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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