

Clinical Practice Guidelines

Surfactant Replacement Therapy in Neonates

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Executive summary

Surfactant replacement therapy has been one of the major breakthroughs in the care of preterm neonates with respiratory distress syndrome (RDS) in the twentieth century.(1) Over the past three decades, its use in neonates has evolved considerably with its utility been evaluated in different pathologies such as meconium aspiration syndrome, pneumonia and pulmonary hemorrhage.(2) This guideline based on PICO questions relevant for clinical care and targeting the Indian scenario, updates the previous one published by National Neonatal Forum (NNF), India in 2011.(3)

An initial set of questions focusing on the patient group, intervention and comparator was selected by the Guideline panel members. This set was distributed to the senior members of NNF to rate them on a scale of 1-9. A final list of 14 questions was selected based on the ratings from this survey (Appendix 1a). A list of outcomes was selected a priori by the panel members based on a rating scale (1-9) and were grouped as critical (7-9), important (4-6) and of limited importance (1-3) based on their relevance to the stakeholders (Appendix 1b). Surrogate outcomes were chosen if the outcomes chosen a priori were not reported by the trials.

A search strategy for the three electronic databases namely, MEDLINE (via Pubmed), EMBASE and CENTRAL was devised by an experienced librarian. The literature search was performed by searching the databases from their inception till 1st October 2020. The retrieved citations were reviewed by two members independently in duplicates and disagreements were sorted by discussing with a third member. The search strategy is given in Appendix 2. There were no language restrictions and Google Translate (California, U.S.A) was used to translate non-English literature. Rayyan – QCRI software (Doha, Qatar) was used for the literature search.(4) The PRISMA flow is given in Appendix 3. Questions for which a systematic review with meta-analysis was available and there were no RCTs published after the publication of the systematic review, the existing meta-analysis was used for generating the summary of finding table (Questions - 6, 7). For the other PICO questions, evidence was generated by synthesizing data through meta-analysis (pairwise or network meta-analysis) (Questions - 1, 2-5, 8-13). Questions for which, it was not possible to synthesize the results of trials through a meta-analysis or when trials were not identified, an expert opinion-based recommendation was given and GRADE evaluation was not performed (3, 14). The risk of bias (RoB) assessment was done using the Cochrane RoB tool version 1.0 (London, U.K.), and the five domains of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias were evaluated. The RoB summary and graph for all the included RCTs is given in Appendix 4.

The certainty of evidence (CoE) was evaluated, and recommendations were made based on the GRADE working group guidelines using GRADE-Pro.(5) The ranking of CoE was as follows: high, moderate, low and very low. The recommendations were made as strong or weak. Parameters such as equity, costs, resources utilized, and feasibility were also taken into consideration before adjudging the recommendations as strong or weak.

The summary of recommendations has been compiled in the next table.

SUMMARY OF RECOMMENDATIONS FOR SURFACTANT REPLACEMENT THERAPY IN NEONATES

S. No.	Recommendations	Strength of Recommendations	Certainty of evidence
1.	Prophylactic surfactant should NOT be administered to preterm neonates <28 weeks' gestation with RDS. Preterm neonates with RDS should be stabilized on CPAP and if indicated selective surfactant replacement therapy should be administered. <i>Sub-group considerations: Clinicians may consider delivery room surfactant in subgroup of neonates <28 weeks' gestation who are intubated in the delivery room for severe RDS.</i>	Strong Strong	Low Moderate
2.	Early INSURE (within 2 hours) may be used for preterm neonates < 34 weeks' gestation with established RDS and who satisfy the criteria for surfactant administration.	Weak	Low
3.	Surfactant may be given to preterm neonates < 34 weeks' gestation with RDS stabilized on CPAP, who require a PEEP of ≥ 6 cm H ₂ O and a FiO ₂ > 0.30 to maintain SpO ₂ $\geq 91\%$.	Weak	Not graded (Expert consensus)
4.	LISA may be preferred over INSURE for surfactant administration in preterm neonates < 34 weeks' gestation with RDS.	Weak	Moderate
5.	LMA should NOT be used for surfactant instillation outside research context in preterm neonates < 37 weeks' gestation with RDS.	Strong	Very low
6.	Poractant-a (200 mg/kg) may be used for treating preterm neonates < 34 weeks' gestation with RDS and who satisfy the criterion for surfactant administration.	Weak	Moderate
7.	Multiple doses of surfactant should be used in the treatment of preterm neonates < 34 weeks' gestation with RDS who satisfy the pre-determined criteria for additional surfactant doses.	Strong	Moderate

8.	A higher threshold (MAP/ PEEP \geq 7 cm H ₂ O and FiO ₂ > 0.4) may be used for repeat doses of surfactant in preterm neonates < 34 weeks' gestation with RDS who are on invasive or non-invasive ventilation. <i>Sub-group considerations: A lower threshold (any mechanical ventilation and FiO₂ > 0.3) may be considered for neonates with RDS and concomitant perinatal asphyxia or sepsis.</i>	Weak	Moderate
9.	Early surfactant may be used in late preterm (34-36 weeks' gestation) and early term neonates (37-38 weeks' gestation) with RDS who satisfy the criteria for surfactant therapy. (FiO ₂ > 0.4, PEEP \geq 7 cm H ₂ O)	Weak	Low
10.	The guidelines panel suggests NOT using surfactant therapy in preterm neonates born at less than 34 weeks of gestation who present with respiratory distress at a referral hospital beyond 72 h of age, irrespective of prior surfactant therapy.	Weak	Not graded, Expert consensus
11.	Early intra-tracheal corticosteroids may NOT be used as an adjunct to surfactant in the treatment of preterm neonates < 34 weeks' gestation with RDS.	Weak	Low
12.	Bolus surfactant may be used in treating late preterm and term neonates with severe MAS requiring invasive ventilation with an oxygenation index of more than 15.	Weak	Low
13.	Surfactant may be considered in late preterm and term neonates with severe bacterial pneumonia requiring invasive ventilation with an oxygenation index of more than 15.	Weak	Very low
14.	Surfactant therapy should be given only in neonatal units with availability of CPAP machine and preferably also a back-up ventilator.	Strong	Not graded, Expert consensus

Clinical Practice Questions

Using the common methodology for this set of clinical practice guidelines described under 'Methods used to develop the guidelines', the group prioritized the following questions:

S No.	Practice Questions
1	Is Prophylactic surfactant superior to stabilization on CPAP and selective surfactant administration in preterm neonates born at less than 28 weeks' gestation at risk for RDS?
2	Is Early Intubate-Surfactant-Extubation (INSURE) strategy superior to CPAP alone (followed by delayed rescue surfactant) in preterm neonates < 34 weeks' gestation with RDS?
3	What is the treatment threshold for giving surfactant in preterm neonates < 34 weeks' gestation with RDS who are on CPAP therapy?
4	Are Less invasive surfactant administration (LISA) techniques superior to INSURE strategy in preterm neonates < 34 weeks' gestation with RDS ?
5	Is Surfactant instillation through supraglottic airway devices (SAD) / laryngeal mask airway (LMA) as effective as through INSURE or LISA in preterm neonates < 37 weeks' gestation with RDS?
6	Is Porcine surfactant (200 mg/kg) superior to bovine surfactant (100 mg/kg) in preterm neonates < 34 weeks' gestation with RDS ?
7	Are Multiple doses superior to single dose exogenous surfactant for treatment of RDS in preterm neonates < 34 weeks' gestation?
8	What is the indication for repeat doses of surfactant in preterm neonates with RDS born at less than 34 weeks' gestation ?
9	Is Early surfactant superior to standard therapy in late preterm and early term neonates with RDS?
10	Is there a role for surfactant administration after 72 hours in preterm neonates less than 34 weeks' gestation with RDS who present late during the disease course?
11	Is Early intra-tracheal administration of corticosteroid and pulmonary surfactant better than pulmonary surfactant alone in preterm neonates <34 weeks' gestation with RDS ?
12	Is Bolus surfactant or surfactant lavage with standard therapy (invasive respiratory support) superior to standard therapy alone in late preterm and term neonates with meconium aspiration syndrome?
13	Does addition of Surfactant to standard therapy (antibiotics with invasive respiratory support) improve outcomes over standard therapy alone in neonates with bacterial pneumonia?
14	What should be the pre-conditions required to safely administer surfactant to neonates?

QUESTIONS, EVIDENCE SUMMARIES AND RECOMMENDATIONS

Practice Question 1 – Is Prophylactic surfactant superior to Stabilization on CPAP and selective surfactant administration in preterm neonates born at less than 28 weeks' gestation at risk for RDS?

Population: Preterm neonates born at less than 28 weeks' gestation with or without signs or symptoms of RDS.

Intervention: Prophylactic surfactant defined as instillation of animal or synthetic surfactant before the first breath.

Comparator: Stabilization of the preterm neonate on CPAP initiated in the delivery room and surfactant administration based on a pre-determined threshold.

Settings: Hospital settings with availability of personnel trained in endotracheal intubation.

Summary of evidence

The evidence was derived from the synthesis of data from two Randomized Controlled Trials (RCTs) published after 2010 as these were the only trials that routinely stabilized the control subjects on CPAP.(6,7) Low CoE suggests that prophylactic surfactant administration increases the risk of combined outcome of death or Bronchopulmonary dysplasia (BPD) at 36 weeks' postmenstrual age (PMA). The evidence was downgraded by two levels due to risk of bias and imprecision. There were no differences between the two interventions for the other outcomes (table 1). A recent RCT from a low-and middle income country (LMIC) had shown that prophylactic surfactant decreased the requirement of additional surfactant doses, the risk of BPD and patent ductus arteriosus (PDA), when compared to early rescue treatment.(8) This study was not included in the meta-analysis as the gestational age of the participants was more than 28 weeks.

Summary of judgements

Balance of benefits and harm: Low CoE indicate that prophylactic surfactant when compared to stabilization on CPAP and selective administration of surfactant in preterm neonates with RDS increases the risk of the critical outcome of death or BPD at 36 weeks' PMA (RR, 95%CI: 1.12, 1.02-1.24)

Resources required: Prophylactic surfactant can result in overuse of a costly drug such as surfactant. The SUPPORT trial had shown that rescue treatment compared to prophylactic therapy decreases the need for surfactant use anytime during the hospital stay by almost one-third (RR, 95%CI - 0.67, 0.64-0.71). The same study also suggests that there was a reduction in requirement of mechanical ventilation [RR - 0.37(0.34-0.42)] as well as the duration of mechanical ventilation days (Mean difference, 95%CI: -3.0, -5.6 to -0.3 days] in the rescue arm. These might indicate that rescue therapy might be associated with less resource utilization when compared to prophylactic surfactant. However, there are no studies on resources required from any LMIC.

Table 1 - Summary of findings - Prophylactic surfactant vs. Stabilization on CPAP and selective surfactant administration for RDS in preterm neonates < 28 weeks' and / or less than 1000 grams.

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with stabilisation on CPAP and selective surfactant administration	Risk difference with prophylactic surfactant
Death or BPD at 36 weeks' PMA	1748 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	RR 1.12 (1.02 to 1.24)	441 per 1,000	53 more per 1,000 (9 more to 106 more)
Neonatal Mortality	1746 (2 RCTs)	⊕⊕○○ LOW ^{a,c}	RR 1.24 (0.97 to 1.58)	115 per 1,000	28 more per 1,000 (3 fewer to 67 more)
BPD at 36 weeks' PMA	1512 (2 RCTs)	⊕⊕○○ LOW ^{a,d}	RR 1.12 (0.99 to 1.26)	379 per 1,000	46 more per 1,000 (4 fewer to 99 more)
Air leak	1316 (1 RCT)	⊕⊕⊕○ MODERATE ^c	RR 1.08 (0.73 to 1.60)	68 per 1,000	5 more per 1,000 (18 fewer to 41 more)
Pulmonary Hemorrhage	431 (1 RCT)	⊕⊕○○ LOW ^{a,c}	RR 2.12 (0.54 to 8.39)	14 per 1,000	15 more per 1,000 (6 fewer to 100 more)
Severe IVH > Grade II	1691 (2 RCTs)	⊕⊕○○ LOW ^{a,c}	RR 0.88 (0.67 to 1.16)	114 per 1,000	14 fewer per 1,000 (38 fewer to 18 more)
Death or Neurodevelopmental impairment follow up: range 18 months to 22 months	1234 (1 RCT)	⊕⊕⊕○ MODERATE ^e	RR 1.07 (0.89 to 1.27)	279 per 1,000	20 more per 1,000 (31 fewer to 75 more)

Explanations

The CoE was downgraded by one level for the outcomes: death or BPD at 36 weeks' PMA, air leak, death or neurodevelopmental impairment at 18-22 months' corrected age. For all the other outcomes, level of evidence was downgraded by two levels. The reasons for downgrading the evidence were : a. The study by Dunn 2011 had not blinded the intervention

b. 95% CI crosses treatment threshold (set as 25% a priori for important outcomes and 10% for critical outcomes)

c. The event rate is low. Also, the 95% CI crosses the line of no-effect

d. Optimal information size (OIS) not met and the 95% CI crosses the line of no effect

e. The 95% CI crosses the line of no effect

RECOMMENDATION

1a. Prophylactic surfactant should not be administered to preterm neonates <28 weeks' gestation with RDS. Preterm neonates with RDS should be stabilized on CPAP and if indicated (Question 3) selective surfactant replacement therapy should be administered.

Strong recommendation, Low certainty of evidence

1b. Clinicians may consider delivery room surfactant in subgroup of neonates <28 weeks' gestation who are intubated in the delivery room for severe RDS.

Strong recommendation, Moderate certainty of evidence

Justification: The strong recommendation against the use of prophylactic surfactant was based on possibility of harm (low CoE suggesting death or BPD).

Sub-group considerations: A subgroup of preterm neonates might require intubation in the delivery room for stabilization. The European Consensus Guidelines on the management of Respiratory Distress Syndrome – 2019 Update recommend using prophylactic surfactant in such neonates in the delivery room.(9) This was based on moderate CoE with a strong recommendation. Clinicians may consider delivery room surfactant in this subgroup of neonates.

Implementation considerations: For CPAP to be effective, it should be started as early as possible in preterm neonates with RDS. Delivery rooms should be equipped with a T-Piece resuscitator, compressed air and oxygen sources and, an air-oxygen blender.

Practice Question 2: Is Early Intubate-Surfactant-Extubation (INSURE) strategy superior to CPAP alone (followed by delayed rescue surfactant) in preterm neonates born at less than 34 weeks' gestation with RDS ?

Population: Preterm neonates born at less than 34 weeks' gestation with signs of RDS.

Intervention: Early INSURE which refers to giving surfactant early in the disease course preferably within two hours and if the FiO₂ requirement is more than 0.3 while on CPAP

Comparator: CPAP is instituted to neonates with RDS starting from the delivery room and surfactant is given only when the neonate gets intubated and requires invasive ventilation. The criteria for intubation may vary between the studies evaluated.

Summary of evidence

Twelve RCTs enrolling 1948 neonates were analyzed by pair-wise meta-analysis through random-effects model.(7,10–20) The included RCTs had used widely varying criteria to administer surfactant in early INSURE arm. Studies had administered surfactant in early INSURE based on: respiratory distress alone, PEEP requirement or varying FiO₂ requirement. The emphasis was more on relatively earlier administration of surfactant in symptomatic preterm neonates with RDS in the early INSURE group when compared to CPAP alone group. The neonates in CPAP alone group in the included studies had received surfactant based on

widely differing treatment threshold criteria, most common of which was requirement of invasive ventilation for respiratory failure. The modality of giving surfactant in CPAP only group also varied with some studies using INSURE and some others using intubation followed by invasive mechanical ventilation.

Meta-analysis indicates that early INSURE resulted in a trend towards lesser risk of BPD at 36 weeks' PMA and combined outcome of death or BPD at 36 weeks' PMA. Early INSURE also resulted in lesser incidence of air leak when compared to CPAP alone (SoF table 2). The CoE for all the three aforementioned outcomes was low. The CoE was downgraded for indirectness related to the interventions and imprecision.

This PICO question is different from 'early rescue' versus 'late rescue' surfactant in preterm neonates with RDS. A Cochrane systematic review by Bahadue et al. (2012) on early versus late rescue surfactant had shown early rescue therapy to be better than late rescue. The review included only neonates with RDS who were on invasive mechanical ventilation.(21)

Table 2 - Summary of findings - Early INSURE vs CPAP alone (followed by delayed rescue surfactant) in preterm neonates with RDS

Outcomes	N _e of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CPAP	Risk difference with INSURE
Mortality or BPD at 36 weeks' PMA	1310 (7 RCTs)	⊕⊕○○ LOW ^{a,b}	RR 0.88 (0.76 to 1.02)	328 per 1,000	39 fewer per 1,000 (79 fewer to 7 more)
BPD at 36 weeks' PMA	1656 (9 RCTs)	⊕⊕○○ LOW ^{a,b}	RR 0.85 (0.72 to 1.00)	233 per 1,000	35 fewer per 1,000 (65 fewer to 0 fewer)
Mortality	1454 (8 RCTs)	⊕⊕○○ LOW ^{b,c}	RR 0.94 (0.67 to 1.32)	88 per 1,000	5 fewer per 1,000 (29 fewer to 28 more)
Air leak	1689 (11 RCTs)	⊕⊕○○ LOW ^{b,c}	RR 0.45 (0.24 to 0.86)	59 per 1,000	33 fewer per 1,000 (45 fewer to 8 fewer)
Severe IVH (> Grade II)	1690 (9 RCTs)	⊕⊕○○ LOW ^{b,c}	RR 0.90 (0.60 to 1.38)	54 per 1,000	5 fewer per 1,000 (22 fewer to 21 more)

Explanations : The CoE was downgraded by two levels for all the outcomes due to imprecision and indirectness. The specific reasons are listed below- a. 95% CI crosses treatment threshold ; b. Indirectness related to intervention. The included studies have used a widely varying FiO₂ criteria for surfactant administration and only looked at the timing of INSURE. b. 95% CI showed benefit as well as harm, b.&c. OIS criterion not met.

Summary of judgements

Balance of benefits and harm: The relative risk reduction (RRR) for the critical outcome of death or BPD at 36 weeks' PMA for early selective administration of surfactant was 12 % (RR, 95%CI: 0.88, 0.76-1.02). The RRR for an important outcome of air leak was 55 % (RR, 95%CI – 0.45, 0.24-0.86). The confidence in the final estimate was low for all these outcomes.

Resources required: There is a probability that surfactant might be overused in early INSURE group. But this should be weighed against the possibility of surfactant therapy becoming less effective with delayed administration. One Indian study had shown that delayed administration when compared to early INSURE was associated with an increased risk of mechanical ventilation. (10) Mechanical ventilation requires additional skilled personnel, consumables (e.g. ventilator circuits, endotracheal tube), additional tests (e.g. chest radiography, blood gases) and may be associated with an increased risk of BPD, hence prolonging the hospital stay. The same could be adjudged when considering early INSURE, where additional surfactant and skilled manpower might be required. Resource utilization and cost effectiveness of these two strategies have not been evaluated in LMICs and hence could not be adjudged with any certainty.

RECOMMENDATION

2. Early INSURE (within 2 hours) may be used for preterm neonates < 34 weeks' gestation with established RDS and who satisfy the criteria for surfactant administration (Question 3).

Weak recommendation, Low certainty of evidence

Justification: The evidence for early INSURE being beneficial compared to CPAP alone and delayed selective administration was low for critical (trend towards decreased risk of death or BPD) and important outcomes (trend towards decreased risk of BPD, statistically significant decrease in risk of air leak) . In view of the low CoE, a weak recommendation was given.

Sub-group considerations: The body of evidence is restricted to preterm neonates of less than 32 weeks' gestational age. There are not enough studies that had studied the sub-group of preterm neonates born at 32-34 weeks' gestation exclusively. Based on evidence extrapolated from lower gestational age neonates, we suggest using a similar strategy in preterm neonates of 32-34 weeks' gestation as recommended above.

Implementation considerations: The effectiveness of surfactant in RDS depends on a multitude of factors such as antenatal corticosteroid administration, early delivery room CPAP, avoiding hypothermia after birth, preventing hyperoxia induced lung injury by using blended oxygen and preventing hospital acquired sepsis. Also, it is emphasized that giving surfactant to a non-intubated neonate in a place other than a level 3 NICU (e.g. delivery room, Pediatric wards, level 2 units) due to delay in shifting the neonate to a level 3 unit or due to bed availability issues is not encouraged. Hence, these factors need to be addressed along with early INSURE.

Practice Question 3: What is the treatment threshold for giving surfactant in preterm neonates born at less than 34 weeks' gestation with RDS who are on CPAP therapy?

Population: Preterm neonates born at less than 34 weeks' gestation with RDS and who are stabilized on CPAP.

Intervention, comparator: Different FiO₂ thresholds to decide on surfactant administration.

Summary of evidence

Different parameters have been used to judge the severity of RDS, of which FiO₂ (while the neonate is stabilized on CPAP) is the most commonly utilized one. However, before the NEOPROM report most studies had targeted different SpO₂ ranges.(22) Till date no RCT has been conducted comparing different thresholds of FiO₂ for surfactant administration targeting the recently adopted SpO₂ range of 91% - 95%.

The guidelines formulated by the American Academy of Paediatrics (AAP) (2014) have not recommended any FiO₂ threshold for surfactant treatment.(2) The Canadian Paediatric Society guidelines (CPS) (2021) have recommended that treatment with surfactant should be given if the FiO₂ requirement exceeds 0.5.(23) The European Consensus Guidelines 2016 update recommended a FiO₂ cut off of > 0.3 for gestational age ≤ 26 weeks' and > 0.4 for gestational age > 26 weeks'.(9) This was modified in its 2019 update to > 0.3 for all gestational ages and a pressure threshold of 6 cm H₂O was also included.(9) This was based on a single observational trial by Dargaville et al., which showed that a FiO₂ requirement of > 0.3 in the first few hours of life predicted CPAP failure and mechanical ventilation requirement.(24) De Jaegere et al. in a similar observational trial, had suggested a FiO₂ cut-off of 0.25.(25) Fuchs et al. showed that a threshold FiO₂ of 0.35 – 0.45 would shorten the time to surfactant delivery without an increase in mechanical ventilation need compared to a threshold of ≥ 0.6.(26) In an Indian study by Pillai et al., a product of CPAP pressure multiplied by FiO₂ of ≥ 1.28 was found to be predictive of future CPAP failure.(27) However, all these trials targeted lower SpO₂ ranges.

Dani et al. in their review based on limited evidence gave a recommendation of using a FiO₂ threshold of > 0.3 on CPAP for surfactant instillation.(28) The Cochrane review (Stevens et al., 2007) comparing early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation reported a stratified analysis by FiO₂ at study entry and found that a lower threshold (FiO₂ < 0.45) resulted in lesser incidence of air leak [RR 0.46 (0.23 - 0.93)] and BPD [RR 0.43, (0.20, 0.92)].(29) A higher threshold (FiO₂ > 0.45) was associated with a higher incidence of patent ductus arteriosus (PDA) requiring treatment[RR 2.15, (1.09 - 4.13)]. It should be noted that this was not a direct pair-wise comparison of RCTs evaluating lower versus higher FiO₂ thresholds and that many of these trials did not use early CPAP.

The summary of evidence is tabulated in table 3.

Table 3 - Surfactant treatment threshold used in different studies and the recommendations by different National Guidelines

RCTs on NCPAP plus prophylactic versus rescue surfactant treatment	
Sandri et al. (13)	FiO ₂ > 0.4 on NCPAP to maintain SpO ₂ of 85 to 92%
SUPPORT study (6)	FiO ₂ > 0.50 to maintain SpO ₂ > 88% for 1 h
Dunn et al. (7)	Intubation was discretionary if FiO ₂ was 0.40 to 0.60 and mandatory if FiO ₂ was > 0.60 to maintain SpO ₂ of 86 to 94%.
RCTs on NCPAP plus low versus high surfactant treatment threshold	
Verder et al. (15)	Early: a/ApO ₂ 0.35–0.22 (FiO ₂ , 0.37–0.55) ; Late: a/ApO ₂ 0.21–0.15 (FiO ₂ , 0.57–0.77)
Kandraju et al. (10)	Early: within first 2 h of life, irrespective of RDS severity Late: FiO ₂ > 0.50 beyond 2 h of life
Other RCTs on NCPAP plus surfactant treatment	
Dani et al. (30)	FiO ₂ > 0.35 to maintain SpO ₂ and PaO ₂ > 50mmHg
Reininger et al. (11)	FiO ₂ > 0.30 from 1995 to 1997; FiO ₂ > 0.21 from 1998 to 2002
NEOCOSUR Study (31)	FiO ₂ > 0.35
Observational studies predicting CPAP failure	
Dargaville et al. (24)	FiO ₂ > 0.30 in the first few hours of life predicted CPAP failure
Fuchs et al. (26)	A threshold FiO ₂ of ≥ 0.35 – 0.45 compared to ≥ 0.6 for intubation would shorten the time to surfactant delivery without a relevant increase in intubation rate.
De Jaegere et al. (25)	FiO ₂ > 0.25 predicted CPAP failure
Pillai et al. (27)	A product of CPAP pressure and FiO ₂ of 1.28 at initiation to maintain SpO ₂ 88% - 93% predicted CPAP failure
Different National Guidelines	
European Consensus Guidelines 2019 (9)	Babies with RDS should be given rescue surfactant early in the course of the disease. A suggested protocol would be to treat babies who are worsening when FiO ₂ > 0.30 on CPAP pressure of at least 6 cm H ₂ O.
CPS Guidelines 2021 (23)	Treatment with surfactant should not be withheld if the FiO ₂ requirements exceed 0.5 on CPAP

RECOMMENDATION

3. Surfactant may be given to preterm neonates < 34 weeks' gestation with RDS stabilized on CPAP, who require a PEEP of ≥ 6 cm H₂O and a FiO₂ > 0.30 to maintain SpO₂ ≥ 91%.

Weak recommendation, Not graded

Justification: A weak recommendation was given due to paucity of RCTs evaluating different FiO₂ thresholds for surfactant administration.

Practice Question 4: Are Less invasive surfactant administration (LISA) techniques superior to INSURE strategy in preterm neonates < 34 weeks' gestation with RDS ?

Population: Preterm neonates born at less than 34 weeks' gestation with RDS and who are stabilized on CPAP.

Intervention: Less invasive surfactant administration using different modalities such as angio catheters, LISA catheters, feeding tubes

Comparator: Surfactant administration through INSURE

Summary of evidence

Data from thirteen RCTs including 1896 neonates was synthesized in a random effects meta-analysis by the working group.(32–44) Included trials were from both HICs and LMICs. Neonates of varying gestational ages were included. The FiO₂ criterion for surfactant administration was similar across studies which was >0.3. There was significant heterogeneity in the modality used to administer surfactant (Angio catheters, orogastric tubes, LISA catheters etc), use of Magill forceps, use of atropine and sedation prior to procedure. Moderate CoE suggests that LISA decreases combined outcome of death or BPD at 36 weeks' PMA, BPD at 36 weeks' PMA, mortality before discharge, pneumothorax and need for mechanical ventilation within the first 72 hours. However, LISA was associated with an increased risk of surfactant reflux (CoE – Moderate). There was no difference in failure rate at first attempt between the two strategies (CoE - Low). The CoE was downgraded by one level for all the critical and important outcomes due to imprecision. The SoF is given in table 4.

Table 4 - Summary of findings - LISA vs. INSURE in preterm neonates with RDS

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with INSURE	Risk difference with LISA/MIST
BPD at 36 weeks' PMA	1112 (7 RCTs)	⊕⊕⊕○ MODERATE a	RR 0.72 (0.56 to 0.93)	209 per 1,000	58 fewer per 1,000 (92 fewer to 15 fewer)
BPD or Mortality at 36 weeks' PMA	895 (6 RCTs)	⊕⊕⊕○ MODERATE a,b	RR 0.75 (0.59 to 0.94)	270 per 1,000	68 fewer per 1,000 (111 fewer to 16 fewer)
Mortality before discharge	1630 (12 RCTs)	⊕⊕⊕○ MODERATE a,b	RR 0.75 (0.57 to 0.99)	121 per 1,000	30 fewer per 1,000 (52 fewer to 1 fewer)
Requirement of MV (within 72 hours)	661 (7 RCTs)	⊕⊕⊕○ MODERATE a,b	RR 0.72 (0.55 to 0.93)	303 per 1,000	85 fewer per 1,000 (136 fewer to 21 fewer)
Pneumothorax	1087 (8 RCTs)	⊕⊕⊕○ MODERATE a,b	RR 0.60 (0.38 to 0.96)	84 per 1,000	34 fewer per 1,000 (52 to 3 fewer)

Explanations : CoE was downgraded by one level for imprecision for all the outcomes. The reasons for imprecision are provided below - a. The upper limit of 95% CI crosses line of treatment threshold b. OIS criterion not met

Summary of judgements

Balance of benefits and harm: LISA results in a decreased risk of death or BPD, BPD, mortality, need for mechanical ventilation and pneumothorax with CoE being moderate for the important and critical outcomes.

Resources required, Feasibility: INSURE has been the most commonly used procedure for surfactant administration. LISA is a newer way of surfactant administration which avoids exposure to positive pressure ventilation.(9) Dedicated LISA catheters are available in certain high-income countries. Several modifications of LISA such as using feeding catheters have been evaluated.(45) LISA method requires specific skills and is therefore only performed by providers experienced in airway management. Szczapa et al. (2020) in their report on the implementation of LISA from Poland had concluded that training, combining theory with practical exercises is an efficient strategy to implement LISA.(46) In the cohort study performed after the training exercise, 76% of the procedures were rated by the Doctors as “easy/very easy” compared to 59% prior to training. In this study, surfactant was administered predominantly using dedicated LISA catheters

RECOMMENDATION

4. LISA may be preferred over INSURE for surfactant administration in preterm neonates < 34 weeks' gestation with RDS.

Weak recommendation, Moderate certainty of evidence

Justification: A weak recommendation was given in view of concerns with resource utilization and feasibility in implementing LISA.

Implementation considerations: The personnel instituting LISA must be properly trained to use a Magill forceps while using a feeding tube (5-6 Fr). In settings where a dedicated LISA catheter is used, they should be trained regarding the depth of insertion. The use of pre-medications including sedatives, analgesics or atropine is debated. Though the use of such drugs improves the pain scores, they can result in decreased respiratory efforts, apnea and chest rigidity.(47) Hence, based on expert consensus we recommend using non-pharmacological measures such as swaddling and / or sucrose during the first attempt. Use of atropine and minimal doses of fentanyl can be considered in neonates who do not tolerate the procedure in the first attempt due to significant discomfort. During the procedure, the nasogastric tube placed in the stomach should be aspirated to look for the amount of spill or accidental displacement of the catheter into the oesophagus. Compared to poractant-a, reflux might be more with beractant where the volume instilled is more.

Practice Question 5: Is Surfactant instillation through supraglottic airway devices (SAD) or laryngeal mask airway (LMA) as effective as through INSURE or LISA in preterm neonates < 37 weeks' gestation with RDS ?

Population: Preterm neonates born at less than 37 weeks' gestation with RDS and stabilized on CPAP

Intervention: Use of a SAD or LMA for surfactant delivery

Comparator: Surfactant administration by INSURE or LISA

Summary of evidence

LMA is an exciting prospect for surfactant delivery, especially in LMICs. The main advantages of LMA are it requires less of technical skill when compared to endotracheal intubation and hence might be easier to implement on a larger scale in resource constrained settings with limited skilled manpower. Data from five RCTs including 288 neonates was synthesized in a random effects meta-analysis by the working group.(48–52) Three different types of LMA devices were evaluated in these RCTs. Though none of the studies had included extremely low gestational age neonates, these studies indicate the feasibility of using LMA in neonates of more than 28 weeks' gestational age. The SoF table is given in table 5. Two RCTs that had compared surfactant administration via LMA versus CPAP alone were excluded.(53,54) Both of these trials had shown that 7.7% - 18% of the neonates who had received surfactant via LMA had > 25-50% of the volume of the surfactant aspirated from the stomach. Very low CoE suggest that SAD or LMA might be non-inferior to INSURE or LISA for the outcomes – requirement of invasive ventilation, air leak, BPD, severe IVH and mortality before discharge. The CoE was downgraded by three levels for risk of bias, inconsistency and severe imprecision for the outcome requirement of invasive mechanical ventilation and by three levels for all the other outcomes because of risk of bias and severe imprecision.

Summary of judgements

Problem: INSURE and LISA mandate the presence of a trained doctor and is instituted in Level III NICUs with back up invasive mechanical ventilation. Surfactant administration via LMA might be a promising approach in level II NICUs in LMICs as it may not require intense training as compared to INSURE or LISA. Henceforth, it is important that such a non-invasive modality of surfactant instillation be evaluated.

Balance of benefit, harm: Very low CoE suggests that surfactant instillation through LMA might be feasible in larger preterm neonates. Efficacy of LMA when compared to INSURE or LISA needs to be evaluated in RCTs with larger sample sizes.

Resources required, Feasibility: The size 1.0 LMA device used in neonates (>2 Kg) is inexpensive. Only one trial (Barbosa et al., 2017) had enrolled neonates with a median weight of approximately 1500 grams.(51) There are no smaller sizes of LMA available for extremely low gestational age neonates. Feasibility of introducing size 1.0 LMA in resource constrained settings will not be an issue considering its cost and the relatively less intensity of training required.

Table 5 - Summary of findings - Surfactant instillation through SAD / LMA versus INSURE / LISA in preterm neonates with RDS

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with INSURE	Risk difference with supraglottic airway devices / Laryngeal mask airway
Requirement of invasive mechanical ventilation	180 (3 RCTs)	⊕○○○ VERY LOW a,b,c	RR 0.93 (0.35 to 2.43)	100 per 1,000	7 fewer per 1,000 (65 fewer to 143 more)
Requirement of second dose of surfactant	288 (5 RCTs)	⊕○○○ VERY LOW a,c	RR 1.61 (0.83 to 3.13)	85 per 1,000	52 more per 1,000 (14 fewer to 180 more)
BPD at 28 days	165 (3 RCTs)	⊕○○○ VERY LOW a,c	RR 1.60 (0.49 to 5.19)	50 per 1,000	30 more per 1,000 (26 fewer to 210 more)
				Study population	
Mortality before discharge	98 (2 RCTs)	⊕○○○ VERY LOW a,c	RR 0.17 (0.01 to 3.37)	43 per 1,000	35 fewer per 1,000 (42 fewer to 101 more)
Severe IVH (> Grade II)	158 (3 RCTs)	⊕○○○ VERY LOW a,c	RR 0.77 (0.22 to 2.76)	65 per 1,000	15 fewer per 1,000 (51 fewer to 114 more)
Pneumothorax	258 (5 RCTs)	⊕○○○ VERY LOW a,c	RR 3.64 (0.41 to 31.89)	36 per 1,000	94 more per 1,000 (21 fewer to 1,103 more)

Explanations

The CoE was downgraded by three levels for risk of bias, inconsistency and severe imprecision for the outcome requirement of invasive mechanical ventilation and by three levels for all the other outcomes because of risk of bias and severe imprecision. The specific reasons are detailed below-

a. Most trials had issues with random sequence generation and allocation concealment

b. I^2 - 59%

c. OIS criterion not met with very small sample size and event rate. Overall effect estimate showed substantial benefit as well as harm

RECOMMENDATION

5. LMA should NOT be used for surfactant instillation outside research context in preterm neonates < 37 weeks' gestation with RDS.

Strong recommendation, Very low certainty of evidence

Justification: A strong recommendation against the use of LMA for surfactant instillation was given in view of the very low CoE. Uncertainty about whether LMA use for surfactant administration is equivalent or better than INSURE or LISA method of surfactant delivery in terms of clinical benefits and its good value for anticipated costs prompted the panel to give a research only recommendation.

Research priorities

RCTs on surfactant instillation with LMA should be conducted in neonates of gestational age more than 28 weeks', with adequate sample size and should report on critical and important outcomes such as mortality, BPD at 36 weeks' PMA, death or BPD at 36 weeks' PMA, air leak, procedure failure rate, requirement of invasive mechanical ventilation, severe IVH, PDA requiring medical or surgical management, NEC stage II or more, severe ROP or ROP requiring intervention and culture proven sepsis. Resources required and cost effectiveness may also be evaluated. Innovations to manufacture smaller sized LMAs tailored for extremely low gestational age neonates may also be encouraged.

Practice Question 6: Is Porcine surfactant (200 mg/kg) superior to bovine surfactant (100 mg/kg) in preterm neonates < 34 weeks' gestation with RDS ?

Population: Preterm neonates born at less than 34 weeks' gestation with RDS and stabilized on CPAP

Intervention: First dose of any porcine surfactant given at 200 mg/kg

Comparator: First dose of any bovine surfactant given at 100 mg/kg

Summary of evidence

The evidence from a recent systematic review and meta-analysis by Tridente et al. (2019) was evaluated, including 14 trials, 1491 neonates comparing porcine surfactant (poractant-a, curosurf) at 200 mg/kg vs bovine surfactants (different types combined as one arm) at 100 mg/kg.(55) Tridente et al.'s analysis indicates that poractant-a is associated with a decreased risk of combined outcome of death or BPD at 36 weeks' PMA, BPD at 36 weeks' PMA, requirement of additional surfactant dosing and air leak. The CoE was moderate for the combined outcome of death or BPD and very low to low for others. (SoF table 6). The CoE was downgraded by one level for the combined outcome of death or BPD due to risk of bias. The

most recent Cochrane review (Singh et al., 2015) which had compared poractant-a with beractant (survanta) had reported similar findings (CoE- Moderate). (56)

Table 6 - Summary of findings table - Porcine surfactant (200 mg/kg) vs. bovine surfactant (100 mg/kg) in preterm neonates with RDS.

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with bovine surfactant (100 mg/kg)	Risk difference with porcine surfactant (200 mg/kg)
Mortality	1194 (12 RCTs)	⊕⊕○○ LOW ^{a,b,c}	OR 0.70 (0.43 to 1.15)	167 per 1,000	43 fewer per 1,000 (87 fewer to 20 more)
BPD	1194 (12 RCTs)	⊕⊕○○ LOW ^{a,d}	OR 0.69 (0.51 to 0.92)	311 per 1,000	74 fewer per 1,000 (123 fewer to 16 fewer)
Death or BPD	1194 (12 RCTs)	⊕⊕⊕○ MODERATE ^a	OR 0.63 (0.49 to 0.81)	460 per 1,000	110 fewer per 1,000 (164 fewer to 52 fewer)
Requirement of additional surfactant doses	1164 (12 RCTs)	⊕⊕○○ LOW ^{a,b}	OR 0.31 (0.19 to 0.52)	454 per 1,000	248 fewer per 1,000 (320 fewer to 151 fewer)
Pulmonary hemorrhage	1034 (10 RCTs)	⊕⊕○○ LOW ^{a,c}	OR 0.62 (0.39 to 1.00)	98 per 1,000	35 fewer per 1,000 (58 fewer to 0 fewer)
Air leak	1154 (11 RCTs)	⊕⊕○○ LOW ^{a,e}	OR 0.505 (0.31 to 0.83)	94 per 1,000	44 fewer per 1,000 (63 fewer to 15 fewer)
Hemodynamically significant PDA	1472 (12 RCTs)	⊕○○○ VERY LOW ^{a,b,f,g}	OR 0.655 (0.46 to 0.93)	341 per 1,000	88 fewer per 1,000 (149 fewer to 16 fewer)

Explanations

The CoE was downgraded by one level for the outcome death or BPD due to risk of bias. CoE was downgraded by two levels for outcomes BPD, mortality, requirement of surfactant, pulmonary hemorrhage and air leak due to risk of bias and imprecision. CoE for hemodynamically significant PDA was downgraded by three levels due to risk of bias, indirectness and imprecision. The specific reasons are listed below:

- There was performance bias in most of the trials.
- $I^2 > 50\%$. The meta-analysis was a pragmatic one and hence heterogeneity was expected by the Authors. So CoE was not downgraded for heterogeneity.
- The 95% CI crosses the treatment of no effect
- The upper limit of 95% CI crosses the treatment threshold cut off (7.5%). Acceptable - 25%
- The upper limit of 95% CI crosses the treatment threshold cut off (17.3%). Acceptable - 25%.
- There was indirectness in relation to the intervention (porcine surfactant of any dose instead of 200 mg/kg). It was restricted to only three of the 12 included studies.
- The upper limit of 95% CI crosses the treatment cut off (7%). Acceptable - 25%.

Summary of judgements

Balance of benefits and harm: Moderate CoE suggests lower risk of critical outcome - death or BPD with no associated significant adverse effects for poractant-a at a dosage of 200 mg/kg when compared to bovine surfactants.

Resources required: There are no studies on comparison of resource requirements between these two surfactants from LMIC. Sekar et al. in their study published from North America had shown that the resources required might be similar for both the surfactants.(57) It was found that the adjusted estimated mean length of hospital stay (Beractant - 26.7 days, Calfactant - 27.8 days, and Poractant-a - 26.2 days) and hospital costs (Beractant- \$50,929; Calfactant-\$50,785; and Poractant-a - \$50,212) were similar between three types of surfactant. Compared to Poractant-a, Beractant and Calfactant were associated with greater odds of mechanical ventilation use on day 3 [Odds ratio (OR) - 1.56 and 1.60, respectively] and day 7 (OR - 1.39 and 1.28, respectively; $p < 0.05$). This study might indicate that the additional cost of poractant-a might be negated by its relative efficacy in reducing the need of mechanical ventilation and consequently resource utilization. Also, it is evident that poractant-a reduces the need for additional surfactant doses which might also contribute towards decreased costs. It is cautioned that resource utilization and cost effectiveness studies from HICs cannot be extrapolated to LMICs. Hence, the aforementioned study was referred to as only an additional consideration and did not influence the strength of the recommendation put forth by the working group.

Acceptability: Sherman et al had studied parental concerns regarding use of animal derived products such as surfactant in the treatment of newborn diseases.(58) It was found that 34% of parents had concerns about animal-derived medications, 41% preferred a synthetic medication of equivalent efficacy, and 69% would like to be informed if a medication was animal-derived. The most important reason for parental concern was safety of using an animal product (49%) followed by religious beliefs (21%).

In a letter to the editor by an author from United Kingdom, it was revealed that two parents had declined the use of animal surfactant.(59) A Hindu family had declined the use of Survanta as cows were considered as sacred and a Muslim family had not consented to Curosurf as they wanted to avoid a porcine product. In their survey of other 42 NICUs, it was found that only 9 routinely discussed the constituents of the surfactant with the family. The aspect of discussing the use of animal surfactant during the consent process has not been well studied. The guideline panel is of the view that its very likely majority of the parents would agree to the use of a lifesaving drug such as surfactant.

RECOMMENDATION

6. Poractant-a (200 mg/kg) may be used for treating preterm neonates < 34 weeks' gestation with RDS and who satisfy the criterion for surfactant administration.

Weak recommendation, Moderate certainty of evidence

Justification: There is moderate CoE suggesting that porcine surfactant at an initial dosing of 200 mg/kg might be more beneficial than bovine surfactants (100 mg/kg). However, the critical aspect of resource utilization has not been studied in India, especially in lieu of poractant-a being costlier than bovine surfactants. Hence a weak recommendation was given.

Implementation considerations: The dose of 200 mg/kg of poractant-a is only for the first dose and subsequent doses should be dosed at 100 mg/kg.

Practice Question 7 : Are Multiple doses superior to single dose exogenous surfactant for treatment of RDS in preterm neonates born at less than 34 weeks' gestation ?

Population: Preterm neonates born at less than 34 weeks' gestation with RDS who had received one dose of surfactant prior and continue to have significant non-invasive or invasive respiratory support requirement

Intervention: Multiple doses of animal or synthetic surfactant given at any time interval after the first dose using a predetermined criteria and not as scheduled doses

Comparator: Continuing respiratory support management alone without any additional dose of surfactant after the first dose

Summary of evidence

The evidence from a Cochrane review (Soll et al., 2009) was evaluated and no new RCTs were identified in the search.(60) Moderate CoE suggest that multiple doses of surfactant result in lesser risk of neonatal mortality, necrotizing enterocolitis (NEC) and pneumothorax. CoE was downgraded by one level for all the outcomes for imprecision, except for severe IVH which was downgraded by two levels due to imprecision and risk of bias. It should be noted that of the three trials evaluated by this review, one had used synthetic surfactant. The SoF is given in table 7.

Table 7: Summary of findings - Multiple doses vs. single dose exogenous surfactant for treatment of RDS in preterm neonates.

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with single dose exogenous surfactant	Risk difference with multiple doses
Neonatal mortality	1220 (3 RCTs)	⊕⊕⊕○ MODERATE ^{a,b}	RR 0.59 (0.44 to 0.78)	115 per 1,000	47 fewer per 1,000 (64 fewer to 25 fewer)
BPD at 28 days	1221 (3 RCTs)	⊕⊕⊕○ MODERATE ^{a,c}	RR 1.13 (0.83 to 1.54)	70 per 1,000	9 more per 1,000 (12 fewer to 38 more)
Severe IVH (> Grade II)	1220 (3 RCTs)	⊕⊕○○ LOW ^{a,c}	RR 0.96 (0.72 to 1.29)	69 per 1,000	3 fewer per 1,000 (19 fewer to 20 more)
Mortality or BPD at 28 days	1170 (2 RCTs)	⊕⊕⊕○ MODERATE ^{a,c}	RR 0.83 (0.68 to 1.01)	180 per 1,000	31 fewer per 1,000 (58 fewer to 2 more)
Necrotizing enterocolitis (NEC)	1169 (2 RCTs)	⊕⊕⊕○ MODERATE ^{a,d}	RR 0.18 (0.07 to 0.44)	51 per 1,000	42 fewer per 1,000 (48 fewer to 29 fewer)
Pulmonary Hemorrhage	1169 (2 RCTs)	⊕⊕⊕○ MODERATE ^{a,c}	RR 1.17 (0.68 to 2.01)	39 per 1,000	7 more per 1,000 (13 fewer to 40 more)
Pneumothorax	1220 (3 RCTs)	⊕⊕⊕○ MODERATE ^{a,e}	RR 0.70 (0.52 to 0.94)	154 per 1,000	46 fewer per 1,000 (74 fewer to 9 fewer)

Explanations

CoE was downgraded by one level for all the outcomes for imprecision except for severe IVH which was downgraded by two levels due to imprecision and risk of bias. The specific reasons for downgrading CoE are given below:

a. Intervention was not blinded in one of the studies. However, the overall weightage of that study was small for all the outcomes except severe IVH.

b. OIS is inadequate

c. 95%CI crosses the line of no effect

d. Event rate is low.

e. The upper limit of the relative risk reduction for pneumothorax is 6% (acceptable - 25%)

Summary of judgements

Problem: Using multiple doses of surfactant to treat RDS is a common practice. However, at what frequency it is to be used is still debated. The manufacturer recommendations for different surfactant preparations as well as the recommendations by different National guidelines differ considerably. While the European Guidelines suggests a total of two additional doses of surfactant, it does not mention the interval between the doses.(9) AAP recommends a gap of 12 hours between the doses.(2) AAP also mentions that in scenarios where surfactant could be denatured rapidly such as involving meconium, blood and an infectious process, surfactant be given more frequently. The CPS suggests that repeated dosing of surfactant should be provided only when there is evidence of ongoing moderate to severe RDS.(23) None mentions separate dosing intervals for the two different animal preparations of surfactant (bovine and porcine) that are commonly utilized.

The manufacturer recommendation for poractant- a is 200 mg/kg (2.5 ml/kg) for the first dose and if required, 1.25 ml/kg for additional two doses at 12-hour intervals for a maximum cumulative dose of 5 ml/kg. Beractant manufacturer recommends a maximum of 4 doses of 4 ml/kg each within the first 48 hours (including the first dose) at 6 hourly intervals. This has been contested by the AAP which based on the pharmacokinetic data from human studies recommends that more frequent dosing than 12 hourly is not evidence based. The cost analysis of multiple dose regiments is also of prime importance in LMICs.

Balance of benefits and harm: The use of multiple doses of surfactant results in significant reduction in adverse outcomes such as mortality, NEC and pneumothorax. The adverse effect often attributed to surfactant use, pulmonary hemorrhage is not significantly different between multiple doses group and single dose group. The overall CoE was rated moderate for all the outcomes, except severe IVH for which it was low.

Resources required, cost effectiveness: There were no studies on resource utilization and cost effectiveness of multiple doses vs single dose surfactant.

RECOMMENDATION

7. Multiple doses of surfactant should be used in the treatment of preterm neonates < 34 weeks' gestation with RDS who satisfy the pre-determined criteria (Question 8) for additional surfactant doses.

Strong recommendation, Moderate certainty of evidence

Justification: A strong recommendation was given despite paucity of evidence determining the dosing intervals as moderate CoE suggest beneficial effects of multiple dose surfactant and outweighed any undesirable consequences.

Implementation considerations: The total doses and the dosing interval for different surfactant preparations have not been well studied. Based on the manufacturer's recommendations as

well as various other National guidelines, it is suggested that for beractant, three additional doses (excluding the first dose) of 4 ml/kg each could be used at an interval of 6 hours within the first 48 hours. For poractant- α , two additional doses at 12 hourly intervals of 1.25 ml/kg each could be used within the first 72 hours (maximum cumulative dose of 5 ml/kg). Other causes of respiratory deterioration such as mechanical collapse, air leak etc. must be ruled out before repeat dosing.

Practice Question 8: What is the indication for repeat doses of surfactant in preterm neonates with RDS born at less than 34 weeks' gestation ?

Population: Preterm neonates born at less than 34 weeks' gestational age who had received one dose of surfactant and were still requiring non-invasive or invasive support warranting repeat surfactant dosing

Intervention/ Comparator: Different thresholds based on FiO₂ , MAP or PEEP to judge the requirement of repeat doses of surfactant

Summary of evidence

No study comparing different thresholds for repeat surfactant in neonates receiving non-invasive respiratory support was identified. Evidence from a single RCT that compared different thresholds for repeat surfactant dosing in neonates on invasive ventilation was evaluated. This study had included neonates who had received the first dose of surfactant as prophylaxis or as a rescue strategy. Moderate CoE indicated a trend towards increased BPD at 36 weeks' PMA with the low threshold strategy when compared to the high threshold strategy. The combined outcome of death or BPD was similar in both the groups, the CoE for which was also moderate. Subgroup analysis based on the presence of infection or asphyxia did not show any difference in the risk of BPD at 36 weeks' PMA (CoE-moderate). Sub-group analysis indicated a trend towards decreased mortality in neonates with perinatal compromise and / or infection who were treated at lower threshold (any mechanical ventilation and FiO₂ > 0.3 as defined by the authors) when compared to a higher threshold (MAP > 7 cm H₂O and FiO₂ > 0.4) (SoF Table - 8). (61) The CoE was downgraded by one level to moderate for all the outcomes due to imprecision.

Table 8 : Summary of findings - Low threshold compared to high threshold for deciding repeat dosing of surfactant in preterm neonates with RDS.

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with high threshold (MAP > 7 cm H ₂ O & FiO ₂ >40%)	Risk difference with low threshold (any mechanical ventilation & FiO ₂ >30%)
BPD at 36 weeks' PMA	1215 (1 RCT)	⊕⊕⊕○ MODERATE ^a	RR 1.16 (0.96 to 1.39)	256 per 1,000	49 more per 1,000 (10 fewer to 100 more)
Mortality at 36 weeks' PMA	1215 (1 RCT)	⊕⊕⊕○ MODERATE ^a	RR 0.89 (0.68 to 1.16)	164 per 1,000	18 fewer per 1,000 (52 fewer to 26 more)
Death or BPD at 36 weeks' PMA	1215 (1 RCT)	⊕⊕⊕○ MODERATE ^a	RR 1.04 (0.91 to 1.18)	433 per 1,000	17 more per 1,000 (39 fewer to 78 more)
BPD at 36 weeks' PMA (Subgroup - neonates with perinatal compromise / infection)	349 (1 RCT)	⊕⊕⊕○ MODERATE ^a	RR 1.25 (0.89 to 1.76)	244 per 1,000	61 more per 1,000 (27 fewer to 186 more)
Mortality at 36 weeks' PMA (Subgroup - neonates with perinatal compromise/ infection)	349 (1 RCT)	⊕⊕⊕○ MODERATE ^a	RR 0.72 (0.52 to 1.01)	343 per 1,000	96 fewer per 1,000 (165 fewer to 3 more)
Death or BPD at 36 weeks' PMA (Subgroup - neonates with perinatal compromise / infection)	349 (1 RCT)	⊕⊕⊕○ MODERATE ^a	RR 0.95 (0.80 to 1.14)	587 per 1,000	29 fewer per 1,000 (117 fewer to 82 more)

Explanations

a. The CoE was downgraded by one level to moderate for all the outcomes due to imprecision as 95% CI crosses the level of no effect.

RECOMMENDATION

8. A higher threshold (MAP/ PEEP \geq 7 cm H₂O and FiO₂ > 0.4) may be used for repeat doses of surfactant in preterm neonates < 34 weeks' gestation with RDS who are on invasive or non-invasive ventilation.

Sub-group considerations: A lower threshold (any mechanical ventilation and FiO₂ > 0.3) may be considered for neonates with RDS and concomitant perinatal asphyxia or sepsis.

Weak recommendation, Moderate certainty of evidence

Justification: There was no beneficial effect of using a lower threshold over a higher threshold in deciding the need for repeat doses of surfactant. Further, there might be more resource utilization with the low threshold approach. A weak recommendation was also due to the absence of RCT evaluating neonates on non-invasive respiratory support.

Sub-group considerations: A lower threshold may be considered for deciding on repeat surfactant dosing for neonates with RDS and concomitant perinatal asphyxia or suspected sepsis. This is due the sub-group analysis of the included RCT showing a trend towards decreased mortality at 36 weeks' PMA in such neonates.

Practice Question 9: Is Early surfactant superior to standard therapy in late preterm and early term neonates with RDS ?

Population: Late preterm (34-36^{6/7} weeks') and early term (37-38^{6/7}) neonates with RDS and stabilized on CPAP

Intervention: Early surfactant defined as giving surfactant at FiO₂ >0.30 while on CPAP

Comparator: Standard therapy where surfactant is given at a higher threshold when the neonate is intubated

Summary of evidence

Data from three RCTs and three observational studies were analyzed.(64–69) The data from observational studies were not synthesized. One large retrospective cohort study from China indicated that surfactant use was associated with a decreased risk of mortality in late preterm neonates with hypoxic respiratory failure secondary to RDS. Dani et al. in their retrospective cohort study and Jasani et al. in their prospective cohort study reported that surfactant use did not result in a decreased risk of invasive mechanical ventilation. Very low to low CoE from meta-analysis of RCTs suggest that surfactant replacement therapy decreases the requirement of invasive mechanical ventilation, air leak and persistent pulmonary hypertension of the newborn (PPHN). The results are given in SoF table 9. The evidence was downgraded by two levels for the outcome mortality and PPHN, and by three levels for all the other outcomes.

Table 9 : Summary of findings - Surfactant therapy vs. conventional therapy alone (noninvasive and/ or invasive respiratory support) in late preterm and early term neonates with RDS.

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with conventional therapy alone (noninvasive and/ or invasive respiratory therapy)	Risk difference with surfactant therapy
Mortality	307 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	RR 0.76 (0.33 to 1.74)	81 per 1,000	19 fewer per 1000 (54 fewer to 60 more)
Requirement of mechanical ventilation	177 (2 RCTs)	⊕○○○ VERY LOW ^{c,d,e}	RR 0.50 (0.34 to 0.73)	534 per 1,000	267 fewer per 1,000 (352 fewer to 144 fewer)
Air leak	352 (3 RCTs)	⊕○○○ VERY LOW ^{c,d,e}	RR 0.42 (0.22 to 0.79)	136 per 1,000	79 fewer per 1,000 (106 fewer to 29 fewer)
Pulmonary Hemorrhage	307 (2 RCTs)	⊕○○○ VERY LOW ^{b,c,d}	RR 1.06 (0.32 to 3.55)	32 per 1,000	2 more per 1,000 (22 fewer to 81 more)
PDA requiring treatment	132 (1 RCT)	⊕○○○ VERY LOW ^{b,c,d}	RR 2.32 (0.75 to 7.16)	60 per 1,000	79 more per 1,000 (15 fewer to 368 more)
PPHN	175 (1 RCT)	⊕⊕○○ LOW ^{d,e}	RR 0.24 (0.10 to 0.55)	254 per 1,000	193 fewer per 1,000 (229 fewer to 114 fewer)

Explanations

The evidence was downgraded by two levels for the outcome mortality and PPHN due to risk of bias and imprecision, and by three levels for all the other outcomes due to risk of bias, imprecision and indirectness. Specific reasons are provided below:

- Allocation concealment not clear in Zhou et al study.
- Imprecision due to 95%CI crossing line of no effect
- There was indirectness in relation to the patient group with one RCT enrolling neonates between age group 32 - 34 weeks' gestation (approximately 1/3rd of the total study population).
- The intervention was not blinded
- OIS and event rates are low

Summary of judgements

Problem(62,63): With 26 million births annually and a preterm rate of 10%, the total number of preterm births would be around 2.6 million in India. Of these, 1.86 million are likely to be constituted by the late preterm group (70% of total preterm population). About 4 - 29% of them end up with respiratory failure. One of the major causes of respiratory failure in this group is RDS. Approximately 2 - 4 % (56,000) of the late preterm neonates might be candidates for surfactant. It is also evident from literature that early term neonates born between 37 - 38 weeks' have worse respiratory outcomes when compared to term neonates of more than or equal to 39 weeks' gestation. Most of the studies on surfactant are concentrated on neonates of lesser gestational ages. Guidelines for use of surfactant in these relatively bigger, but vulnerable babies are scarce. Hence, it is important that evidence regarding the use of surfactant in late preterm and early term neonates with RDS be reviewed and recommendations be made.

Balance of benefits and harm: The critical outcome of mortality was studied by one large observational trial from China.(67) The overall effect estimate for reduction in mortality with surfactant use was 0.39 (0.29 - 0.53) [unadjusted OR (95% CI)]. However, this study had evaluated late preterm neonates who had hypoxic respiratory failure requiring invasive ventilation. Evidence from RCTs indicates beneficial effects of early surfactant therapy in late preterm neonates with RDS in relation to decreased need for invasive mechanical ventilation.(64–66) The incidence of pulmonary hemorrhage was similar in both the groups. One trial had evaluated the incidence of ventilator associated pneumonia (VAP) and found that it was not different between the groups.(66) The incidence of other transient adverse effects of surfactant instillation such as bradycardia and desaturation were not studied.

Equity: Surfactant is a costly drug and has been proven to be effective in decreasing the risk of many adverse outcomes in very and extreme preterm neonates. Hence, use of surfactant in late preterm or early term neonates using similar thresholds used for smaller preterm neonates, especially in financially constrained settings might result in inequity.

Feasibility: It is more likely for a late preterm or an early term neonate to be treated in a level II center. The feasibility of giving surfactant in such settings might be an issue.

RECOMMENDATION

9. Early surfactant may be used in late preterm (34-36 weeks' gestation) and early term neonates (37-38 weeks' gestation) with RDS who satisfy the criteria for surfactant therapy. (FiO₂ > 0.4, PEEP ≥ 7 cm H₂O)

Weak recommendation, Low certainty of evidence

Justification: The overall CoE was very low to low for some important outcomes. Hence, a weak recommendation for the option was given. The recommended FiO₂ and PEEP thresholds for

surfactant instillation in preterm neonates of lesser gestational ages are 0.30 and 6 cm H₂O, respectively. Use of such low thresholds for late preterm neonates might result in overuse of surfactant. Most of the included studies have used a FiO₂ cut off of 0.4 in the late preterm and term gestation group. Hence, it is recommended that late preterm and early term neonates with RDS and requiring a PEEP \geq 7 cm H₂O and a FiO₂ > 0.4 be considered for surfactant therapy, provided other causes of respiratory distress are ruled out.

Sub-group considerations: This recommendation is for late preterm and early term neonates with RDS diagnosed based on clinical examination and radiographic evidence. Other causes of respiratory distress in this subgroup of neonates such as PPHN (not secondary to RDS), transient tachypnea of newborn, etc. are not included in this recommendation.

Practice Question 10: Is there a role for surfactant administration beyond 72 hours of age in preterm neonates less than 34 weeks' gestation with RDS who present late during the disease course?

Population: Preterm neonates born at less than 34 weeks of gestational age with RDS who present late or are transferred to a tertiary care center beyond 72 hours of life.

Intervention: Animal or synthetic surfactant administration

Comparator: Standard therapy including non-invasive or invasive respiratory support

Summary of evidence

No RCT comparing surfactant administration versus standard therapy in preterm neonates with RDS who presented late to a tertiary care center was found. Data from three RCTs were synthesized in a meta-analysis.(70–72) The patient population and the intervention evaluated was different from the intended PICO. All the studies were conducted in HICs. Preterm neonates of gestational age less than 28 weeks were enrolled by two RCTs and less than 33 weeks' by one RCT. Surfactant was given at varying postnatal ages from 3-14 days in the included studies. All the studies predominantly enrolled neonates who had received at least one dose of surfactant early in the course of the disease. Low to very low CoE suggest that delayed administration of surfactant might not be beneficial in improving the outcomes of preterm neonates with RDS. While the CoE was downgraded by two levels for indirectness and imprecision for the outcomes – mortality, BPD, death or BPD at 36 weeks' PMA and severe IVH, it was downgraded by three levels for the outcomes re-hospitalization in the first year and sepsis for inconsistency in addition to indirectness and imprecision. The SoF table is provided in table 10.

Table 10 : Summary of findings - Surfactant administration after 72 hours in preterm neonates less than 34 weeks' gestation with RDS who present late during the disease course

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo (air)	Risk difference with delayed surfactant (> 3 days)
Mortality	765 (3 RCTs)	⊕⊕○○ LOW ^{a,b}	RR 0.99 (0.66 to 1.48)	110 per 1,000	1 fewer per 1,000 (38 fewer to 53 more)
BPD at 36 weeks' PMA	647 (3 RCTs)	⊕⊕○○ LOW ^{a,b}	RR 1.01 (0.92 to 1.11)	680 per 1,000	7 more per 1,000 (54 fewer to 75 more)
Mortality or BPD at 36 weeks' PMA	621 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	RR 1.03 (0.90 to 1.17)	598 per 1,000	18 more per 1,000 (60 fewer to 102 more)
Re-Hospitalisation in the first year	519 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	RR 0.92 (0.71 to 1.20)	313 per 1,000	25 fewer per 1,000 (91 fewer to 63 more)
Sepsis	765 (3 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	RR 0.90 (0.77 to 1.04)	307 per 1,000	31 fewer per 1,000 (71 fewer to 12 more)
Severe IVH (>Grade II)	647 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	RR 1.35 (0.93 to 1.94)	139 per 1,000	49 more per 1,000 (10 fewer to 130 more)

Explanations

CoE was downgraded by two levels for indirectness and imprecision for the outcomes – mortality, BPD, death or BPD at 36 weeks' PMA and severe IVH. CoE was downgraded by three levels for the outcomes re-hospitalization in the first year and sepsis for inconsistency, indirectness and imprecision. The specific reasons are stated below:

a. There was indirectness in relation to the patient population and the intervention. None of the studies had enrolled neonates with severe RDS who have not received surfactant in the first 72 hours and only one study had enrolled neonates between 3 - 7 days. Also, there was indirectness in relation to the intervention with one study using iNO in both the groups.

b. 95% CI crosses the line of no effect

c. I² value of > 50%.

Summary of judgements

Problem: Early use of surfactant has been shown to be more beneficial than late therapy in RDS. However, there are scenarios where surfactant might need to be considered at a later stage of the disease process. In LMICs, transfer of the neonate from peripheral to referral center could often be delayed. Also, some neonates with severe RDS might have worsening disease after an initial response. Hence, this question of whether delayed administration of surfactant will be beneficial in RDS is important.

Balance of benefits and harm: The three RCTs comparing the effect of delayed surfactant beyond the first 72 hours did not show any substantial benefits. Two of the included studies (Ballard et al., Laughon et al.) have shown that the neonates who received late surfactant had statistically significant increased episodes of desaturations and bradycardia during the instillation of the drug and all were transient in nature. The other serious adverse events such as PDA and pulmonary hemorrhage were comparable between the groups.

RECOMMENDATION

10. The guidelines panel suggests not using surfactant therapy in preterm neonates born at less than 34 weeks of gestation who present with respiratory distress at a referral hospital beyond 72 h of age, irrespective of prior surfactant therapy.

Weak recommendation, Ungraded (Expert consensus)

Justification: All the included studies were from the developed countries with most neonates studied having received surfactant doses in the initial 72 hours of life for the treatment of RDS. In LMICs, there might be a subset of preterm neonates less than 34 weeks' gestation with severe RDS who present beyond 72 hours of age to the tertiary center and have not received even a single dose of surfactant. There were no RCTs that had evaluated this specific subset of neonates. Natural course of RDS is to usually peak at 24-48 h followed by either resolution, or death, or transition into evolving BPD. Surfactant is not needed in first two and not proven to be of any benefit in the last instance. In a neonate who has CXR suggestive of RDS beyond 72 h, other differential diagnoses like pneumonia or lung injury become more important. The indirect evidence also does not show any benefit in critical or important outcomes.

Practice Question 11: Is Early intra-tracheal administration of corticosteroid and pulmonary surfactant better than pulmonary surfactant alone in preterm neonates born at less than 34 weeks' gestation with RDS ?

Population: Preterm neonates born at less than 34 weeks' gestation with RDS and stabilized on CPAP

Intervention: Intratracheal administration of corticosteroids using surfactant as a vehicle

Comparator: Animal or synthetic surfactant alone

Summary of evidence

Evidence from a network meta-analysis (NMA) evaluating different types of postnatal corticosteroids was evaluated.(73) Three RCTs evaluating intra-tracheal administration of corticosteroids using surfactant as a vehicle had reported on the outcomes – BPD, BPD or

mortality at 36 weeks' PMA, mortality and were included by the NMA.(74–76) Low CoE suggest that intra-tracheal budesonide might be beneficial in decreasing the risk of BPD and combined outcome of death or BPD at 36 weeks' PMA. Further, there was no increased risk of neurodevelopmental impairment at 18 - 22 months' corrected age (CoE - low) as reported by the systematic review and NMA. The CoE was downgraded by two levels for heterogeneity and imprecision. A summary of evidence is provided in Table 11. Detailed explanation regarding how the CoE is derived for a NMA is provided in the systematic review and NMA. (72)

Table 11: Network estimates and quality of evidence for early intra-tracheal administration of corticosteroid and pulmonary surfactant compared to pulmonary surfactant alone in preterm neonates with RDS

	Indirect Evidence	Direct Evidence	Network Meta-analysis	
Studies / n / events	Certainty of evidence	Certainty of evidence	Risk Ratio(95% Credible Interval)	Certainty of evidence
BPD or mortality at 36 weeks PMA				
3 / 467 / 263	-	Low ^{&+}	0.73(0.57, 0.91)	Low
BPD				
2 / 317 / 130	-	Low ^{&+}	0.53 (0.37, 0.72)	Low
Mortality				
2 / 381/ 67	-	Low ^{&+}	0.65 (0.33, 1.16)	Low
+Heterogeneity. &Imprecision. Values in bold are statistically significant				

Summary of judgements

Balance of benefits and harm: In vivo studies have indicated that mixing budesonide with surfactant does not affect the potency of the surfactant. Two studies that have reported on long term neurodevelopmental data have found intra-tracheal budesonide to be safe. Intratracheal budesonide using surfactant as a vehicle decreased the risk of BPD or mortality at 36 weeks' PMA and BPD.

Resource utilization: A nebulizing suspension of budesonide was used in conjunction with surfactant in a concentration of surfactant: budesonide - 50: 1 in the largest RCT included. Use of budesonide warrants its procurement and storage, which might result in more costs and resource utilization. But no cost analysis study has been done.

RECOMMENDATION

11. Early intra-tracheal corticosteroids may not be used as an adjunct to surfactant in the treatment of preterm neonates < 34 weeks' gestation with RDS.

Weak recommendation, Low certainty of evidence

Justification: The overall CoE was low for all the critical and important outcomes. Feasibility of preparing the mixture, resource utilization and with only three RCTs contributing to the evidence, the panel was of the judgement that further RCTs evaluating intra-tracheal budesonide are warranted.

Practice Question 12: Is bolus surfactant or surfactant lavage along with standard therapy (invasive respiratory support) superior to standard therapy alone in late preterm and term neonates with meconium aspiration syndrome ?

Population: Late preterm and term neonates diagnosed with meconium aspiration syndrome and requiring invasive ventilation

Intervention(s): Animal or synthetic surfactant given as bolus doses or as lavage after dilution along with standard care of invasive ventilation

Comparator: Standard care of invasive ventilation alone

Summary of evidence

Nine RCTs (bolus surfactant - 6, surfactant lavage - 3) including 728 neonates (Bolus surfactant – 580 neonates, surfactant lavage – 148 neonates) were analyzed.(77–85) Low CoE indicates that bolus surfactant might be beneficial in decreasing the risk of mortality and combined outcome of death or requirement of extracorporeal membranous oxygenation (ECMO). The CoE was downgraded by two levels for inconsistency and imprecision. Also, low CoE suggests that surfactant lavage might be efficacious in decreasing the risk of combined outcome death or ECMO. The CoE was downgraded by two levels for risk of bias and imprecision. The SoF is given in tables 12a and 12b.

Table 12a : Summary of findings table - Bolus surfactant vs. standard therapy in neonates with meconium aspiration syndrome

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard therapy	Risk difference with bolus surfactant
Mortality	(5 RCTs)	⊕⊕⊕○ MODERATE ^a	RR 0.80 (0.39 to 1.66)	-	-
Requirement of ECMO	208 (2 RCTs)	⊕⊕○○ LOW ^{b,c}	RR 0.64 (0.46 to 0.91)	475 per 1,000	171 fewer per 1,000 (257 fewer to 43 fewer)
Death or requirement of ECMO	208 (2 RCTs)	⊕⊕○○ LOW ^{b,c}	RR 0.68 (0.49 to 0.93)	495 per 1,000	158 fewer per 1,000 (252 fewer to 35 fewer)
Pneumothorax	269 (3 RCTs)	⊕⊕○○ LOW ^{a,b}	RR 0.82 (0.39 to 1.73)	99 per 1,000	18 fewer per 1,000 (61 fewer to 72 more)
Duration of mechanical ventilation	(5 RCTs)	⊕⊕⊕○ MODERATE ^d	-		MD 5.4 days lower (9.76 lower to 1.03 lower)
Duration of hospital stay	(4 RCTs)	⊕⊕⊕○ MODERATE ^d	-		MD 4.68 Days lower (7.11 lower to 2.24 lower)

Explanations

CoE was downgraded by two levels for the outcomes requirement of ECMO, death or ECMO and pneumothorax due to inconsistency and imprecision. CoE was downgraded by one level for the outcomes mortality, duration of mechanical ventilation and hospital stay due to imprecision. The specific reasons are given below-

a. 95% CI crosses line of no effect

b. $I^2 > 50\%$

c. Event rate is low. 95% CI crosses therapeutic threshold

d. OIS low

Table 12b : Summary of findings table - Surfactant lavage vs. standard therapy in neonates with meconium aspiration syndrome

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard treatment	Risk difference with surfactant lavage
Mortality	148 (3 RCTs)	⊕○○○ VERY LOW _{a,b,c}	RR 0.87 (0.43 to 1.75)	197 per 1,000	26 fewer per 1,000 (112 fewer to 148 more)
Requirement of ECMO	47 (2 RCTs)	⊕⊕○○ LOW _{a,c}	RR 0.27 (0.04 to 1.86)	190 per 1,000	139 fewer per 1,000 (183 fewer to 164 more)
Requirement of ECMO or Mortality	88 (2 RCTs)	⊕⊕○○ LOW _{a,d}	RR 0.33 (0.11 to 0.96)	286 per 1,000	191 fewer per 1,000 (254 fewer to 11 fewer)
Pneumothorax	148 (3 RCTs)	⊕⊕○○ LOW _{a,c}	RR 0.62 (0.18 to 2.15)	85 per 1,000	32 fewer per 1,000 (69 fewer to 97 more)
Duration of mechanical ventilation	(2 RCTs)	⊕⊕○○ LOW _{a,e}	-	The mean duration of mechanical ventilation was 0 Days	MD 1.31 Days lower (1.91 lower to 0.72 lower)
Duration of hospital stay	(1 RCT)	⊕⊕○○ LOW _{a,e}	-	The mean duration of hospital stay was 0 Days	MD 2 Days lower (0.34 lower to 3.66 lower)

Explanations

CoE was downgraded by three levels for the outcome mortality due to risk of bias, inconsistency and imprecision. All other outcomes were downgraded by two levels for risk of bias and imprecision. Specific reasons are listed below-

a. Performance bias in view of non-blinding of the intervention in all the three trials

b. I² - 58%

c. 95% CI crosses line of no effect

d. Upper limit of 95%CI crosses treatment threshold. Low event rate and OIS not adequate

e. Upper limit of MD crosses treatment threshold. OIS low.

Summary of judgements

Problem: The incidence of meconium stained amniotic fluid is around 9 - 20% of total deliveries.⁽⁸⁵⁾ Of these, around 3 - 5% of the neonates develop meconium aspiration syndrome (MAS). The severity of MAS can range from being a mild disease to a devastatingly severe one requiring ECMO or resulting in death. With the introduction of advanced therapies such as inhaled nitric oxide and ECMO, the mortality of MAS has come down significantly in developed nations. In LMICs, the mortality rate is still high in view of non-availability of such interventions in many settings. Hence, it is important that the use of a drug such as surfactant in MAS, which is available in most of the LMICs be evaluated.

Balance of benefits and harm: The critical outcome of mortality or ECMO is reduced by 32% (7-52%) with bolus surfactant therapy and by 67% (4-89%) with surfactant lavage. There were no serious adverse events noted in the studies. However, lavage where a large quantity of fluid (15ml/kg of diluted surfactant with final concentration of 5mg/ml) is instilled into the airways theoretically has plausible risks of desaturations and bradycardia when compared to bolus instillation. Also, lavage is a laborious procedure requiring at least an hour. As lavage requires dilution of the surfactant, there is a risk of contamination. Finally, lavage mandates training of the personnel for the same.

Resource utilization: Surfactant is a costly drug and since MAS is a disease mostly seen in term neonates, the amount of surfactant that will be required will be more when compared to treating preterm neonates with RDS. However, the possibility of reduction in requirement of ECMO, duration of mechanical ventilation duration and hospital stay may negate the cost incurred by the surfactant. There are no studies evaluating the costs or resources required in LMIC.

RECOMMENDATION

12. Bolus surfactant may be used in treating late preterm and term neonates with severe MAS requiring invasive ventilation with an oxygenation index > 15.

Weak recommendation, Low certainty of evidence

Justification: The CoE was low. There were no studies on resource utilization or cost analysis. Bolus surfactant application is more feasible and less labor intensive when compared to lavage. Hence, a weak recommendation for bolus therapy over lavage therapy was given.

Implementation considerations: Studies have used both porcine and bovine surfactants. Varying doses of surfactant were utilized, with dose range for bovine surfactant being 70-150 mg/kg and curosurf being 120-200 mg/kg. The severity of MAS has been judged based on several criteria such as Oxygenation index (OI), FiO₂ requirement, a/A O₂ ratio as well as MAP. Included studies have predominantly used OI criteria and hence our recommendation is based on that. Most of the studies have given repeat doses of surfactant in MAS based on differing thresholds. Hence, it is recommended that repeat doses may be used in selective

cases with continued requirement of invasive ventilation with an OI >15. The doses should be spaced as per the recommendations of the manufacturer.

Practice Question 13: Does addition of Surfactant to standard therapy (antibiotics with invasive ventilation) improve outcomes over standard therapy alone in neonates with bacterial pneumonia ?

Population: Term or preterm neonates with severe bacterial pneumonia who require invasive ventilation

Intervention: Surfactant administration along with standard therapy including antibiotics and invasive ventilation

Comparator: Standard therapy alone

Summary of evidence

Data from subgroup analysis of one RCT and post hoc analysis of another RCT was synthesized in a meta-analysis, and evidence from one observational study was also assessed separately.(80,86,87) The two RCTs had enrolled sick late preterm or term neonates who had hypoxic respiratory failure (OI > 15) of which one of the causes was bacterial pneumonia.(80,86) While one trial had used inhaled nitric oxide (iNO) in both the arms, one had not indicated the use of iNO. The observational study had included neonates of median gestational age of 35 weeks who were diagnosed with severe pneumonia and who were on invasive ventilation.(87) Very low CoE suggests that surfactant use in late preterm or term neonates with severe pneumonia with an OI>15 might decrease the risk of combined outcome of mortality or ECMO. The CoE was downgraded for risk of bias, indirectness and imprecision. Further, use of surfactant in neonates with severe pneumonia might reduce the duration of invasive mechanical ventilation as well as hospital stay (CoE- very low). CoE was downgraded for imprecision. The SoF is given in table 13.

Table 13 : Summary of findings table - Surfactant compared to standard therapy in neonates with bacterial pneumonia

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard therapy	Risk difference with surfactant
Death or need for ECMO	140 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	RR 0.45 (0.22 to 0.92)	277 per 1,000	152 fewer per 1,000 (216 fewer to 22 fewer)
Mechanical ventilation duration assessed with: Hours	208 (1 observational study)	⊕○○○ VERY LOW ^d	-	-	MD 24 Hours lower (35.26 lower to 12.74 lower)
Length of stay assessed with: Days	208 (1 observational study)	⊕⊕○○ VERY LOW ^d	-	-	MD 3 days lower (1.52 lower to 4.48 lower)

Explanations

The CoE was downgraded for risk of bias, indirectness and imprecision for the outcome death or requirement of ECMO. CoE was downgraded for imprecision for all the other outcomes. The specific reasons are detailed below-

a. The two included studies were post hoc analysis of RCTs which had done a subgroup analysis of surfactant use versus standard therapy in sepsis/ bacterial pneumonia. Since subgroup analyses are prone for selection bias, the risk of bias was adjudged as very serious

b. One trial had included sepsis and pneumonia together. Hence there was indirectness in relation to patient population. Also, the second trial had used inhaled nitric oxide in both the groups. Hence there was indirectness in relation to the intervention as well as the comparator.

c. 95% CI crosses treatment threshold. Event rates are low and OIS not met

d. Trial design - Observational and low sample size

Summary of judgements

Balance of benefits and harm: The need for ECMO or death is reduced by 55% (8% - 78%) with surfactant therapy in neonates with bacterial pneumonia. Lotze et al. had observed that there were significantly more infants ($p < 0.001$) in the surfactant group (32.8%) who had dosing-related problems than in the placebo group (8.0%), and, in particular, hypoxia ($p < 0.001$) and endotracheal tube occlusion ($p < 0.001$). However, all of these were transient.

Resources required: The hospital costs for the intervention was studied by Qiu et al. from China and found no difference between surfactant therapy and conventional treatment. [4.8+/-1.6 (surfactant) vs 5.3+/-2.1 (conventional therapy) ten thousand Yuan, $p = 0.29$].(87) However, no studies are available from India.

RECOMMENDATION

13. Surfactant may be considered in late preterm and term neonates with severe bacterial pneumonia requiring invasive ventilation with an oxygenation index > 15.

Weak recommendation, Very Low certainty of evidence

Justification: A weak recommendation for the therapy was given in view of the very low CoE.

Practice Question 14: What should be the pre-conditions required to safely administer surfactant to neonates?

Background

Surfactant use is a standard of care for treating RDS in preterm neonates in developed nations. A recent systematic review and meta-analysis had indicated that surfactant use in LMICs might result in a significant decrease in mortality [(relative risk (RR) 0.67; 95% confidence interval (CI) 0.57 to 0.79)].(62) There was also a significant reduction in the incidence of air leak with surfactant use [(RR 0.51; 0.29 to 0.90)]. The review also tried to address the safety of surfactant use in LMICs and concluded that it was safe and was not associated with increased adverse events. Finally, it was recommended that surfactant use should be restricted to NICUs with availability of mechanical ventilation. This conclusion was based on the high failure rate of INSURE strategy in the studies from LMICs (34% - 45%). Most of these studies included preterm infants 25 weeks and above.

This question is addressed under the following sub-headings:

- Obstetric practices
- Delivery room requirements
- NICU/SNCU requirements

Obstetric practices

In utero transfer : Most studies from high income countries have shown that delivering high risk pregnancies in a tertiary center with level 3 NICU would result in better neonatal outcomes.(88) Hence, it is of vital importance that pregnancies where complications such as RDS is anticipated be transferred in utero to appropriate level of neonatal unit as per gestation.

Antenatal corticosteroids : All pregnant women who are at risk of delivering prematurely be given corticosteroids as per the existing obstetric protocol to maximize the efficacy of surfactant. It is well known that antenatal corticosteroids act synergistically with surfactant and

decrease the risk of RDS as well as the complications of prematurity such as neonatal mortality, NEC, PDA, neonatal sepsis and hemodynamic instability in the immediate newborn period.(89)

Delivery room requirements

Personnel adequately trained in preterm newborn resuscitation and intubation should be present in the delivery room. The delivery room should have adequate provisions for maintaining normothermia in the preterm newborns such as a radiant warmer and plastic bag. It is well known that delivery room hypothermia can result in secondary surfactant deficiency and hence worsen RDS severity.(90)

Blended oxygen and pulse oximeter : It is desirable that the delivery rooms are equipped with adequate provisions for blended oxygen as well as a pressurized source of air, and pulse oximeter. Use of 100% oxygen can result in lung injury and worsen RDS severity.(91)

T-Piece resuscitator / Delivery room CPAP: T-piece resuscitators can deliver peak inspiratory pressure (PIP) as well as PEEP consistently and are used to give delivery room CPAP. It is desirable to equip labor room with provision to provide PEEP/CPAP during resuscitation by use of T-piece resuscitator or self-inflating bag with a PEEP valve.

Transport incubator : It is important that all the preterm neonates with RDS who are stabilized in the delivery room be shifted to the NICU/SNCU ensuring normothermia and ongoing CPAP therapy. It is desirable to use a transport incubator equipped with provisions for CPAP.

NICU/SNCU requirements

The neonatal care units providing respiratory support and *surfactant to preterm neonates should follow the appropriate norms for accreditation and providing respiratory support including adequate space, trained personnel, adequate equipment and supplies, infection control and prevention and, written protocols.*

CPAP and Ventilators : CPAP is the primary mode of respiratory support in neonates with RDS. Therefore, CPAP machines along with air-oxygen blender, humidifier, circuit and nasal interface should be available. Due to high risk of INSURE or CPAP failure in neonates with severe RDS, ideally back-up ventilators should also be available. If ventilators are not available e.g. in most of SNCUs, a clearly identified referral pathway must be used for timely transport of neonates at high risk of needing invasive ventilation (gestation less than 30 weeks, mother not received antenatal steroids or high (>60%) FiO₂ requirement before administration of surfactant).

RECOMMENDATION

14. Surfactant therapy should be given only in neonatal units with availability of CPAP machine and preferably also a back-up ventilator. If a ventilator is not available and the risk of INSURE/LISA failure is high (gestation less than 30 weeks, mother not received antenatal steroids or high (>60%) FiO₂ requirement before administration of surfactant) arrangements should be made to transport the neonate to an appropriate health facility for ventilation.

Strong recommendation, Not graded (Expert consensus)

Justification: The success of surfactant therapy is dependent on multiple factors including effective but gentle resuscitation, early adequate CPAP support and infection control and prevention. Many infants, especially those larger than 30 weeks gestation can be managed successfully on CPAP alone. However, since respiratory failure is possibility, arrangements for back-up ventilation are required preferably in the unit, or in near-by units.

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Appendices

Appendix 1 – Rating of the outcomes

Appendix 2 - Search strategy for the three databases – MEDLINE, EMBASE, CENTRAL

Appendix 3 - Literature search - PRISMA Flow

Appendix 4 - Risk of bias of the included studies (Figures 1-12)

Please see the online version at www.nnfi.org/cpg for the above documents

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