

**Less invasive surfactant administration for neonatal respiratory distress syndrome –  
A consensus guideline**

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**Short title:** Less invasive surfactant administration for neonatal RDS – A consensus guideline

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## **Abstract**

### **Introduction**

Less Invasive Surfactant Administration (LISA) is a method of surfactant delivery to preterm infants for treating respiratory distress syndrome (RDS), which can reduce the composite risk of death or bronchopulmonary dysplasia and the time on mechanical ventilation.

### **Methods**

Systematic literature search of studies published up to April 2021 on minimally invasive catheter surfactant delivery in preterm infants with RDS. Based on these studies, with parental feedback sought via an online questionnaire, nine UK-based specialists in neonatal respiratory disease developed their consensus for implementing LISA. Recommendations were developed following a modified, iterative Delphi process using a questionnaire employing a nine-point Likert scale and an *a priori* level of agreement/disagreement.

### **Results**

Successful implementation of LISA can be achieved by training the multidisciplinary team and following locally agreed guidance. From the time of the decision to administer surfactant, LISA should take <30 minutes. The comfort of the baby and requirements to maintain non-invasive respiratory support are important. While many infants can be managed without requiring additional sedation/analgesia, fentanyl along with atropine may be considered. Parents should be provided with sufficient information about medication side-effects and involved in treatment discussions.

### **Conclusion**

LISA has the potential to improve outcomes for preterm infants with RDS and can be introduced as a safe and effective part of UK-based neonatal care with appropriate training.

## **Introduction**

Respiratory distress syndrome (RDS) can affect infants of all gestational ages. It is most common in preterm infants, affecting nearly all infants born at or less than 28 weeks of gestation (1, 2). Exogenous surfactant administered after intubation through the endotracheal tube and followed by mechanical ventilation (MV) has been the established, evidence-based cornerstone of RDS treatment for decades (3, 4).

MV is a major risk factor for bronchopulmonary dysplasia (BPD) and variations in surfactant application methods have been developed to minimise MV, including INTubation-SURfactant-Extubation (INSURE) and Less Invasive Surfactant Administration (LISA), also referred to as minimally invasive surfactant therapy (MIST) (5-10). With LISA, surfactant is instilled directly into the trachea via a thin/small bore catheter whilst the baby continues to receive non-invasive respiratory support (8, 9, 11). Meta-analysis of trials comparing LISA with other methods of surfactant delivery indicated that LISA reduces the need for MV at any time during neonatal intensive care and reduces the composite risk of death or BPD without increasing the risk of pneumothorax, even in extremely preterm infants (12). Smaller subsequent studies have also shown improved outcomes (13, 14). A recent systematic review of randomised controlled trials (RCTs) identified that LISA resulted in significantly reduced early intubation rates and BPD compared with INSURE (15). A recent 2-year follow-up demonstrated that premature infants treated with LISA demonstrated no significant differences in weight, length or neurodevelopmental outcome compared with infants who received standard treatment (16). LISA is a standard of care in many European neonatal units (17-19) with good safety (16); in the United Kingdom the uptake of LISA is still gaining momentum (20, 21).

Recent evidence-based consensus guidelines on the use of surfactant for RDS (4, 22) recommend LISA for breathing infants with RDS. This manuscript aims to provide practical guidance to UK neonatal teams who are considering or are in the process of implementing LISA. Our recommendations are based upon available evidence, consensus view and a survey of parental opinion/values.

## **Materials and Methods**

### **Literature search**

A systematic literature search to identify studies that investigated the use of minimally invasive techniques to deliver surfactant via a catheter that were published up to 28 April 2021 was performed on PubMed and Google Scholar databases. Combinations of Medical Subject Headings

(MeSH) and non-MeSH keywords used in the search are listed in **Table 1**. A PRISMA flow diagram detailing how relevant articles were selected is provided in **Supplementary File 1**. Only human studies in English language were included, but study type was unrestricted. Duplicates were removed based on title and abstract. One investigator screened abstracts for eligibility before dissemination to the panel. References were manually cross-referenced for duplicates or initially unidentified records, and potentially eligible publications reviewed.

## **Panel selection**

Nine UK specialists in neonatal care were selected based on their previous clinical and scientific experience on the use of minimally invasive surfactant administration techniques in the management of RDS.

## **Development of consensus**

A modified, iterative Delphi approach was used to develop this consensus (23). In the first round, the group discussed the identified published evidence on LISA (**Supplementary File 1**) and agreed the following key areas for a guideline: Background and Evidence, Patient Selection, Equipment, Developing Local Practice (Training and Audit, Personnel), Performing LISA (Preparing the Baby, Performing the Procedure) and Parental Experience. In the second round, a 113-question questionnaire was developed based on the key areas (**Supplementary File 2**). Preference hierarchy was established by a nine-point Likert scale and an *a priori* level of agreement/disagreement was applied (**Supplementary File 3**). In the final third round, statements and key areas were clarified (**Supplementary File 4**).

Parental experience and opinion were sought using an online questionnaire posted to all followers on the Facebook site of Bliss (UK Registered Charity 1002973 Fourth Floor, Maya House, 134-138 Borough High Street, London SE1 1LB; [www.bliss.org.uk](http://www.bliss.org.uk)) from 26–27 June 2019 (**Supplementary File 5**). All responses from parents whose premature babies required ventilation support formed the target sample and were assessed. The questionnaire was developed by the Chiesi Medical Team with the aim to understand parents' views on the decision-making process in neonatal units and their involvement in medical care and choice of medication. While the questionnaire was not developed specifically for RDS and LISA use, it allowed compiling information about parents' opinions on the decision-making process.

This process was supported by an unconditional grant from Chiesi UK Limited. The authors maintained full control over all content.

## Results

In the literature search, 168 records were screened based on the title and/or abstract, of which 66 were excluded as they did not meet the inclusion criteria. Full-texts of the remaining 102 records were evaluated, of which 53 were included in the evidence base for consideration by the group. Consensus was reached for all 113 questions at the conclusion of the modified Delphi process.

## Recommendations

This manuscript describes our recommendations for implementing LISA in the management of RDS based on evidence, consensus and parental survey. Training and an agreed local guideline are key elements for successful introduction.

### i. Patient selection

If a baby is stable on non-invasive respiratory support, but requires surfactant in line with published guidelines (4, 22), the success of the LISA procedure will depend on the experience of the team and the baby's tolerance of handling. While non-invasive ventilation may fail in infants of <1 kg weight or <26 weeks gestational age, the outcomes vary individually. There is therefore no lower/upper gestational limit for consideration of LISA, and clinician expertise will improve over time.

It is not always necessary to obtain a chest X-ray or chest ultrasound scan to confirm eligibility for LISA; however, clinicians should consider the risk of other pathology (e.g. pneumothorax). For babies >32 weeks, we recommend that imaging should be performed to confirm RDS, as surfactant deficiency is less common in infants older than 32 weeks. Whilst LISA would most often occur in the neonatal unit, it can be performed in the delivery room. The dose of surfactant by LISA is the same as that given by INSURE or in ventilated patients, and repeat doses may be given by LISA. A failed LISA attempt can be followed by another; a maximum of two attempts at LISA are recommended for giving a dose of surfactant.

The consensus view was that there should not be an absolute upper threshold of the fraction of inspired oxygen ( $FiO_2$ ) for LISA, although clinical instability, frequent apnoea or other clinical indicators of imminent requirement for intubation and ventilation would be relative contraindications to LISA.

### ii. Equipment

Use of different catheters are described for LISA, such as a nasogastric tube with the use of Magill forceps, or use of a vascular catheter such as an Angiocath™ (Becton Dickinson, Sandy, UT, USA). However, we recommend that catheters designed for the purpose of LISA should be used.

A laryngoscope should be used to visualise the vocal cords, and a video-laryngoscope was felt to be particularly useful. Whilst LISA may be perceived as being less technically difficult than intubation, confirming correct catheter placement requires confidence in the operator's capability to recognise appropriate placement, and video-laryngoscopy enhances that.

### **iii.Developing local practice**

#### **Training and audit**

We recommend neonatal team members should receive training and meet agreed competencies to facilitate safe and successful execution of LISA. Endotracheal intubation and LISA are different procedures both in terms of required training and purpose. Neonatal team members competent in endotracheal intubation can learn LISA and agreed competencies through specific training, for example through simulation followed by supervised practice; the use of video-laryngoscopy is helpful. It may be useful to ask experienced clinical teams in other neonatal units to provide local training and development, or to visit units where LISA is an established procedure.

We recommend that audit of local guidelines (such as time from decision to administer surfactant to time procedure is completed) should be performed to evaluate compliance, competence, effectiveness and complications, and that tools such as the Learn-See-Practice-Prove-Do-Maintain training approach are used for developing competency in LISA (24). Mannequin training for LISA has been shown to be useful in evaluation of preferred technique (25).

#### **Personnel**

The active assistance of a member of the neonatal team, ideally a nurse, is essential for successful LISA. Nursing staff may require specific training for assisting with the LISA procedure, and should be involved in the development and agreement of local clinical guidelines. There should be a checklist for babies undergoing LISA, an example of which is presented in **Supplementary File 6**. We also recommend following the local safety standards for invasive procedures (LocSSIP) checklist.

### **iv.Performing LISA**

#### **Preparing the baby**

All babies should be assessed for comfort, and although LISA is normally a brief procedure, good thermal management during LISA is important; hypothermia may affect the outcome of the procedure (4). A naso/oro-gastric tube should be placed prior to commencing the LISA procedure. Given that LISA is not an emergency procedure, the requirement for additional medications can be reconsidered as part of the overall procedure. While babies undergoing LISA in a Neonatal Intensive Care Unit (NICU) would normally have intravenous (IV) access secured, it is not necessary to

187 routinely use IV medications for this procedure. Rather, babies should be assessed individually, as  
188 their age, maturity and responsiveness will determine the need for medications and route of  
189 administration. The experience of the practitioner is also an important factor (26).

190 *Non-pharmacological comfort:* We recommend that babies should be swaddled to alleviate pain and  
191 improve comfort (27), and oral/buccal sucrose and/or breast milk should be considered for analgesia  
192 (28-30). Our experience is that most babies can be satisfactorily managed with these non-  
193 pharmacological options.

194 *Caffeine:* Most preterm babies <30 weeks gestation undergoing LISA will have received IV caffeine  
195 citrate, which is recommended to maintain non-invasive respiratory support (4). The decision for  
196 LISA should not be delayed by the need to administer caffeine.

197 *Atropine:* The use of atropine to prevent vagally-induced bradycardia is not routinely recommended.  
198 Whilst lower incidence of bradycardia has been reported (31), a single IV dose of 10 µg/kg atropine  
199 can be administered if a baby has a bradycardia, which is deemed by the team to be clinically  
200 significant.

201 *Sedation/analgesia:* There is no single medication that can be recommended as being preferred if  
202 sedation/analgesia is required, but fentanyl and propofol are often used. Sedation should  
203 particularly be considered in babies >32 weeks, but the need for sedation should be considered in all  
204 babies. Fentanyl, an analgesic, was used (at a dose of 1 µg/kg) in one small RCT of LISA and was  
205 generally well tolerated (32). Propofol (1 mg/kg) has been shown to improve comfort compared with  
206 no premedication in two small studies (1 observational, 1 RCT) (33, 34), but concerns regarding  
207 associated transient arterial hypotension and need for non-invasive positive-pressure ventilation  
208 (NIPPV), together with potential for neurotoxicity following extended exposure to high doses, exist  
209 (35, 36). For these reasons we preferred fentanyl (0.7 µg/kg) if pharmacological sedation/analgesia is  
210 required. In our experience, this fentanyl dose can achieve light sedation while preserving  
211 respiratory drive. Fentanyl should be instilled slowly to avoid interference with breathing. No dosing  
212 for propofol was recommended. Ketamine and midazolam were not recommended. If  
213 sedation/analgesia is being administered, the recommendation is to refrain from drawing up  
214 additional intubation drugs.

215 *Naloxone:* Some units may routinely prepare naloxone if bolus IV opiates are being used for  
216 premedication. However, naloxone should not be routinely given after LISA in an attempt to ensure  
217 adequate respiration. It is unlikely that any short-term discomfort encountered during LISA will  
218 result in long-term developmental harm, but the side effects of sedative/analgesic drugs, particularly  
219 respiratory depression (37), should always be considered.

220 Performing the procedure

221 The time from the decision to administer surfactant to performing LISA should ideally be <30  
222 minutes, with timely intervention requiring effective communication between the medical and  
223 nursing teams. The plan to administer surfactant should be discussed with the parents soon after  
224 NICU admission, to give them enough time to make an informed decision. Prior to instillation,  
225 surfactant should be removed from the refrigerator and allowed to warm in ambient room  
226 temperature. As a minimum, all babies should be monitored continuously for pulse rate and oxygen  
227 saturations (SpO<sub>2</sub>). It is good practice to introduce a 'time out' prior to the commencement of  
228 the LISA procedure, which should form a part of the LISA procedure checklist  
229 **(Supplementary File 6).**

230 Non-invasive respiratory support should continue throughout the procedure. The catheter should be  
231 passed 1.5–2 cm below the vocal cords under direct laryngoscopy, after which the laryngoscope is  
232 removed. Connecting an IV cannula extension to the catheter before placing it may be useful to  
233 reduce risk of subsequent dislodgement. Some users find a neck roll useful. Surfactant should be  
234 very slowly administered over 2–5 minutes (our recommended rate: 0.5–1.0 mL/minute) to  
235 minimise reflux and episodes of hypoxia-bradycardia.

236 Oxygen requirements usually fall quickly after LISA and may continue to fall for a few hours  
237 afterwards.

#### 238 **v. Parental experience**

239 Parent opinions were collected via random sampling using an online questionnaire posted on the  
240 Bliss charity Facebook page. Overall, 54 parents provided answers to questions about their  
241 experiences of the care their babies received while staying in a NICU; most babies (38%) were born  
242 with <28 gestational weeks and 51% were diagnosed with RDS.

243 When considering a short but potentially uncomfortable medical procedure, where there is an  
244 option to use pain-relieving medications that have potential side effects, 43% of parents felt the  
245 success of the procedure was the most important, while for 35% making their baby comfortable  
246 while accepting a risk of side effects was most important. Interestingly, 35% agreed (and 4% strongly  
247 agreed), that they would rather not use any medication that made their babies more comfortable  
248 even if that meant that a short and potentially uncomfortable procedure might be less likely to be  
249 successful. Overall, 86% of parents trusted the doctors with decision making regarding best  
250 medication choices for their babies. These results suggest that appropriate information needs to be  
251 provided for the parents, alongside a sufficient explanation of risk, to ensure that parents are



making informed decisions, following the British Association of Perinatal Medicine shared decision-making framework (38).

## **Implications for Research**

Several of the recommendations in this guideline are based on the authors' experience, and further research would be valuable. The choice of a thin/small bore catheter, the speed at which the surfactant is administered, the timings of the doses and the use of sedation/analgesia are all areas where further evidence would strengthen the recommendations.

## **Conclusion**

LISA is an evidence-based strategy that augments non-invasive respiratory support for RDS in preterm infants. Clinicians aiming to introduce LISA to a neonatal unit are advised to have a bespoke guideline for when and how to perform LISA. There needs to be a focus on staff training with clear demonstration of LISA competency; the recommendations in this manuscript may be used for staff training and skill retention. Parents are often concerned about the potential side effects of medications and should be involved in treatment discussions. It is our view that LISA can be implemented safely and effectively and that, with increasing experience, any eligible baby can be treated for RDS by LISA.

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## **Statement of Ethics**

Ethics approval was not required.

## **Conflict of Interest Statement**

**PR** has previously received honoraria and travel support from Chiesi, Vapotherm, Inspiration Healthcare, Fisher and Paykel. **PB** has received honoraria from Chiesi for lectures and meetings. **CD** has received honoraria from Chiesi for educational session. **RF** has received honoraria and travel support from Chiesi. **GF** has received honoraria from Chiesi for educational sessions. **SJ** has nothing to disclose. **SJR** has received honoraria and travel support from Chiesi. **VV** has received honoraria and travel support from Chiesi. **CCR** has received honoraria from Chiesi, Abbott Pharmaceuticals, Fisher & Paykel Healthcare and Inspiration Healthcare for lectures and educational session.

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## **Author contributions**

All authors made equal contributions to the development of the statements, preparation and critical revision of the manuscript, and provided final approval of the version published. All authors agree to be accountable for all aspects of the work.

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