premature infants. J Perinatol 1993;13(3):197-200.
77. Soll R, Ozek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. Cochrane Database Syst Rev 2009(1):CD000141.
78. Sinha S, Moya F, Donn SM. Surfactant for respiratory distress syndrome: are there important clinical differences among preparations? Curr Opin Pediatr 2007;19(2):150-154.
79. Suresh GK, Soll RF. Overview of surfactant replacement trials. J Perinatol 2005;25(Suppl 2):S40-S44.
80. Halliday HL. Synthetic or natural surfactants. Acta Paediatr 1997; 86(3):233-237.
81. Singh N, Hawley KL, Viswanathan K. Efficacy of porcine versus bovine surfactants for preterm newborns with respiratory distress syndrome: systematic review and meta-analysis. Pediatrics 2011; 128(6):e1588-d1595.
82. Sinkin RA, Kramer BM, Merzbach JL, Myers GJ, Brooks JG, Palumbo DR, et al. School-age follow-up of prophylactic versus rescue surfactant trial: pulmonary, neurodevelopmental, and educational outcomes. Pediatrics 1998;101(5):E11.
83. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. J Paediatr Child Health 2002;38(6):597-600.
84. Abdel-Latif ME, Osborn DA. Pharyngeal instillation of surfactant before the first breath for prevention of morbidity and mortality in preterm infants at risk of respiratory distress syndrome. Cochrane Database Syst Rev 2011(3):CD008311.
85. Roberts KD, Lampland AL, Meyers PA, Worwa CT, Plumm BJ, Mammel MC. Laryngeal mask airway for surfactant administration in a newborn animal model. Pediatr Res 2010;68(5):414-418.
86. Rey-Santano C, Alvarez-Diaz FJ, Mielgo V, Murgia X, Lafuente H, Ruiz-Del-Yerro E, et al. Bronchoalveolar lavage versus bolus administration of lucinactant, a synthetic surfactant in meconium aspiration in newborn lambs. Pediatr Pulmonol 2011;46(10):991-999.
87. Sinha SK, Lacaze-Masmonteil T, Valls i Soler A, Wiswell TE, Gadzinowski J, Hajdu J, et al; Surfaxin Therapy Against Respiratory Distress Syndrome Collaborative Group. A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. Pediatrics. 2005;115(4):1030-1038.
88. Anzueto A, Baughman RP, Guntupalli KK, Weg JG, Wiedemann HP, Raventos AA, et al. Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. Exosurf Acute Respiratory Distress Syndrome Sepsis Study Group. N Engl J Med 1996; 334(22):1417-1421.
89. Broadbent R, Fok TF, Dolovich M, Watts J, Coates G, Bowen B, et al. Chest position and pulmonary deposition of surfactant in surfactant depleted rabbits. Arch Dis Child Fetal Neonatal Ed 1995;72(2): F84-F89.
90. Restrepo RD. AARC Clinical Practice Guidelines: from "reference-based" to "evidence-based". Respir Care 2010;(55)6:787-788.