

ARTICLE OPEN



The effect of postnatal steroids on lung ultrasound scores and extubation readiness in very low birth weight infants

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OBJECTIVE: We assessed the utility of lung ultrasound scores (LUSs) to predict extubation readiness in VLBW infants and determined the effect of postnatal steroids on LUSs in babies who were chronically ventilated for > 30 days.

STUDY DESIGN: We measured infants' LUS scores before planned extubations and determined the success of the subsequent extubation attempts.

RESULTS: Overall, LUSs were lower in successfully extubated compared with unsuccessfully extubated infants in the entire population. Similar differences were seen in LUSs between successfully and unsuccessfully extubated chronically ventilated infants. In chronically ventilated infants, LUSs did not differ between infants who did and did not receive dexamethasone. However, dexamethasone-treated infants who extubated successfully had lower scores compared to those who did not.

CONCLUSIONS: While LUS scores do not predict the need for dexamethasone treatment to promote successful extubation, they do predict subsequent extubation success, irrespective of both dexamethasone treatment and duration of ventilation.

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BACKGROUND

Although non-invasive ventilation is increasingly used, a significant number of very low birth weight (VLBW; birth weight <1500 grams) infants still require invasive mechanical ventilation [1, 2]. Prolonged mechanical ventilation is associated with increased mortality and morbidities, including bronchopulmonary dysplasia and neurodevelopmental delays [3, 4]. Thus, extubating mechanically ventilated infants as soon as they are ready is an important goal of care in neonatology. However, predicting extubation readiness in VLBW infants is difficult, with rates of reintubation following extubation (extubation failure) reported to be as high as 30–50% [5, 6].

Current predictors of successful extubation are unreliable, and the decision to extubate relies primarily on clinical judgment [7]. Extubation readiness tests, such as spontaneous breath tests, have added little value in assessing extubation readiness in premature infants [8], and a recent meta-analysis concluded that there is a lack of evidence to support their use [9]. Use of pneumotachography to assess respiratory load and respiratory muscle strength [10] and automated machine learning have produced promising results, but are presently difficult to incorporate into clinical use [5, 11].

More recently, point-of-care lung ultrasound (LUS) in the neonatal intensive care unit has been validated as a straightforward and quick evaluation of lung aeration and oxygenation in neonates [12, 13]. Lung ultrasound quantifies the air/fluid ratio in the lung on a region-by-region basis, and has been validated against multiple measures of lung aeration [14]. The thinness of the newborn chest wall makes identification of pleural lines, the ultrasound finding on which all evaluations are based, relatively

easy [13, 15, 16]. Lung ultrasound has already been shown to be useful in predicting the need for intubation and surfactant administration in preterm infants [12, 17, 18].

In adults, LUS scores, along with the diaphragm thickening index, have proven to be good predictors of weaning success from mechanical ventilation [19]. LUS scores have also been employed to predict extubation readiness in preterm infants who were ventilated for less than 2 weeks [20–22]. However, many premature infants are difficult to wean from mechanical ventilation, so that their ventilator courses can last weeks. Such chronically ventilated babies are commonly provided with corticosteroids to either treat their chronic lung disease or promote extubation. It is not known whether LUS has a role in predicting extubation readiness in corticosteroid-treated, chronically ventilated preterm infants.

The aims of our study were to assess the utility of a neonatal-adapted LUS score to predict extubation readiness in VLBW infants and to determine the effect of postnatal steroids on LUS scores in chronically ventilated preterm infants.

METHODS

Study setting

This was a single-center, observational, prospective study done at The Margaret M. and George A. Stephen neonatal intensive care unit (NICU) at the University of Chicago Comer Children's Hospital. Recruitment occurred from November 2019 through May 2021 with written parental informed consent and approval by the institutional review board (IRB) at the University of Chicago. Of note, enrollment and data collection were paused for 6 months from March 2020 through September 2020 due to the SARS-CoV-2 pandemic.

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Study population

All VLBW infants who required mechanical ventilation and were admitted to the NICU were eligible for this study. Those with major congenital anomalies, including congenital heart disease, malformations of the thoracic cavity and upper airway, congenital defects of the abdominal wall, and major chromosomal abnormalities were excluded. Infants extubated within 24 hours of intubation were also excluded.

Study design

VLBW infants intubated for respiratory distress syndrome and acute respiratory failure were enrolled. Patients were followed prospectively on a daily basis, and clinical data were collected. On the day that extubation was planned by the clinical team, the investigators were informed, and a lung ultrasound was performed within three to six hours of the extubation attempt and scored. If the patient was subsequently reintubated within seven days of the extubation attempt, the extubation was recorded as a failure. Infants were grouped according to whether the extubation was successful or not, and the LUS scores between the groups were compared.

Ventilator management and extubation attempts

All clinical decisions, including ventilator management and decisions to extubate or re-intubate were made by the clinical team caring for the babies. The clinical team was unaware of the LUS findings.

Lung Ultrasound examination

LUS was performed using a high-resolution L25 XP linear transducer, 6-13 MHz (Fujifilm Sonosite X Porte Ultrasound System). In each lung, aeration in each of the upper anterior, lower anterior, and lateral regions was evaluated and scored according to standardized criteria [12]. Accordingly, the total number of areas for both the right and left lungs was six. Each area was scored on a 0-3 point score system [12] and summed to obtain a neonatal adapted LUS score. The maximal summed score was thus 18. A lung that was well aerated in all zones received a score of zero, with progressively poorly aerated lung regions receiving progressively higher scores.

We used the following formula for calculating aeration of the lungs from the LUS scores:

Aeration of lungs

$$= \frac{\text{Total Lung Ultrasound Score} - \text{Observed Lung Ultrasound Score} \times 100}{\text{Total Lung Ultrasound Score}}$$

Clinical data collection

At the time of the planned extubation, baseline infant characteristics were collected, including birth weight, gestational age, gender, race, Apgar scores, and maternal characteristics, including antenatal steroids and mode of delivery. At the time of extubation, the following were recorded: medications (e.g., steroids, surfactant), duration of ventilation, weight, age, corrected gestational age, and post-extubation respiratory support. Lastly, if extubation failure did occur, the time to reintubation and the reason for reintubation were recorded.

Data analysis

Lung ultrasound scores in the group of infants who were successfully extubated were compared with those of infants with extubation failure. Secondary analyses were done to evaluate the correlation of lung ultrasound scores with extubations in babies who did and did not receive postnatal steroids and with extubations occurring before and after 30 days of age. We also compared lung ultrasound scores among successful and unsuccessful extubations in those infants ventilated for > 30 days who received postnatal steroids. For our study, we defined infants who were ventilated > 30 days as chronically ventilated, and infants ventilated <30 days as non-chronically ventilated infants.

Sample size estimation

Sample size was estimated based upon the area under the curve (AUC) in the receiver operating characteristic (ROC) curves. Based upon existing data in adults [19], the AUC of the ROC curve predicting successful extubation is 0.76. The sample size was calculated for a beta of 0.80, an alpha of 0.05, and the ratio of failed to successful extubation of 1 to 3.

Accordingly, the total sample size required was calculated to be 46 patients.

Statistical analysis

The normality of the data was tested by the Shapiro-Wilk test. Data are expressed in means and standard deviations, if normally distributed, and if not normally distributed, expressed in medians and interquartile ranges (IQR). We used the t-test to compare the means and the Wilcoxon rank-sum/Mann-Whitney U test to compare the medians, and the chi-square test to compare proportions. We also used logistic regression models to assess the association of successful extubation with lung ultrasound scores, controlling for potential confounders. Lastly, ROC curves with AUC were generated to predict extubation readiness. Statistical significance was set at p -value of <0.05. We used MedCalc to calculate sample size and STATA 17th Ed for our statistical analysis.

RESULTS

During the study period, 166 VLBW infants were admitted to the NICU, of which 104 were eligible for the study (Fig. 1). Thirty-seven infants were excluded from the study because of parental refusal of consent, unavailability of investigators to perform LUS, suspension of the study due to the SARS-COV2 pandemic, or because they were extubated within 24 hours of intubation. Accordingly, 67 infants were enrolled. Of these, additional infants were excluded because they died prior to extubation ($n = 1$), had sub-glottic stenosis ($n = 1$), were extubated when research activity was suspended due to the SARS COV2 pandemic ($n = 4$), were not extubated by study end ($n = 3$), or either successfully extubated on an unplanned basis or were transferred to another hospital prior to extubation ($n = 13$). Our sample study population included 45 patients who had a total of 53 extubation events.

The mean gestational age of the population was 27 weeks \pm 2 (SD) and the mean birth weight 859 g \pm 289 (SD). A total of 40 of 45 mothers received at least one dose of antenatal steroids, and 30 of these 45 mothers (67%) received two doses. Other clinical characteristics of the infants studied appear in Table 1.

Extubation was successful in 40 of 53 attempts (75%) and unsuccessful in 13 of 53 attempts (25%). Babies in whom extubation was unsuccessful had a lower mean gestational age (*successful*: 27 weeks \pm 2 SD; *unsuccessful*: 26 weeks \pm 1.5 SD, $P = 0.01$, Table 2). Notably, the mean post-conceptional age at extubation attempt in successfully extubated infants (30 week \pm 2 weeks) was not significantly different from that of infants who failed extubation trials (31 \pm 3 weeks). The median time until reintubation following attempts that proved to be unsuccessful was two days (1-4 days, interquartile range (IQR)). Neither birth weight nor the weight at the time of the extubation attempt differed between the groups (Table 2). Maternal factors, including the number of antenatal steroid doses and the mode of delivery, and infant factors, including doses of surfactant received, one- and five-minute Apgar scores and the age at extubation attempt did not differ between successful and failed extubation groups (Table 2).

Lung ultrasound score prior to extubation distinguishes between extubation success and failure

In the study population, the median LUS score on the day of extubation attempt was 6 (IQR: 3-11; median lung aeration 55%; IQR 83-39%). A total of 23 of 45 (51.1%) infants were successfully extubated. In infants in whom extubation failure occurred, the median lung ultrasound score was markedly and significantly higher (12; 9-12 IQR) compared with the median LUS score of infants who were successfully extubated (5; 2-8 IQR, $P < 0.0001$). Using the 75th centile of the lung ultrasound score of all infants who were successfully extubated (lung ultrasound score=8, lung aeration 56%) as the cutoff, the sensitivity of LUS scores for extubation success was 85% (95% CI: 67-95%) and specificity was 77% (95% CI 46-95%). Of note, no infant with LUS < 7 (61% aeration) failed extubation.

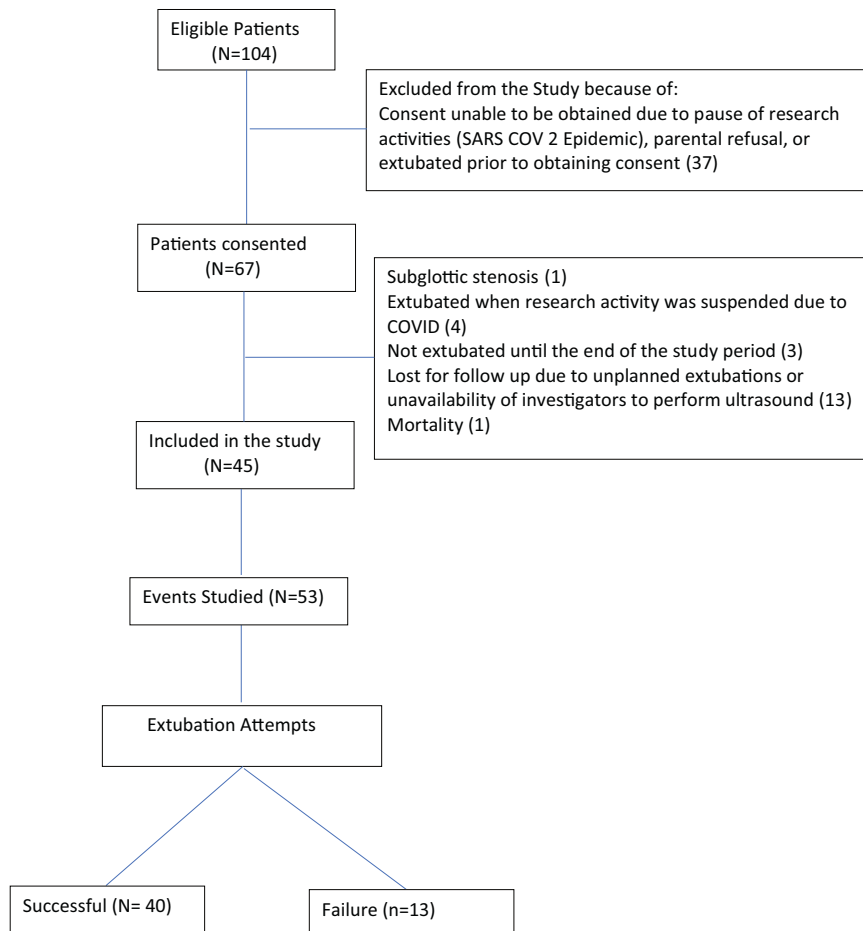


Fig. 1 Flow chart.

We next used logistic regression to assess the association of LUS scores with successful extubation controlling for gestational age at birth, days ventilated and the use of postnatal steroids. For these analyses, we used the infants with LUS scores ≤ 6 (all of whom were successfully extubated) as the comparison group. For each unit increase in LUS score >6 , we found 45% decreased odds of extubation success (adjusted OR 0.55; 0.40–0.75, $P < 0.001$). We generated receiver operating characteristic curves to estimate the area under the curve (AUC) of LUS scores to predict successful extubation (AUC 0.93, 95% CI 0.85–1.00; Fig. 2).

Lung ultrasound scores and the duration of ventilation

Of the 23 infants who were successfully extubated on the first attempt, the median duration of ventilation was four days (IQR: 2–16 days). Of these 23 infants, 20 (87%) were extubated without corticosteroids and their median length of ventilation was three days (IQR: 2–5 days). In contrast, the 22 infants with extubation failure had a median duration of ventilation of 38 days (IQR: 6–59 days). Accordingly, we stratified infants into two categories: infants who were ventilated for fewer than 30 days (non-chronically ventilated, $N = 29$) and those who were ventilated for 30 or more days (chronically ventilated, $N = 16$, Table 3). In non-chronically ventilated infants, the median LUS score was also significantly lower in infants who were successfully extubated (3; IQR 2–6) than in those who had an extubation failure (10; IQR 8–12, $p = 0.001$).

Infants who were chronically ventilated had lower gestational ages and birthweights, compared with non-chronically ventilated infants ($p = 0.001$). In contrast, their mean corrected gestational age and weight at extubation were higher compared with non-chronically ventilated infants ($p = 0.001$, Table 3). Chronically ventilated infants

had higher LUS scores at extubation attempt (median 10, IQR 7–12) than did infants ventilated for fewer than 30 days (4; IQR 2–8, $P < 0.005$). In these chronically ventilated infants, the median lung ultrasound score was lower in infants who were successfully extubated (7, IQR 6–11) than in those who were not (median 12; IQR 9–13, $p = 0.02$). However, infants successfully extubated after chronic ventilation had a significantly higher median LUS score than did successfully extubated infants who were not chronically ventilated (chronically ventilated: 7, IQR 6–11 vs not chronically ventilated 3; IQR 2–6, $p = 0.002$). Thus, although successful extubation is associated with significantly lower lung ultrasound scores regardless of length of ventilation, chronically ventilated infants demonstrated decreased lung aeration at successful extubation.

Lung ultrasound scores after dexamethasone treatment to promote extubation

No babies ventilated for <30 days received postnatal steroids. Although steroids were provided on an individualized basis, in general, steroids were considered for premature infants who were not extubated by 30 days of age, who were on ventilator support from which extubation would fail, and who weighed more than 1.0 kg. Accordingly, we asked how dexamethasone treatment of infants ventilated for more than 30 days affected extubation and LUS scores. Of the 16 chronically ventilated infants, 12 (75%) received postnatal steroids. Of these, two infants (17%) received peri-extubation dexamethasone for presumed airway edema [23], and 10 infants (83%) received postnatal dexamethasone using the DART protocol [24].

Median lung ultrasound scores in chronically ventilated infants who received postnatal dexamethasone (10, IQR 8–12) were not

Table 1. Demographic Characteristics of Very Low Birth Weight (VLBW) Infants.

Characteristics	(N = 45)
Gestational Age, weeks, mean (SD)	27 ± 2
Birth Weight g, mean (SD)	Mean: 859 grams ± 289
Antenatal Steroids N, (%)	None: 5 (11%) Incomplete (1 dose): 10 (22%) Complete (≥2 doses): 30 (67%)
Vaginal/Cesarean Section N (%)	C-section: 35 (78%)
Race, N (%)	
African American	35 (78%)
Hispanic	4 (9%)
Caucasian	4 (9%)
Other	2 (4%)
Sex, N (%)	Females: 30 (67%)
One-minute APGAR score <7, N (%)	44 (97%)
Five-minute APGAR score <7, N (%)	28 (62%)
Surfactant N, (%)	
None	None: 3 (7%)
1 dose	1 Dose: 5 (11%)
2 doses	2 Doses: 20 (44%)
3 doses	3 Doses: 17 (38%)

different from scores of chronically ventilated infants who did not receive postnatal dexamethasone (9, IQR 6–12). Notably, only five of 12 babies who received postnatal dexamethasone (42%) were successfully extubated. Although LUS scores in chronically ventilated infants did not distinguish between dexamethasone-treated and untreated infants, lung ultrasound scores did distinguish dexamethasone-treated infants who were successfully extubated from dexamethasone-treated infants who were not: The median LUS score of the five infants who were successfully extubated following dexamethasone (7, IQR 6–8) was lower than the median score of the seven dexamethasone-treated infants (58%), who were not successfully extubated (12, IQR 9–13, $p < 0.02$).

Of the dexamethasone-treated infants, no infant with LUS < = 7 failed extubation. In dexamethasone-treated infants, for each unit increase in LUS score >8, we found 54% decreased odds of extubation success (adjusted OR 0.46; 0.21–0.99, $P < 0.05$). Using the 75th centile of the lung ultrasound score of the successfully extubated babies (lung ultrasound score = 8, lung aeration 56%) as the cutoff, the sensitivity of LUS scores for extubation success was 80% (95% CI: 28%, 99%), and the specificity was 85% (95% CI 42–97%). We generated ROC curves to estimate the AUC of LUS scores to predict successful extubation (AUC 0.93, 95% CI 0.79–1.00).

DISCUSSION

Our study shows that the neonatal-adapted lung ultrasound score, performed on the same day as a planned extubation, is an excellent predictor of extubation success in mechanically ventilated VLBW infants. In addition, dexamethasone treatment of the subpopulation of chronically ventilated babies is not associated with lower lung ultrasound scores compared with those of untreated chronically ventilated infants.

Our findings are consistent with those of several prospective cohort studies [20–22] demonstrating the utility of lung ultrasound scores in predicting extubation success in premature infants ventilated for five to seven days. Thus, El Amrousy et al. [20] studied 80 infants using the same methodology [12]. However, in contrast with the present study, they found that a LUS of 4 (78% aeration) constituted the cutoff for successful extubation. Our finding of a higher cutoff value of 8 (56% aeration) is likely due to the larger percentage of extremely preterm

Table 2. Successful vs Unsuccessful Extubation Events in VLBW Infants.

	Successful	Unsuccessful	P Value
Number of Events	40 (75%)	13 (25%)	
Gestational Age at Birth (weeks)	27 ± 2	26 ± 1.5	0.01*
Birth Weight (Grams)	900 ± 300	729 ± 110	0.09
Corrected Gestational Age at Extubation (Weeks)	30 ± 2	31 ± 3	0.95
Weight at Extubation (Grams)	1198 ± 447	1168 ± 328	0.88
Antenatal Steroids			
Yes	34	6	0.86
No	12	1	
Mode of Delivery			
Vaginal	10	1	0.18
C-section	30	12	
1 min Apg <7	38	13	0.56
5 min Apg <7	25	9	0.66
Surfactant Doses			
0	3		0.26
1	6		
2	19	6	
3	12	7	

Mean ± SD; * t test.

infants in our population compared with that study's population which included infants < 35 weeks gestation. In contrast, Soliman et al. [21] obtained LUS scores on the third and seventh days of life and found markedly higher median lung ultrasound scores at extubation (11.5/18) equivalent to lung aeration of 36%, compared with the median lung aeration value of 56% that we observed in our study. These differences may reflect earlier extubation to non-invasive ventilation than in use in our clinical setting. In our clinical setting, infants were routinely extubated to CPAP only. In contrast, infants in the Soliman et al. study, infants were extubated to either CPAP or non-invasive ventilation based on their work of breathing. More recently, Mohsen et al. [22] obtained pre-extubation LUS scores in 44 infants with gestational age <28 weeks. In contrast to the present study, these authors employed a different scoring system, such that they observed extubation success at a lung ultrasound score of 15/24, equivalent to lung aeration of 38%. This degree of lung aeration, allowing successful extubation was much poorer than the 56% lung aeration cutoff we observed. Unlike infants in the present study, infants in the Mohsen et al. study were extubated to nasal positive pressure ventilation. Non-invasive, positive pressure ventilation is more likely to reduce the loss of lung functional residual capacity over time after extubation [25, 26] compared with CPAP, and reduce the risk of extubation failure. Finally, differences in lung ultrasound scores, which are a proxy for lung aeration in predicting extubation success, may also be partially due to differences between the study populations' respiratory disease severity, which is influenced by genetic factors [27].

We found that dexamethasone treatment of chronically ventilated babies is not associated with lower lung ultrasound scores compared with those of chronically ventilated infants who successfully extubate without dexamethasone treatment. That is, LUS scores in infants who extubated successfully without dexamethasone were not, contrary to our anticipations, significantly lower than those of infants who required dexamethasone for successful extubation. This finding suggests that the degree of lung aeration, however achieved, is the key determinant of extubation success. However, it is possible that, had LUS scores

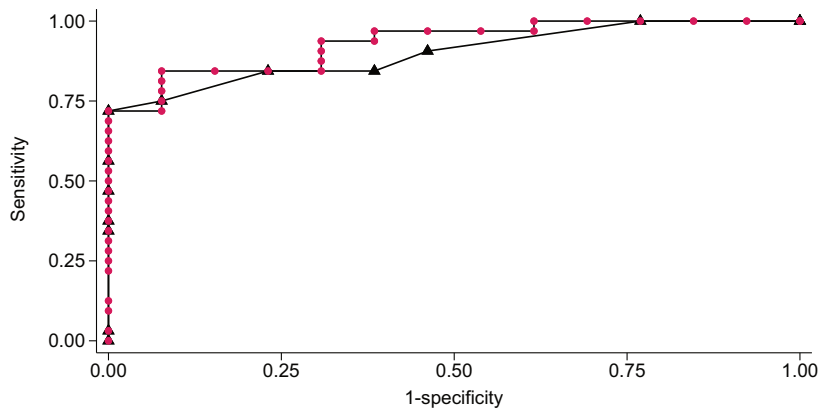


Fig. 2 Unadjusted and Adjusted ROC curves for Lung Ultrasound Scores and Extubation Readiness in VLBW Infants (▲) Unadjusted ROC Curve: AUC 0.90 (●) Adjusted ROC Curve: AUC 0.93. Adjusted for gestational age, postnatal steroids, and ventilatory days.

Table 3. Extubations at ≤ 30 vs > 30 Postnatal Days in VLBW Infants.

	≤ 30 Postnatal Days ($N = 29$)	>30 Postnatal Days ($N = 16$)	<i>P</i> Value
Successful Extubation	23 (80%)	9 (57%)	0.10
Unsuccessful Extubation	6 (20%)	7 (43%)	
Gestational Age at Birth	28 \pm 2	25 \pm 2	0.001*
Birth Weight	977 \pm 265	643 \pm 190	0.001*
Corrected Gestational Age at Extubation	28 \pm 2	33 \pm 3	0.001*
Postnatal Day at Extubation	4 days (2–6)	55 days (45–65)	0.001 [†]
Weight at Extubation	1005 \pm 286	1456 \pm 353	0.001*

Mean \pm SD; Median (IQR); * *t* test; [†] Wilcoxon rank-sum/Mann-Whitney U test.

been obtained in dexamethasone-treated infants prior to dexamethasone treatment, those scores would have been significantly higher compared with infants who extubated without dexamethasone treatment. Finally, because the number of infants who extubated without dexamethasone treatment was low, it is possible that the absence of a significant difference in LUS scores between groups is due to the limited power of the analysis.

Overall, LUS scores of chronically ventilated infants did predict subsequent extubation success, irrespective of both dexamethasone treatment and duration of ventilation. Our findings are congruent with those of a recent Italian study of the effect of dexamethasone/budesonide treatment on LUS scores [28]. In this study, of the 12 VLBW infants undergoing invasive mechanical ventilation, dexamethasone (9 of 12) or budesonide inhalation (3 of 12) resulted in marked decreases in LUS scores (from a median of 10 to 5) and increased lung aeration (from a median of 44% to 72%). Notably, the cumulative dose of dexamethasone employed in that study (2.625 mg/kg) is almost threefold higher than the cumulative dexamethasone dosage provided in the DART protocol we and most centers employ in the US.

The findings of our single-center study are consistent with those of previous single-center, prospective studies, and support the use of LUS scores to define extubation readiness in VLBW infants. The increasing availability of point-of-care ultrasound will provide real-time, non-invasive determination of an infant's readiness for extubation, reducing the complications associated with failed extubation.

CONCLUSIONS

Lung ultrasound scoring is an excellent predictor of extubation readiness in VLBW infants, even in chronically ventilated infants. However, lung ultrasound scores are higher in chronically ventilated (>30 days) babies, demonstrating poorer lung aeration.

While LUS scores do not predict the need for dexamethasone treatment to promote successful extubation, they do predict subsequent extubation success, irrespective of both dexamethasone treatment and duration of ventilation.

SUMMARY

Article summary

- Lung ultrasound scores are shown to be excellent predictors of extubation readiness in VLBW infants. Lung ultrasound scores are higher in chronically ventilated infants (> 30 days), compared with infants ventilated < 30 days. LUS scores do not predict the need for dexamethasone treatment to promote successful extubation in chronically ventilated infants.

What is known

- Lung ultrasound scores can predict extubation readiness in preterm infants who have been ventilated for <2 weeks duration.

What this adds

- Lung ultrasound scores predict extubation readiness in babies ventilated >30 days. In chronically ventilated infants, postnatal steroid treatment does not differentiate LUSs from those of infants not treated with steroids. However, lung ultrasound scores predict extubation success in infants treated with postnatal steroids.

DATA AVAILABILITY

Non-identified datasets analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Dr. Madhavi Singhal conceptualized and designed the study, performed lung ultrasounds, collected data and drafted the initial manuscript, and critically reviewed and revised the manuscript for important intellectual content. Dr. Kate Feinstein provided essential methodological expertise in obtaining lung ultrasounds and scoring, and critically reviewed and revised the manuscript for important intellectual content. Dr. Michael Schreiber collaborated on the interpretation of data and critically reviewed the manuscript for important intellectual content. Dr. Jeremy Marks critically reviewed and revised the manuscript for important intellectual content. Dr. Sudhir Sriram conceptualized and designed the study, supervised data collection, drafted the initial manuscript, and critically reviewed and revised the manuscript for important intellectual content.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board at the University of Chicago (approval code 19-1082) and conducted in accordance with the principles of Helsinki. Informed consent was obtained from the parents of all infants participating in our study.

ADDITIONAL INFORMATION

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