Lung Ultrasound Score Predicts Surfactant Need in Extremely Preterm Neonates

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abstract

BACKGROUND AND OBJECTIVES: There are several lung ultrasound scores (LUS) for evaluating lung aeration in critically ill adults with restrictive lung disorders. A modified LUS adapted for neonates correlates well with oxygenation and is able to be used to predict the need for surfactant in preterm neonates with respiratory distress syndrome (RDS). However, no data are available for extremely preterm neonates for whom timely surfactant administration is especially important. We hypothesized that LUS might be reliable in extremely preterm neonates with RDS who are treated with continuous positive airway pressure. We aimed to determine the diagnostic accuracy of LUS in predicting the need for surfactant treatment and re-treatment in this population.

METHODS: We performed a prospective cohort diagnostic accuracy study between 2015 and 2016 in a tertiary-care academic center. Inborn neonates at ≤30 weeks' gestation with RDS treated with continuous positive airway pressure were eligible. Surfactant was given on the basis of oxygen requirement thresholds derived from European guidelines, and a LUS was not used to guide surfactant treatment. We calculated the LUS after admission and analyzed its diagnostic accuracy to predict surfactant treatment and re-treatment.

RESULTS: We enrolled 133 infants; 68 (51%) received 1 dose of surfactant and 19 (14%) received 2 surfactant doses. A LUS is significantly correlated with oxygenation index ($\rho = 0.6$; $P < .0001$) even after adjustment for gestational age ($P < .0001$). A LUS can be used to accurately predict the need for the first surfactant dose (area under the curve = 0.94; 95% confidence interval: 0.90–0.98; $P < .0001$) and also the need for surfactant redosing (area under the curve = 0.803; 95% confidence interval: 0.72–0.89; $P < .0001$). The global accuracy for the prediction of surfactant treatment and re-treatment is 89% and 72%, respectively.

CONCLUSIONS: LUS may be used to predict the need for surfactant replacement in extremely preterm neonates with RDS.

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Drs De Martino and Yousef drafted the manuscript, designed the data collection instruments, collected and/or interpreted data, and critically revised the manuscript for important intellectual content; Drs Ben-Ammar and Shankar-Aguilera helped in the collection and interpretation of data, gave administrative, technical, and material support, and critically revised the manuscript for important intellectual content; Drs Raimondi and De Luca conceptualized, designed, coordinated, and supervised the study, performed the data analysis and interpretation, and critically reviewed

WHAT'S KNOWN ON THIS SUBJECT: A lung ultrasound can be used to easily diagnose respiratory distress syndrome, and a semiquantitative score based on ultrasound findings may reveal lung aeration and help to predict surfactant need in a general newborn population.

WHAT THIS STUDY ADDS: The lung ultrasound score can be used to predict the need for a first surfactant dose (area under the curve = 0.94; 95% confidence interval: 0.90–0.98; $P < .0001$) in extremely preterm neonates, and this is unaffected by gestational age. Lung ultrasound scores can be used to guide early surfactant replacement in extremely preterm neonates.

To cite: De Martino L, Yousef N, Ben-Ammar R, et al. Lung Ultrasound Score Predicts Surfactant Need in Extremely Preterm Neonates. *Pediatrics*. 2018;142(3):e20180463

Continuous positive airway pressure (CPAP) is the first-line therapy for respiratory distress syndrome (RDS), and current international guidelines recommend surfactant replacement only when CPAP fails.[1,2] Early surfactant administration within the first 2 to 3 hours of life reduces risk of death and/or bronchopulmonary dysplasia.[3] According to European guidelines, surfactant replacement should be performed when oxygen requirements are increasing.[1] However, arbitrary thresholds of the fraction of inspired oxygen (F_{IO_2}) might not accurately reveal the oxygenation status, and F_{IO_2} requirements may be slow to increase, thus delaying surfactant administration well after the best time frame for optimal efficacy.

In the last decade, lung ultrasounds have been increasingly used in critically ill patients, and evidence-based international guidelines are already available for the use of lung ultrasounds in adult critical care.[4] Many lung ultrasound scores (LUS) are currently used to perform a semiquantitative assessment of lung aeration and guide respiratory care in restrictive lung disorders[5–8] because this is strongly recommended (level of evidence A) by current guidelines.[4] We recently described the usefulness of a simplified LUS adapted from adult critical care[8] for term and preterm infants with RDS treated with CPAP.[9] The LUS was significantly correlated with various indices of oxygenation and revealed good diagnostic accuracy for predicting the surfactant need in neonates <34 weeks' gestational age (GA).[9] Other authors have also shown that qualitative lung ultrasounds can be used to predict the need for intubation in neonates of variable GA and/or different causes of respiratory failure.[10,11]

Extremely preterm neonates benefit the most from an optimized and timely surfactant administration because they are at a higher risk of long-term respiratory sequelae[12] and may require repeated surfactant treatment.[13] There are no data available on the use of a LUS in a homogeneous population of only extremely preterm neonates with RDS, and we hypothesize that LUS might be reliable in these patients. Our aim was to study the diagnostic accuracy of LUS in predicting the need for surfactant treatment and re-treatment in extremely preterm neonates with RDS on CPAP.

METHODS

Patients

We designed a prospective diagnostic accuracy cohort study that follows the Standards for the Reporting of Diagnostic Accuracy Studies guidelines.[14] The study was conducted in an academic tertiary-care referral NICU with ~4000 deliveries per year. All inborn neonates ≤30 weeks' GA born between 2015 and 2016 were eligible for the study. Exclusion criteria included (1) chromosomal abnormalities or complex congenital malformations, (2) congenital lung diseases, (3) early onset severe sepsis and/or septic shock (as defined elsewhere),[15] (4) the need for surgery in the first week of life, (5) congenital heart defects, and (6) delivery room surfactant administration, which was performed only if a neonate needed intubation for stabilization per current European guidelines.[1] Delivery room intubation was performed only on infants with persistent apnea or bradycardia who were unresponsive to face mask ventilation according to the international guidelines on neonatal resuscitation.[16]

We use a formal respiratory care protocol derived from European guidelines[1,9]: all eligible neonates are started on continuous flow CPAP immediately from birth in the delivery room and then transferred on a transport incubator that is equipped with the same CPAP delivery system (Fabian Evo; Acutronic Medical Systems, Hirzel, Switzerland); appropriately sized nasal masks (FlexiTrunk; Fisher and Paykel, Auckland, New Zealand) are used in the delivery room and during the transfer. In the NICU, which is adjacent to the delivery room, a variable flow CPAP generator (Infant Flow SiPAP; Vyaire Medical, Mettawa, IL) and dedicated, appropriately sized nasal masks were used. CPAP was set at 6 cm H_2O, and F_{IO_2} levels were adjusted to maintain oxygen saturation levels within the 90% to 95% target range, while pacifiers of adequate size with drops of 30% glucose solution were used to reduce leaks and provide sedation, if needed.[9,17] We administered 200 mg/kg of poractant α (Curosurf; Chiesi Farmaceutici, Parma, Italy) through the intubation–surfactant–extubation technique if the F_{IO_2} was >0.3 or >0.4 for infants ≤28 and >28 weeks' GA, respectively; these thresholds have been modified from those suggested by European guidelines.[1] A second 100 mg/kg dose was given if the F_{IO_2} remained higher than the cutoff F_{IO_2} value ≥10 hours after the first administration. Surfactant re-treatment was not performed <10 hours after the first administration because this is the median half-life of dipalmitoylphosphatidylcholine in preterm neonates who require multiple surfactant doses.[13] Per our routine NICU policy, the transcutaneous partial pressure of oxygen ($Ptco_2$) was measured through a device (TCM4; Radiometer Medical, Copenhagen, Denmark) used according to the American Association for Respiratory Care guidelines[18] and advice to obtain the most accurate measurement.[19] The $Ptco_2$ was measured after NICU admission and always before surfactant administration.[9] The oxygenation index (OI) was calculated after NICU admission as follows: $CPAP \times F_{IO_2} \times 100/Ptco_2$; for the OI calculation, leaks were

minimized by closing the mouth with gentle pressure on the jaw.[19] All new residents and fellows are trained in the respiratory protocol every 6 months.

All pregnancies received full prenatal care; GA estimate was based on the last menstrual date and early gestation ultrasound findings, and antenatal betamethasone was administered as two 12 mg doses 24 hours apart unless delivery occurred earlier. Infants who were small for GA were evaluated according to Fenton curves.[20] NICU clinical protocols did not change during the study. Participation in the study did not modify our routine clinical care. The study protocol was approved by the ethical board (SRLF-16-58), and written informed consent was obtained from parents after NICU admission.

Lung Ultrasound Protocol

Lung ultrasounds were routinely performed after NICU admission and always before surfactant administration. In our NICU, all attending physicians and senior fellows are trained to perform lung ultrasounds, which has been our first-line imaging technique since 2014.[21] Fellows and residents are regularly trained on a 6-month basis; the lung ultrasound protocol has been derived from the one previously described in our preliminary study on a general newborn population.[9]

In detail, lung ultrasounds are performed in a standardized manner once the CPAP is well transmitted and the infants are in a quiet state. Transversal and longitudinal scans of the anterior and lateral chest walls are performed by using a new high-resolution, microlinear, 15 MHz hockey stick probe (CX50; Philips Healthcare, Eindhoven, Netherlands).[9] The LUS is calculated on the basis of 3 chest areas for each side (upper anterior, lower anterior, and lateral). A score of 0 to 3 points is given for each area (the total score ranges from 0 to 18, inversely correlating with lung aeration).[9] Pictorial descriptions of the LUS are provided in Supplemental Fig 2. The decision to administer surfactant was made according to the F_{IO_2} thresholds described above, and a LUS was not used to guide surfactant treatment; surfactant administration was decided on by the attending physician, whereas a lung ultrasound was performed by a senior neonatal fellow and recorded on a dedicated electronic spreadsheet that was not included in the patient's files.[9] Masking the clinical conditions to the physicians performing the ultrasounds is impossible. However, a high interobserver agreement for LUS calculation has already been demonstrated under these conditions.[9] Statistical analyses were performed by an investigator who was not directly involved in the clinical care. All data were anonymously recorded and analyzed on a dedicated computer, secured, and used only for research purposes.

Statistics

The sample size was calculated as follows: in the 6 months before the study, surfactant had been administered to ~50% of NICU-admitted infants who fulfilled the same inclusion criteria of the study and followed the same surfactant administration protocol (negative-to-positive case ratio 1:1). By targeting an area under the curve (AUC) of ≥0.7, as previously published,[9] with an α error of = .05 and 95% power, 100 neonates would have been needed. We decided to continue the study beyond this threshold, given the simplicity of the study design, to have a sample size similar to that in our previous study.[9]

Data were tested for normality with the Kolmogorov–Smirnov test and expressed as a mean (SD) or median (interquartile range) as appropriate. The whole population was divided into 2 subgroups consisting of infants of ≤28 and >28 weeks' GA, respectively. The analyses were performed both on the whole population and as subgroup analyses as was done earlier.[9] Basic population data were compared between the 2 subgroups by using Student's t, Mann–Whitney, χ^2, or Fisher's exact tests as appropriate. Correlations were analyzed with a Spearman coefficient (ρ) and with partial correlation ($_{adj}r$) adjusted for GA.[22] Correlation coefficients were compared as previously published.[23] Receiver operating characteristic (ROC) analysis was used to evaluate the reliability of the LUS to predict the need for surfactant treatment and re-treatment; AUC and reliability data were reported with confidence intervals (CIs). Posttest probability was estimated according to the Fagan nomogram.[23] The AUCs were compared by using the method by Hanley and McNeil.[24] Analyses were performed with SPSS 15.0 (SPSS Inc, Chicago, IL) and MedCalc 13.3 (MedCalc bvba, Ostend, Belgium), and $P < .05$ was considered statistically significant.

RESULTS

During the study period, 205 eligible infants were admitted to the NICU; however, 72 were excluded because they met ≥1 exclusion criterion (40 outborn, 21 with early onset severe sepsis and/or septic shock, 5 treated with surfactant in the delivery room, 5 with complex malformation or congenital lung diseases, and 1 with a congenital heart defect), and ultimately, 133 neonates were enrolled in the study. Table 1 reveals the characteristics of the whole study population and for the 2 subgroups of infants ≤28 and >28 weeks' GA. Surfactant replacement was performed in the whole population at mean 4 (SD 3) hours of life; a second surfactant dose was administered at mean 28 (SD 24) hours of life. The LUS was significantly correlated with

TABLE 1 Basic Population Details

	All Neonates (N = 133)	GA ≤28 Wk (n = 83)	GA >28 Wk (n = 50)	P
GA, wk, mean (SD)	28 (2)	27 (1)	29 (0.5)	<.001
Birth wt, g, mean (SD)	1043 (273)	955 (254)	1187 (241)	<.001
SGA neonates, *n* (%)	6 (4)	2 (2)	4 (8)	.197
5′ Apgar score, median (interquartile range)	9 (8–10)	9 (7–10)	10 (8–10)	.03
Male sex, *n* (%)	66 (50)	43 (52)	23 (46)	.516
Antenatal steroids, any dose, *n* (%)	117 (88)	72 (87)	45 (90)	.576
Antenatal steroids, full course, *n* (%)	76 (57)	50 (60)	26 (52)	.352
Cesarean delivery, *n* (%)	63 (47)	34 (41)	29 (58)	.06
Surfactant replacement, first dose, *n* (%)	68 (51)	53 (64)	14 (28)	<.001
Surfactant replacement, re-treatment, *n* (%)	19 (14)	18 (22)	1 (2)	.002
OI, median (interquartile range)	3 (2–5)	4 (3–6)	3 (2–4)	.013
CRIB-II, median (interquartile range)	9 (7–10)	9 (8–12)	7 (5–8)	<.001
LUS, median (interquartile range)	8 (4–12)	10 (4–12)	6 (3–11)	.032

P values refer to comparisons between the 2 subgroups of neonates (≤28 and >28 wk GA). Apgar, OI, CRIB-II, and LUS values are dimensionless numbers. CRIB-II, Critical Risk Index for Babies II; SGA, small for gestational age.

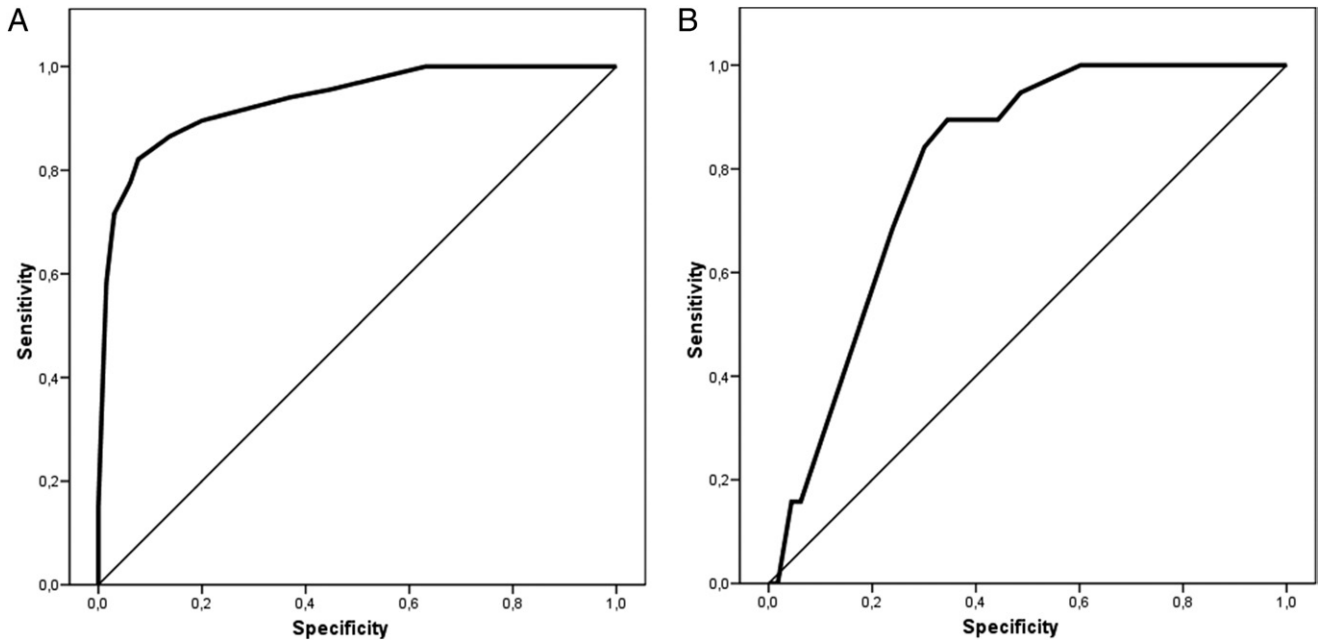

FIGURE 1
A, ROC analysis for the prediction of surfactant treatment. B, ROC analysis for the prediction of surfactant re-treatment. Diagonal lines indicate the prediction by chance (AUC = 0.5).

the OI (whole population: ρ = 0.6, P < .001; GA ≤28 weeks: ρ = 0.5, P < .001; GA >28 weeks: ρ = 0.6, P < .0001), and the correlation remained significant after adjustment for GA ($_{adj}r$ = 0.4; P < .001). There was no significant difference between the correlation coefficients of the subgroups (P = .548). Only 1 lung ultrasound per patient was performed; it was always well tolerated and lasted on average 3 (SD 2) minutes.

An ROC analysis used to predict the need of surfactant treatment revealed an AUC of 0.94 (95% CI: 0.90–0.98; P < .001) for the whole population (Fig 1A), whereas a subgroup analysis revealed AUCs of 0.93 (95% CI: 0.88–0.98; P < .001) and 0.98 (95% CI: 0.94–1; P < .0001) for infants of ≤28 and >28 weeks' GA, respectively. The AUCs for the 2 subgroups did not significantly differ (P = .328).

For surfactant re-treatment, an ROC analysis revealed an AUC of 0.803 (95% CI: 0.72–0.89; P < .0001; Fig 1B) for the whole population, whereas it was 0.78 (95% CI: 0.68–0.88; P < .0001) for infants of ≤28 weeks' GA. The subgroup analysis for infants >28 weeks' GA was not performed because only 1 patient received a second surfactant dose in this subgroup. The AUCs used for the prediction of surfactant treatment and re-treatment differed significantly (P = .039).

Table 2 reveals reliability data for LUS used to predict surfactant treatment and re-treatment. In our population, having a LUS of >6

TABLE 2 Reliability of LUS to Be Used to Predict Surfactant Treatment and Re-treatment

Cutoff Value	Sensitivity, % (95% CI)	Specificity, % (95% CI)	+LR, % (95% CI)	−LR, % (95% CI)	+PV, % (95% CI)	−PV, % (95% CI)	Posttest Probability, % (95% CI)
Surfactant treatment							
>6	90 (80–96)	80 (68–89)	4.5 (3–7)	0.13 (0.06–0.3)	82 (72–90)	88 (77–95)	82 (76–88)
>8	82 (71–90)	92 (83–98)	11 (5–25)	0.19 (0.1–0.3)	92 (82–97)	83 (73–91)	92 (84–96)
Surfactant re-treatment							
>10	84 (60–97)	70 (61–78)	2.8 (2–3.9)	0.23 (0.08–0.6)	32 (20–47)	96 (90–99)	31 (25–39)

For the prediction of surfactant treatment, the cutoff values associated with sensitivity and specificity >80% are shown. For surfactant redosing, the cutoff value with sensitivity >80% and the best specificity is shown. Reliability data are reported with a 95% CI. −LR, negative likelihood ratio; +LR, positive likelihood ratio; −PV, negative predictive value; +PV, positive predictive value.

or 8 increased the probability for surfactant replacement from 51% to 82% or 92%, respectively. Moreover, having a LUS >10 increased the probability of needing a second surfactant dose from 14% to 31%. Global accuracy to predict surfactant treatment and re-treatment increased from 85% to 89% and 72%, respectively. Supplemental Table 3 reveals reliability data for subgroup analysis.

DISCUSSION

We demonstrated a good diagnostic accuracy of using semiquantitative lung ultrasounds for predicting the surfactant replacement in extremely preterm neonates with RDS. A LUS can be used to accurately predict the need for the first surfactant dose and reveals fair accuracy when it comes to predicting surfactant re-treatment. These results are not influenced by GA within the age range of the enrolled population.

Some important comments arise. First, when we tested the LUS in a general newborn population, its diagnostic accuracy was significantly lower in late-preterm and term infants than in preterm infants.[9] With the current study, our aim was to verify if a LUS was accurate enough for the lowest GAs. We found that its diagnostic accuracy is comparable to that obtained in preterm infants <34 weeks' GA.[9] A LUS is therefore more useful in preterm infants (even at extremely low GAs) than in more mature neonates >34 weeks' GA. This is likely because of the homogeneity of the preterm population, which is predominantly affected by RDS.[9] The late-preterm and term neonates may present with various respiratory disorders,[25] different degrees of surfactant injury,[26] and varying extents of the disease process, with a restrictive or mixed pattern.[19] The LUS has clear limitations in lung conditions that are not purely restrictive, which may be due to the fact that lung ultrasounds cannot be used to detect overdistension and gas trapping.[5] Moreover, the LUS diagnostic accuracy is comparable among extremely preterm neonates of different GAs (≤28 or >28 weeks). We also evaluated oxygenation, although this was not our study aim, and the LUS turned out to be well correlated with the OI irrespective of the GA. This is consistent with the correlation between the LUS and several measures of oxygenation in neonates of various GAs.[9]

Secondly, the diagnostic accuracy to predict surfactant re-treatment is good but lower than that of the first dose. This may be due to the small number of patients needing surfactant readministration or reasons that are related to surfactant biology. The LUS essentially is used to describe lung aeration by using an analysis of air-generated artifacts,[27] and this explains its ability to be used to predict the need for surfactant. However, the response to surfactant administration depends on several factors, such as the type of mechanical ventilation,[13] the dose,[28] the degree of surfactant catabolism, and lung inflammation that is often present in these extremely preterm neonates,[29,30] among others. Thus, although a LUS may be used to describe the baseline situation and detect the need for surfactant at a given time, it cannot be used to predict the clinical response to surfactant administration with the same degree of accuracy given all of the influencing factors.

Third, extremely preterm neonates are those who benefit the most from optimized and early surfactant replacement. However, surfactant replacement is currently guided only by the F_{IO_2} cutoff levels, and this may lead to late administration or possibly unnecessary treatment. Both situations are potentially harmful because late surfactant replacement is less efficacious,[3] and giving surfactant when it is not needed may be invasive and seems to increase lung inflammation in animal models.[31] A LUS cutoff level with a high specificity and sensitivity allows us to screen infants who need surfactant replacement at an early age and those who are at risk for unnecessary surfactant administration.

A LUS has a diagnostic accuracy comparable to that of biological tests used to measure surfactant availability or quality, whereas chest radiography is known to have a lower diagnostic accuracy than lung ultrasounds.[32–35] Moreover, a lung ultrasound is quick, radiation

free, minimally invasive, and holds the characteristics of a point-of-care technique; a LUS calculation is easy and does not require any biological sample collection or treatment. In practice, it is easy to perform, whereas amniotic, gastric, or tracheal fluids may be too viscous to be analyzed. Interestingly, LUS findings are well correlated with the results of a surfactant adsorption test, an assay that can be used to measure the quality of surfactant in terms of its air–liquid interface adsorption.[34]

The main strength of our study is that it is based on a formal protocol for respiratory management, with well-defined and standardized criteria for CPAP and surfactant use[1,17] applied in a homogeneous population of extremely preterm neonates with good perinatal care (as revealed by the relatively high Apgar score). Because surfactant administration was performed relatively late (at ∼4 hours of life) and a lung ultrasound was performed after NICU admission (at ∼30 minutes of life, on average), an ultrasound was not performed right before surfactant replacement; thus, the technique was actually able to be used to predict future surfactant need. The study was performed in a NICU with extensive experience in the use of lung ultrasounds. Therefore, we did not repeat certain analyses described in our previous work or in other articles, such as an interoperator concordance for lung ultrasound image interpretation, the correlations with other indices of oxygenation, or a suitability analysis.[9,21,36]

Conversely, these strong points may also represent relative weaknesses because our results may only be applied in similar settings. However, a lung ultrasound is known to have a steep learning curve and is easy to learn.[27] Other study limitations may be the fact that oxygenation was studied with transcutaneous monitoring rather than with arterial blood gas analysis. However, transcutaneous measurement is recognized to be accurate if it is performed according to available clinical guidelines.[18] Moreover, arterial blood gas analysis is invasive and not feasible in all infants. Noninvasive monitoring is currently the most common policy for preterm infants. A lung ultrasound is a minimally invasive technique, and we did not want to combine it with an invasive procedure. We did not study the possible usefulness of more refined lung ultrasound strategies. For instance, the combination of a LUS and a surfactant adsorption test, lamellar body count, serially repeated lung ultrasound, or an increased number of scanned areas could theoretically lead to better performance and be used to provide a more individualized surfactant replacement. Furthermore, the use of different probes may influence the details of lung ultrasound findings and the score calculation.[4] We used a microlinear, high-frequency probe in our population of extremely preterm infants because they have small lungs, and this probe provides high resolution in this setting.[37] Probes of a larger size or lower frequencies have been previously used for neonatal lung ultrasounds,[9–11] and the effect of varying probes deserves to be investigated; appropriate LUS cutoff values should be preliminarily calculated for each type of probe. We do not have data about intubation–surfactant–extubation failure because this was out of our scope. Therefore, we do not know if lung ultrasound can be used to predict it; because we have an aggressive noninvasive ventilation policy using multiple techniques, it is likely that the majority of failures were not due to a respiratory cause. Anyway, this is an intriguing issue that deserves to be investigated in dedicated diagnostic studies. Finally, we cannot provide data about clinical usefulness of ultrasound-guided surfactant therapy because this was not our study purpose. However, our findings are sufficient to design a study to verify if a personalized, LUS-guided surfactant replacement may be used to provide clinical benefits beyond an earlier surfactant administration, and we are working on it.

CONCLUSIONS

A LUS can be used to accurately predict the need for surfactant replacement in CPAP-treated extremely preterm neonates with RDS. A LUS cutoff value between 6 and 8 provides optimal sensitivity and specificity for predicting the need for the first surfactant dose, whereas a cutoff value of 10 predicts the need for surfactant re-treatment.

ACKNOWLEDGMENT

We are grateful to Alexandra Benachi, MD, PhD, who did not receive any honorarium, for the critical review of the article.

ABBREVIATIONS

AUC: area under the curve
CI: confidence interval
CPAP: continuous positive airway pressure
FIO_2: fraction of inspired oxygen
GA: gestational age
LUS: lung ultrasound score
OI: oxygenation index
$PtcO_2$: transcutaneous partial pressure of oxygen
RDS: respiratory distress syndrome
ROC: receiver operating characteristic

the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2018-0463

Accepted for publication Apr 24, 2018

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2018-1621.

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