Lung Ultrasonography Score to Evaluate Oxygenation and Surfactant Need in Neonates Treated With Continuous Positive Airway Pressure

Roselyne Brat, MD; Nadya Yousef, MD; Roman Klifa, MD; Stephanie Reynaud, MD; Shivani Shankar Aguilera, MD; Daniele De Luca, MD, PhD

**IMPORTANCE** Lung ultrasonography (LUS) is a bedside technique useful to diagnose neonatal respiratory problems, but, to our knowledge, no data are available about its use for monitoring lung function or eventually guiding surfactant therapy.

**OBJECTIVE** To determine the diagnostic accuracy of a neonatal-adapted LUS score to evaluate oxygenation and predict need for surfactant administration.

**DESIGN, SETTING, AND PARTICIPANTS** Prospective diagnostic accuracy study following STARD (Standards for the Reporting of Diagnostic Accuracy Studies) guidelines at a tertiary level academic neonatal intensive care unit in 2014. All neonates admitted to the neonatal intensive care unit with signs of respiratory distress were eligible, and 130 neonates were enrolled. The LUS score was calculated in the first hours of life under continuous positive airway pressure. The transcutaneous partial pressure of oxygen (Ptco₂) to fraction of inspired oxygen (FiO₂) ratio, alveolar-arterial gradient, oxygenation index, and arterial to alveolar ratio were calculated within 30 minutes from LUS, using transcutaneous blood gas monitoring. Surfactant was administered according to 2013 European guidelines.

**MAIN OUTCOMES AND MEASURES** Correlation between LUS score and indices of oxygenation and prediction of surfactant administration.

**RESULTS** Among the 130 neonates in this study, the LUS score was significantly correlated with all indices of oxygenation, independent from gestational age (GA) (Ptco₂ to FiO₂ ratio: GA ≥34 weeks: p = −0.57; GA <34 weeks: p = −0.62; P < .001; alveolar-arterial gradient: GA ≥34 weeks: p = 0.62; GA <34 weeks: p = 0.59; P < .001; oxygenation index: GA ≥34 weeks: p = 0.63; GA <34 weeks: p = 0.69; P < .001; and arterial to alveolar ratio: GA ≥34 weeks: p = −0.60; GA <34 weeks: p = −0.56; P < .001). The LUS score predicted the need for surfactant better in preterm babies with a GA less than 34 weeks (area under the curve = 0.93; 95% CI, 0.86-0.99; P < .001) than in term and late-preterm neonates with a GA of 34 weeks or greater (area under the curve = 0.71; 95% CI, 0.54-0.90; P = .02); the areas under the curve for these 2 GA subgroups are significantly different (P = .02). In babies with a GA less than 34 weeks, a LUS score cutoff of 4 predicted surfactant administration with 100% sensitivity and 61% specificity, yielding a posttest probability of 72%.

**CONCLUSIONS AND RELEVANCE** The LUS score is well correlated with oxygenation status in both term and preterm neonates, and it shows good reliability to predict surfactant administration in preterm babies with a GA less than 34 weeks under continuous positive airway pressure.
Lung ultrasonography (LUS) is becoming a bedside point-of-care technique in critical care because it is performed and immediately interpreted by the frontline clinician. A comprehensive and standardized ultrasonography semiology has been described and validated across ages, as LUS signs are recognizable in both adult and pediatric patients. Lung ultrasonography makes possible an easy and quick recognition of a normal aerated lung in contrast to an interstitial or alveolar pattern. Recognition of these patterns may be even easier in neonates owing to the small patients’ size and the absence of obesity or heavy musculature. Thus, LUS findings have been described for typical neonatal respiratory conditions such as meconium aspiration syndrome, hyaline membrane disease (respiratory distress syndrome [RDS]), transient tachypnea of the neonate (TTN), and pneumothorax.

The most common neonatal respiratory conditions are RDS and TTN, and they are often treated with continuous positive airway pressure (CPAP). A certain degree of surfactant damage is possible in severe or long-lasting TTN, causing loss of functional residual capacity that can be overcome by CPAP. In RDS, treating most preterm babies with early CPAP and selective surfactant administration has proven to reduce death and chronic lung disease as compared with surfactant prophylaxis. Thus, the American Academy of Pediatrics considers selective surfactant administration after early CPAP and the European Association of Perinatal Medicine advises surfactant administration in CPAP-treated preterm infants with increasing oxygen requirements. Raimondi et al described the usefulness of LUS in predicting neonatal intensive care unit (NICU) admission or need for intubation, using only 3 simple LUS patterns. However, the use of a more quantitative LUS evaluation would be useful to better describe the clinical condition. Lung ultrasonography scores have already been used in adults to evaluate lung aeration and oxygenation and might be useful for this purpose in neonates. Conversely, there are no data, to our knowledge, about LUS to estimate oxygenation through the evaluation of lung aeration in neonates receiving CPAP. Moreover, a reliable tool to predict the need for surfactant administration in preterm babies is still needed.

Our aim is to study the diagnostic accuracy of a neonatal-adapted LUS score to evaluate oxygenation and need for surfactant administration. We hypothesized that because the LUS score reflects lung aeration, it correlates with oxygenation and may be useful to predict surfactant administration at least in preterm babies with RDS.

Methods

Patients

We designed a prospective diagnostic accuracy study following STARD (Standards for the Reporting of Diagnostic Accuracy Studies) guidelines. The study was conducted at an academic tertiary referral center in 2014. All inborn neonates admitted to the NICU with respiratory distress were considered eligible for the study and were divided into 2 groups according to gestational age (GA; <34 and ≥34 weeks). Because this was the first study on this topic to our knowledge, we enrolled babies irrespective of their GA, as we were interested to determine whether this new tool was equally useful for babies with different respiratory conditions. Exclusion criteria were the following: (1) chromosomal abnormalities or complex congenital malformations; (2) congenital lung diseases; (3) severe sepsis or septic shock; (4) meconium aspiration syndrome; and (5) delivery room surfactant administration, as per European guidelines. The study protocol was approved by the ethical board of our hospital group (South Paris University Hospitals), and oral informed consent was obtained from parents.

In our institution, delivery room intubation is performed only on babies unresponsive to face-mask ventilation, according to American Academy of Pediatrics guidelines on neonatal resuscitation. Our surfactant protocol is based on European guidelines: in detail, preterm babies (≤32 weeks’ gestation) unresponsive to face-mask ventilation and intubated at birth received poractant alfa (Curosurf) in the delivery room and were also excluded from the study. In all other cases, poractant alfa was administered whenever the fraction of inspired oxygen (Fio₂) was greater than 0.3 or 0.4 for babies with a GA less than or greater than 28 weeks, respectively.

Nasal CPAP was started in the delivery room just after stabilization or on NICU admission for babies with a GA of 32 weeks or less or a GA greater than 32 weeks, respectively: babies with signs of respiratory distress were under CPAP unless they met some exclusion criteria.

A variable flow generator (InfantFlow SiPAP; Carefusion) and appropriately sized nasal prongs or masks (Fisher and Paykel Healthcare) were used. Pacifiers of adequate size with drops of 30% glucose solution were used to reduce leaks and provide sedation. The CPAP was set at 4 cm H₂O and increased up to 6 cm H₂O if needed, according to the severity of respiratory distress; oxygen was added to the CPAP if 6 cm H₂O was not enough to keep oxygen saturation between 90% and 95%.

All pregnancies received full prenatal care: GA estimate was based on the postmenstrual date and early gestation ultrasonographic findings; antenatal betamethasone sodium phosphate was administered as two 12-mg doses 24 hours apart, whenever delivery was expected to occur before 34 weeks. Small-for-GA babies were classified according to Fenton’s curves. The clinical diagnosis of the respiratory condition was...
Lung Ultrasonography, Oxygenation, and Surfactant Need

Original Investigation Research

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Given integrating prenatal and postnatal clinical data (eg, GA, lamellar body count, inflammatory markers, microbiological test results, and physical examination findings) and routine chest radiography performed between 6 and 12 hours of life. The LUS findings were not used for the diagnosis. The NICU clinical protocols did not change during the study. Participation in the study did not modify the standard clinical care.

**LUS Score**

Lung ultrasonography was performed as soon as possible on NICU admission and in any case before surfactant administration. It was performed by physicians who received 2 months of formal training before the study. This training was based on a 2-day course including exercises first on adults and then on babies. For 2 months, in-training physicians performed LUS under senior supervision. Results were recorded on a dedicated sheet, not included in patients' files and masked to other clinicians: this was the best way to mask the clinical conditions to the colleagues performing LUS and the LUS results to other clinicians. While the second point was more easily achieved, masking the baby is impossible; in about 10% of cases LUS might have been performed quickly before surfactant administration, as the baby fulfilled criteria for it. However, a single image was recorded for each lung area by the initial operator (who could not avoid observing the patient) and was reanalyzed after the study by 2 senior neonatologists with expertise in LUS and blinded to the clinical condition (N.Y. and D.D.). There was a very high interobserver agreement (between R.B. and S.R. and between N.Y. and D.D.) for image interpretation ($\kappa = 0.89$).

The LUS score was modified from an index proposed for adult patients. $^{35}$ Basically, each lung was divided into 3 areas (upper anterior, lower anterior, and lateral) and examined using a linear microprobe through both transverse and longitudinal scans. For each lung area, a 0- to 3-point score was given (total score ranging from 0-18). The LUS score encompassed signs typical of TTN and RDS $^{5,6}$ and described the total spectrum of possible conditions (a normal aerated lung, an interstitial pattern, an alveolar pattern, and consolidation). In detail, the LUS score was assigned as follows: 0 indicates A-pattern (defined by the presence of the only A-lines); 1, B-pattern (defined as the presence of $\geq$3 well-spaced B-lines); 2, severe B-pattern (defined as the presence of crowded and coalescent B-lines with or without consolidations limited to the subpleural space); and 3, extended consolidations. A-lines represent reflection of pleura due to ultrasound diffusing through an air-filled lung; B-lines are due to fluid filling the interstitium (and the alveolar space if they become confluent). $^{1,2}$ Figure 1 summarizes the LUS score characteristics.

As per our routine policy, transcatheter pulmonary blood gas (transcatheter partial pressure of oxygen [Ptco$_2$] and transcatheter partial pressure of carbon dioxide [Ptcco$_2$]) were measured using a calibrated probe (TCM4; Radiometer Medical) when the baby had a stable and normal temperature without hemodynamic troubles. $^{29}$ The Ptco$_2$ and Ptcco$_2$ were measured 30 minutes before LUS and registered as soon as stable measures were obtained. All these data were anonymously analyzed on a dedicated computer, secured, and used only for research purposes.

**Calculations and Outcomes**

The following indices were calculated to describe oxygenation: (1) Ptco$_2$ to FiO$_2$ ratio; (2) alveolar-arterial gradient $\Delta$Pa = Ptco$_2$ - Pa; and is given by (FiO$_2$ x [760 - 47]) - (Ptcco$_2$/0.8); (3) oxygenation index $\Delta$Pa = FiO$_2$ x 100/Ptco$_2$; and (4) arterial to alveolar ratio = Ptco$_2$/Pa. Study outcomes were as follows: (1) describing the correlation between LUS score and oxygenation status; and (2) predicting the need for surfactant administration using the LUS score in a cohort of term and preterm neonates.

**Statistical Analysis**

Data were tested for normality with Kolmogorov-Smirnov test and expressed as mean (standard deviation) or median (interquartile range) as appropriate. The curve estimation procedure was performed to find the best-fitting data models describing relationships between LUS score and indices of oxygenation. $^{23}$ Correlations were analyzed using Spearman coefficient ($\rho$), and the partial correlation coefficient was adjusted for GA. $^{23}$ Receiver operating characteristic (ROC) analysis was used to evaluate the ability of the LUS score to predict surfactant administration: areas under the curves (AUCs) and cutoff values showing the highest sensitivity were reported. The AUCs were compared using the method by Hanley and McNeil. $^{24}$ The Cohen $\kappa$ coefficient was calculated to estimate interobserver agreement between neonatologists performing LUS and senior colleagues reanalyzing images after the study. $P < .05$ was considered statistically significant.

A sample size was calculated as follows. In the 6 months before the study, surfactant had been administered in 17% of babies in the NICU fulfilling the same inclusion criteria of the study and following the same surfactant administration protocol (negative to positive ratio of 5). Considering these data, 120 neonates would have been needed to have an area under the ROC curve of 0.7 or higher with $\alpha = .05$ and 80% power. Analyses were performed using SPSS version 15.0 (SPSS Inc) and MedCalc version 13.3 (MedCalc bvba) statistical software.

**Results**

Basic population details are summarized in Table 1. During the study, 199 babies were admitted to the NICU; 69 were excluded, as they met at least 1 exclusion criterion (40 outborn, 10 with complex malformation or congenital lung diseases, and 19 with early sepsis), and 130 neonates were enrolled in the study. The GA range was 27 to 41 weeks and the birth weight range was 700 to 4280 g. The mean (SD) CPAP level was 5 (1.7) cm H$_2$O. There was a significant correlation between LUS score and CPAP level ($P = 0.429; P < .001$). A complete course of antenatal steroids was administered in 96.9% of babies born at a GA less than 34 weeks. The LUS lasted a mean (SD) of 5 (2) minutes. All babies with a GA less than 34 weeks were diagnosed...
ashavingRDS;amongbabieswithaGAof34weeksorgreater, 35 (53.8%) were diagnosed as having TTN, 23 (35.4%) as hav- ing RDS, and 7 (10.7%) as having pneumonia. Significant correlations were found between LUS score and oxygenation indices (Figure 2). Subgroup analysis gave similar correlations for PtcO₂ to FiO₂ ratio (GA ≥34 weeks: ρ = −0.57;}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Babies (N = 130)</th>
<th>GA &lt;34 wk (n = 65)</th>
<th>GA ≥34 wk (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA, wk, mean (SD)</td>
<td>33 (3)</td>
<td>30 (2)</td>
<td>36 (2)</td>
</tr>
<tr>
<td>Birth weight, mean (SD), g</td>
<td>2067 (852)</td>
<td>1448 (419)</td>
<td>2684 (706)</td>
</tr>
<tr>
<td>Small for GA, No. (%)</td>
<td>9 (6.9)</td>
<td>7 (10.8)</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Cesarean delivery, No. (%)</td>
<td>32 (24.6)</td>
<td>20 (30.8)</td>
<td>12 (18.5)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>67 (51.5)</td>
<td>32 (49.2)</td>
<td>35 (53.8)</td>
</tr>
<tr>
<td>Surfactant administered, No. (%)</td>
<td>30 (23.1)</td>
<td>16 (24.6)</td>
<td>14 (21.5)</td>
</tr>
<tr>
<td>Postnatal age at LUS, mean (SD), h</td>
<td>2.7 (1)</td>
<td>2.2 (1)</td>
<td>2.8 (1)</td>
</tr>
<tr>
<td>LUS score, median (IQR)</td>
<td>5 (3-10)</td>
<td>5 (2-9)</td>
<td>5 (3-10)</td>
</tr>
<tr>
<td>Alveolar-arterial gradient, median (IQR)*</td>
<td>42 (22-66)</td>
<td>38 (28-62)</td>
<td>42 (24-79)</td>
</tr>
<tr>
<td>PtcO₂ to FiO₂ ratio, median (IQR)*</td>
<td>286 (191-381)</td>
<td>307 (191-387)</td>
<td>276 (192-364)</td>
</tr>
<tr>
<td>Oxygenation index, median (IQR)*</td>
<td>2 (1.2-3.1)</td>
<td>1.8 (1.2-3.0)</td>
<td>2.1 (1.3-3.3)</td>
</tr>
<tr>
<td>Arterial to alveolar ratio, median (IQR)*</td>
<td>0.6 (0.4-0.8)</td>
<td>0.6 (0.4-0.8)</td>
<td>0.6 (0.4-0.7)</td>
</tr>
</tbody>
</table>

Abbreviations: FiO₂, fraction of inspired oxygen; GA, gestational age; IQR, interquartile range; LUS, lung ultrasonography; PtcO₂, transcutaneous partial pressure of oxygen.

* The indices representing oxygenation are in absolute numbers.

Each lung has been divided into 3 areas, as shown in the upper part of the figure. For each area, a score of 0 to 3 has been assigned. Score values correspond to 4 different patterns as shown in the ultrasonograms. Patterns were photographed during a longitudinal scan with a high-resolution linear probe (12-18 MHz; GE Logiq E9; GE Healthcare). Scores are given as follows, for any lung area: 0 indicates A-pattern (defined by the presence of only A-lines [arrowheads]); 1, B-pattern (defined as the presence of ≥3 B-lines [arrowheads], well spaced); 2, severe B-pattern (defined as the presence of crowded and coalescent B lines with or without consolidations limited to subpleural space); and 3, extended consolidation (box).
GA <34 weeks: \( \rho = -0.62; \ P < .001 \), alveolar-arterial gradient (GA ≥34 weeks: \( \rho = 0.62; \ P < .001 \), GA <34 weeks: \( \rho = 0.59; \ P < .001 \), oxygenation index (GA ≥34 weeks: \( \rho = 0.63; \ P < .001 \), GA <34 weeks: \( \rho = -0.60; \ P < .001 \), and arterial to alveolar ratio (GA ≥34 weeks: \( \rho = -0.60; \ P < .001 \), GA <34 weeks: \( \rho = -0.56; \ P < .001 \).

The ROC analysis for the whole population yielded an AUC of 0.83 (95% CI, 0.74-0.92; \( P < .001 \)). Figure 3 shows the ROC analysis for the subgroups: AUC = 0.93 (95% CI, 0.86-0.99; \( P < .001 \) for babies with a GA less than 34 weeks and AUC = 0.71 (95% CI, 0.54-0.90; \( P = .02 \) for babies with a GA of 34 weeks or greater. The AUCs are significantly different for the 2 subgroups (\( P = .02 \)). Table 2 shows reliability data for the LUS score to predict surfactant administration. In our population, having a LUS score greater than 2 or greater than 4 increases the probability to need surfactant administration from 21% to about 39% for babies with a GA of 34 weeks or greater and from 25% to about 72% for babies with a GA less than 34 weeks.

**Discussion**

We used a LUS score for the first time, to our knowledge, in a general newborn population consisting of both term and preterm neonates and this was easy and quick. Good concordance was found for LUS image interpretation, consistent with previous data about LUS diagnosis of TTN and RDS showing independence from operators’ experience.25,26 In study outcomes, our findings partially depend on the GA.

The LUS score was significantly correlated with indices of oxygenation, and these correlations were similar in babies with a GA of 34 or greater or a GA less than 34 weeks. Lung ultrasonography has been already used to provide qualitative diagnosis in neonatal critical care,4-6 but our findings showed that the LUS score may also be able to describe oxygenation, independent from the type of respiratory condition or GA.
Moreover, because LUS semiology uses artifacts due to the presence of air in the lung parenchyma, essentially this correlation describes lung aeration. Consistent results have been found in adult patients with other respiratory conditions. A more complex LUS score based on 12 lung areas has been used in adult patients with acute respiratory distress syndrome undergoing lung recruitment: the LUS score adequately estimated recruitment but failed to assess hyperinflation. Being based on fewer lung areas, our LUS score is easier to calculate and our findings in neonates seem promising. Different strategies should be tested to improve the correlation between LUS score and oxygenation. Should this be possible, the LUS score might be considered to evaluate lung aeration and alveolar recruitment. Futures studies might try to improve LUS using different probes, repeated scans, or more lung areas on larger neonatal populations.

Conversely, the LUS score shows varying diagnostic performance in predicting need for surfactant administration, depending on GA. It shows very good reliability only for babies with a GA less than 34 weeks. This is most likely due to the homogeneity of this subgroup, which consists of babies exclusively affected by RDS. On the contrary, babies with a GA of 34 weeks or greater presented with different clinical diagnoses; surfactant machinery may be damaged during TTN and pneumonia, but this injury may be variable. For example, the available surfactant, as represented by lamellar body count, may not always be deficient enough to need replacement therapy. Conversely, preterm babies with RDS represent a very homogeneous population with a well-defined surfactant administration policy; because surfactant is selectively given in babies under CPAP, we need a tool to identify babies who will need it. The LUS score may help to correctly identify these babies and give them surfactant as early as possible, without waiting for further oxygenation worsening. In our study, LUS was performed at a mean postnatal age of about 2 hours, which is approximately the threshold to define early surfactant administration. A recent meta-analysis of early vs delayed surfactant administration concluded that mortality, air leaks, and chronic lung disease were decreased in babies treated early.

We have chosen to report the threshold of LUS score with the highest sensitivity to not miss any surfactant administration, and a cutoff value of 4 allowed 100% sensitivity in this regard. The use of this LUS score cutoff in our population increases the probability to receive surfactant from 25% to about 72% in babies with a GA less than 34 weeks.

Further studies should try to increase the clinical value of the LUS score. For example, an earlier LUS or a repeated examination (ie, at 1 and 2 hours of life) might have a higher diagnostic accuracy or might allow evaluation of the disease evolution and reduce false-positive results. The use of different probes or more lung areas might also result in better accuracy. Because LUS is an easy, quick, and radiation-free technique, multiple looks are always possible; thus, it is an ideal candidate to become a screening tool to identify babies needing surfactant. Conversely, chest radiography is well known to lack diagnostic accuracy in this regard. Because no other technique is easily available at the bedside, LUS may fill an empty space in neonatal critical care imaging.

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 use and surfactant administration. Our data are slightly different from those of Raimondi et al, who considered a single LUS pattern on a single lung scan with a bigger linear transducer encompassing the whole neonatal chest. Thus, they used a much simpler evaluation with no lung areas and without taking consolidations into account. However, even using a simpler classification of LUS findings, results are similar in terms of predicting noninvasive ventilation failure. Conversely, our refined score using several lung areas may be more useful to de-

<table>
<thead>
<tr>
<th>GA, wk</th>
<th>Best Cutoff LUS Score</th>
<th>% Sensitivity</th>
<th>Specificity</th>
<th>LR Positive</th>
<th>LR Negative</th>
<th>PPV</th>
<th>NPV</th>
<th>Posttest Probability, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥34</td>
<td>2</td>
<td>91</td>
<td>25</td>
<td>1.2</td>
<td>0.4</td>
<td>20</td>
<td>93</td>
<td>39</td>
</tr>
<tr>
<td>&lt;34</td>
<td>4</td>
<td>100</td>
<td>61</td>
<td>2.6</td>
<td>0.0</td>
<td>54</td>
<td>97</td>
<td>72</td>
</tr>
</tbody>
</table>

Abbreviations: GA, gestational age; LR, likelihood ratio; LUS, lung ultrasonography; NPV, negative predictive value; PPV, positive predictive value.
scribe lung aeration and oxygenation, as reported in adult
patients.14,15,27,28

We acknowledge some study limitations. Echography is
generally thought to be operator dependent; however, this may
be easily solved by formal brief training as demonstrated by
the high interobserver agreement coefficient. This concor-
dance has been reported by other authors25,26 and indicates
that the LUS learning curve is quite short.20 The consistency
of our data as compared with those of other groups confirms
that LUS is not significantly affected by the operator’s expe-
rience even if the technique is used to calculate a score and
to give a definite clinical diagnosis.14 Oxygenation was stud-
ied in our data as compared with those of other groups confirms
the usefulness of the LUS score in more mature babies or in
those affected by conditions other than RDS.

Conclusions

Our scoring system allows a more quantitative use of LUS find-
ings and seems promising for further applications in neo-
natal critical care. The LUS score is well correlated with the
oxygenation status in both term and preterm neonates, and this
correlation does not depend on the respiratory conditions. The
LUS score shows good reliability to predict surfactant admin-
istration in preterm babies with a GA less than 34 weeks who
are treated with nasal CPAP from birth.

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of the data in the study and takes responsibility for the integrity of the data and the
accuracy of the data analysis.

Study concept and design: Brat, Yousef, Shankar
Aguilera, De Luca.

Acquisition, analysis, or interpretation of data: All
authors.

Drafting of the manuscript: Brat, Yousef, De Luca.

Critical revision of the manuscript for important intellectual content: Yousef, Klifa, Reynaud, Shankar
Aguilera.

Statistical analysis: De Luca.

Administrative, technical, or material support:
Yousef, Reynaud, Shankar Aguilera, De Luca.

Study supervision: Yousef, Shankar Aguilera, De Luca.

Conflict of Interest Disclosures: None reported.

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Pediatric Intensive Care Unit, South Paris University
Hospitals, Kremlin-Bicêtre Medical Center, Paris,
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