SURFACTANT REPLACEMENT THERAPY
Supporting information

This guideline has been prepared with reference to the following:

Sweet DG, Carnielli, V, Greisen G et al. European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants – 2013 Update. Neonatology 2013;103:353–68

Does the routine administration of antenatal steroids impact on the need for prophylactic surfactant?
A placebo-controlled randomised double-blind study in 157 pregnant women (Kari, 1994) found that dexamethasone 6 mg 4 times at 12-hour intervals resulted in a lower incidence of RDS (44% vs 79%, P<.01), lower requirement for surfactant (22% vs 53%, P<.01), and shorter duration of ventilatory support (2.0 days vs 5.3 days, P<.05) and oxygen therapy (2.0 days vs 7.0 days, P<.01) compared to the placebo group. Mortality was also lower (6 vs 9, P<.05).
An earlier retrospective study using data from 2 randomised trials in a total of 1223 infants came to similar conclusions (Jobe, 1993).

Jobe AH, Mitchell BR, Gunkel JH. Beneficial effects of the combined use of prenatal corticosteroids and postnatal surfactant on preterm infants. Am J Obstet Gynecol 1993;168:508-13

Kari MA, Hallman M, Eronen M, et al. Prenatal dexamethasone treatment in conjunction with rescue therapy of human surfactant: a randomized placebo-controlled multicenter study. Pediatrics 1994;93:730-6

Evidence Level: II

What surfactant preparations are recommended?
Both animal derived surfactant extracts and protein free synthetic surfactant extracts are effective in the treatment and prevention of respiratory distress syndrome. Comparative trials demonstrate greater early improvement in the requirement for ventilator support, fewer pneumothoraces (RR 0.65, 95% CI 0.55 to 0.77), and fewer deaths (RR 0.89, 95% CI 0.79 to 0.99) associated with animal derived surfactant extract treatment. Animal derived surfactant may be associated with an increase in necrotizing enterocolitis (RR 1.38, 95% CI 1.08 to 1.76) and intraventricular hemorrhage (RR 1.07, 95% CI 0.99 to 1.15), though the more serious hemorrhages (Grade 3 and 4) are not increased. Despite these concerns, animal derived surfactant extracts would seem to be the more desirable choice when compared to other available protein free synthetic surfactants.

Ardell S, Pfister R, Soll R. Animal derived surfactant extract versus protein free synthetic surfactant for the prevention and treatment of respiratory distress syndrome. The Cochrane Database of Systematic Reviews 2015, Art. No.: CD000144
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000144.pub2/full

Evidence Level: I

What advantages and disadvantages does surfactant have?
The benefits of surfactant administration (particularly natural preparations as opposed to synthetic) have been demonstrated in several Cochrane reviews (Stevens, 2007; Bahadue 2012; Soll 1997). A systematic review of 13 RCTs in a total of 2218 treated and 2090 control infants (Sinn, 2002) found a lower rate of mild disability in the treated group at follow-up at 1 year (OR 0.79; 95% CI 0.66-0.95). The treated group also showed a reduction in combined adverse outcome (death or severe disability) at 1 year (OR 0.8; 95% CI 0.72-0.89).
Surfactant treatment has, however, failed to have a significant impact on the incidence of chronic lung disease in survivors (Ainsworth, 2002).
Recorded side effects of surfactant treatment include increased cerebral blood flow velocity, which, due to the lack of cerebral vascular autoregulation in many sick preterm infants, can lead to intraventricular haemorrhage or periventricular leukomalacia. Evidence for this is, however, equivocal (Hentsche, 2002).

Ainsworth SB. Surfactant therapy for respiratory distress syndrome in premature neonates: a comparative review. Am J Respir Med 2002;1:417-33

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Hentsche R, Jorch G. Acute side effects of surfactant treatment. J Perinat Med 2002;30:143-8

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;38:597-600

Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. The Cochrane Database of Systematic Reviews 1997, Issue 4. Art. No.: CD000511 (Assessed as up-to-date: 7 MAR 2010)
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000511/full

Stevens TP, Harrington EW, Blennow M, et al. 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
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003063.pub3/full

Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD001456
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001456.pub2/full

Evidence Level: I

How many doses of surfactant are recommended?

An updated Cochrane systematic review (Soll, 2009) of 2 RCTs comparing single with multiple doses of surfactant showed a reduction in the risk of pneumothorax (RR 0.51, 95% CI 0.30-0.88) and a trend towards a reduction in mortality (RR 0.63, 95% CI 0.39-1.02) associated with the use of multiple doses. The review also identified an additional study of multiple vs. single dose synthetic surfactant in infants at high risk of respiratory distress syndrome. This reported a decrease in necrotizing enterocolitis (relative risk 0.20, 95% CI 0.08, 0.51; risk difference-0.05, 95% CI -0.07, -0.02) and mortality (relative risk 0.56, 95% CI 0.39, 0.81; risk difference-0.07, 95% CI -0.12, -0.03)
The OSIRIS (Open Study of Infants at High Risk of or with Respiratory Insufficiency – the role of Surfactant) trial (Anon, 1992) randomised 2690 infants to either 2 doses of surfactant 12 hours apart, or the option of third and fourth doses at 12-36 hour intervals if signs of RDS persisted or recurred. 4067 infants who later developed RDS were also added, giving a total of 3376 infants allocated up to four doses (45% of whom received more than two). No evidence of improved outcomes associated with more than 2 doses was found.

Anon. Early versus delayed neonatal administration of a synthetic surfactant – the judgment of OSIRIS. Lancet 1992;340:1363-9

Soll R, Özek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. Cochrane Database of Systematic Reviews 2009, Issue 1
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000141.pub2/full

Evidence Level: I

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