Clinical Applications in Lung Point-of-Care Ultrasound Assessment in Neonates

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Contents

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Y. Singh et al. (eds.), *Point-of-Care Ultrasound for the Neonatal and Pediatric Intensivist*,
https://doi.org/10.1007/978-3-031-26538-9_13

Introduction

The field of neonatal lung point-of-care ultrasound (POCUS) is rapidly expanding. Lung POCUS is a safe and rapid bedside tool used for the diagnosis of the most common acute respiratory diseases in the newborn period. In addition, lung POCUS can be used to monitor postnatal adaptation, predict the need for ventilation and/or surfactant, and evolving chronic lung disease (CLD) [1]. Lung POCUS is especially attractive in neonates because of concerns about the potential long-term effects of radiation from repeated X-rays during thier hospitalization stay in the neonatal intensive care unit [2, 3]. LU is used as an adjunct to the clinical examination and it must be always interpreted in light of available clinical findings and laboratory data [4]. The described findings for specific neonatal respiratory disorders are therefore only valid for the neonatal period when these pathologies are present.

Technical Considerations

The lungs are superficial organs. Since newborns have small chests with little subcutaneous tissue, almost any ultrasound transducer can be used to perform lung ultrasound. In order to obtain good quality images of the neonatal lung, high-frequency linear or micro-linear probes, usually with a frequency of 10 MHz or above, are most frequently utilized [5–7]. Since lung POCUS is based on the analysis of artifacts, machine settings need to be adjusted to minimize filters and facilitate the analysis of pleural sliding and artifacts as discussed in Chap. 10.

Clinical Applications of Lung Ultrasound for the Diagnosis of Neonatal Respiratory Diseases

Transitional Period

The transitional period from fetus to neonate is a unique period in life that involves complex physiological processes that must occur within a short period of time. The use of lung POCUS has helped clinicians gain additional insight into the pulmonary transition.

In healthy term and near-term neonates, lung aeration and partial airway fluid clearance occur within the first few minutes of life and complete fluid clearance is usually accomplished within 3-4 hours after birth [8, 9]. A significant decrease in the number of B-lines, as an estimation of lung fluid, is observed over the first 24 hours after birth and is associated with an increase in static lung compliance [10]. Regional differences in airway clearance have been observed and may be quantified using a lung ultrasound score [11].

Most infants quickly and smoothly complete the adaptation process, but some will experience delay and present signs of distress and/or underlying disease. Lung POCUS emerges as a promising tool for the early identification of infants at risk for pulmonary maladaptation. Raimondi et al. demonstrated that early use of lung POCUS using a simple 3-point classification based on ultrasound patterns (type-1, white lung; type-2, black/white lung; type-3, normal lung) predicts the need for NICU admission for respiratory support in term and near-term infants [12]. Poerio et al. confirmed the reliability of lung POCUS performed at 30 min after birth to predict NICU admission for term and near-term infants born by cesarian section [13]. These findings may have practical implications in the management of infants born in facilities without a NICU on-site when decisions regarding transfer to another facility and separation of mother and child are required.

Transient Tachypnea of the Newborn

Transient tachypnea of the newborn (TTN) is a common cause of respiratory distress in the immediate newborn period. Lung edema observed in TTN is the result of delayed alveolar fluid resorption and clearance during the transitional period. Copetti and Cattarossi first described LU signs in TTN characterized by

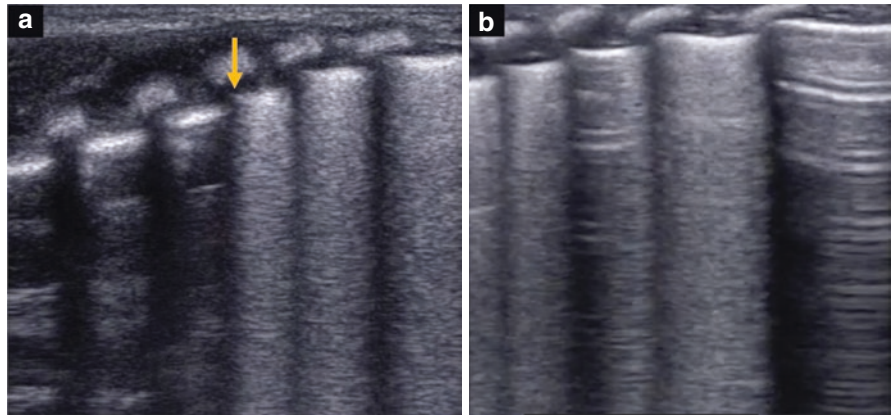

Fig. 1 Transient tachypnea of the newborn (TTN). The lung shows a mix of A- and B-lines with a well-defined pleural line. Areas with B-lines alternate with intercostal spaces with multiple A-lines and a "double lung point" (DLP) (arrow) may be observed sharply separating both areas. The DLP is not necessary for diagnosis as shown in panel **b**

areas of B-lines (interstitial syndrome) in the lower lung fields with normal or almost normal areas (A-lines) in the upper lung fields [14]. A sharp transition between the two patterns called the "double lung point" (DLP) is typical for TTN and has not been described for any other neonatal respiratory diseases [14] (Fig. 1a). The presence of spared areas (with A-lines) in a late preterm or term neonate, with mild to moderate respiratory failure, is suggestive of TTN [14]. A regular pleural line with no consolidation is a consistent finding in TTN and may be a reliable sign to exclude other lung disorders [15]. However, future studies are needed to determine the diagnostic accuracy of these signs. Raimondi et al. demonstrated that although the presence of a DLP is a specific finding in TTN, it is not necessary for its diagnosis [15–17] (Fig. 1b). In these studies, DLP was present in roughly 50% of patients, and serial scanning showed that it could present later in the course of the disease [15]. A lung ultrasound aeration score correlates with the work of breathing in TTN and may be useful to monitor changes in lung aeration throughout the course of the disease [15].

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS), originally called hyaline membrane disease, is primarily observed in preterm infants and is the result of insufficient surfactant production. The risk and severity of RDS is inversely proportional to gestational age. Surfactant deficiency leads to reduced pulmonary compliance and increased alveolar surface tension leading to alveolar collapse and reduced surface area for gas exchange. RDS may present with other conditions including pneumonia, early onset sepsis, and/or air leaks [1].

Lung ultrasound imaging in RDS reflects the underlying pathophysiology with loss of aeration and decreased air/fluid ratio in the lungs. The lungs show severe diffuse alveolo-interstitial syndrome with an irregular pleural line, microconsolidations ("subpleural consolidations"), and uncountable, "confluent" B-lines giving rise to a bilateral uniform "white lung" appearance as first described by Copetti et al. [6] (Fig. 2). There are no spared areas, i.e., no areas with A-pattern, in severe RDS. Lung sliding is preserved. Other findings include "subpleural" microconsolidations and/or an irregular pleural line [6]. An adapted neonatal lung ultrasound score may be used to predict the need for surfactant in preterm infants with RDS and guide surfactant administration (see below).

Lung Ultrasound in RDS and TTN

Lung POCUS can accurately and reliably diagnose and differentiate TTN and RDS and little

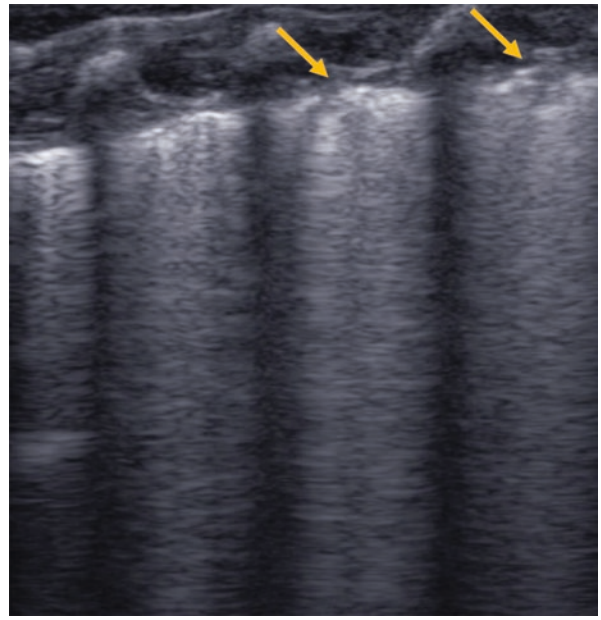

Fig. 2 Respiratory distress syndrome (RDS). The lung has a "white" lung appearance with no spared areas. The pleural line is thick and irregular with "subpleural" microconsolidations (arrows)

previous experience is needed to achieve a high level of inter-operator concordance. From a pathophysiological point of view, RDS is a more severe and homogeneously diffuse condition than TTN. The absence of spared areas (with A-pattern) on lung ultrasound is the main difference between RDS when compared to TTN. Furthermore, ultrasound findings in RDS do not show short-term changes as is the case with TTN [15]. Interestingly, there appears to be a mixed-type RDS/TTN respiratory condition when fluid retention is associated with partial surfactant deficiency [1]. The clinical picture in these mixed cases is often more severe than the "classic" TTN, with longer recovery times, high noninvasive respiratory support and, occasionally, the need for surfactant administration [1]. Lamellar body count for these babies with mixed-type RDS/TTN is decreased, and although spared areas on lung POCUS are seen, these are often limited to a few areas compared with the "classic" TTN [18]. A semi-quantitative lung ultrasound aeration score correlates well with the quality of available endogenous surfactant and may be an interesting tool in studying this patient subgroup [19].

Pneumothorax

The diagnosis of pneumothorax in neonates is based on the same signs described in the adult literature and described in Chap. 10 [20]:

1. Loss of lung sliding and lung pulse with the presence of the "stratosphere sign" on the M-mode
2. The exclusive presence of A-lines with the absence of any other artifact (e.g., B-lines, Z-lines or consolidation)
3. The presence of a lung point (which may not be found in a large pneumothorax)

Lung POCUS can be used to rapidly diagnose or rule out tension pneumothorax in the newborn and shows excellent diagnostic accuracy which is superior to chest X-rays a time to diagnosis that is significantly shorter [21–23]. The diagnostic accuracy of lung POCUS for the diagnosis of pneumothorax in newborns appears to be higher than in adults. A meta-analysis performed by Dahamarde showed a sensitivity of 96.7% (88.3–99.6%), a specificity of 100% (97.7–100%), with an odds ratio of 1343.1% (167.20–10788.9) in neonates compared to a sensitivity of 82.9%

(78.3–86.9%), a specificity of 98.2% (97.0–99.0%), and an odds ratio of 423.13% (45.222–3959.1) in adults [24]. According to current recommendations, lung POCUS should be used to not only diagnose pneumothorax in children and neonates but also to provide guidance for thoracentesis [25].

Meconium Aspiration Syndrome

Meconium aspiration syndrome (MAS) is a common cause of neonatal respiratory distress which carries variable severity. The presence of meconium in the airways leads to airway obstruction and alveolar collapse, while the chemical properties of meconium induce lung tissue inflammation, chemical alveolar injury, and surfactant damage [26]. When lung injury is sufficiently severe and diffuse, it may lead to a severe oxygenation deficit fulfilling the criteria for neonatal acute respiratory distress syndrome (nARDS) [27]. The heterogeneous nature of MAS is reflected in the lung POCUS findings (Fig. 3) with signs of airway obstruction by meconium plugs (atelectasis and/or consolidation) and lung inflammation (interstitial syndrome and consolidation) [28, 29]. Mild or moderate pleural effusion may also be present. Images for the same patient may include normal lung areas, interstitial pattern, alveolar pattern, and consolidations with bronchograms and atelectasis [28, 29]. These images are dynamic and change rapidly over the course of the disease. The lung ultrasound score (LUS) in MAS shows a significant negative correlation with the quality of available endogenous surfactant [30].

Pneumonia

Diagnosis of congenital pneumonia currently relies on clinical, biological, and radiological findings. Adding lung POCUS to the investigation of a newborn with suspected congenital pneumonia may increase the specificity of the diagnosis, especially for complicated cases [31]. The typical lung POCUS signs of pneumonia are the presence of consolidations with air bronchograms, and an irregular pleural line with areas of B-lines with or without pleural effusion (Fig. 4). These signs have a high diagnostic accuracy according to the study performed by Liu et al. [32]. Similar results were found by Chen et al. in a larger cohort of 3405 Chinese neonates who were routinely scanned using lung ultrasound [33]. This is consistent with data from the pediatric population where a meta-analysis of eight diagnostic studies (765 patients including both neonates and children) yielded a sensitivity and a specificity of 96 and 93%, respectively, which is superior to the accuracy of chest X-rays and comparable to that obtained combining radiology and laboratory exams [34].

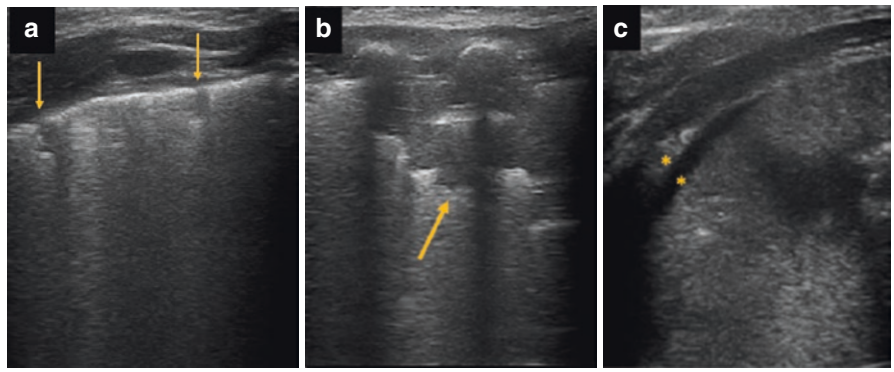

Fig. 3 Meconium aspiration syndrome (MAS). Lung ultrasound images from a neonate presenting with severe MAS. Lung ultrasound reveals heterogeneous findings related to injury and obstruction by meconium. Panel **a**: scan of the anterior chest wall showing an irregular pleural line with small consolidations (arrows) and multiple B-lines. Panel **b**: scan of the lateral chest wall showing multiple B-lines and a large consolidation with irregular borders (arrow). Panel **c**: horizontal (transcostal) scan of the posterior chest wall showing consolidation with a rim of pleural effusion (*)

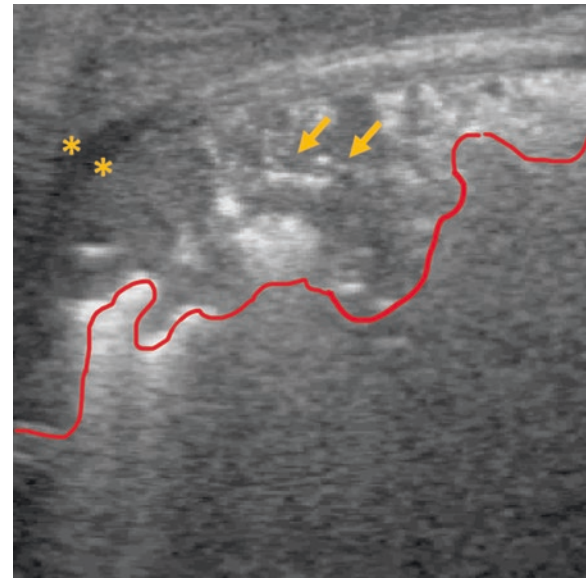

Fig. 4 Pneumonia. Horizontal (transcostal) scan of the anterolateral region of the chest. Typical signs of pneumonia are shown and include consolidation with shred sign (traced in red) with air bronchograms (arrows), areas with B-lines, and pleural effusion (*)

Many questions still remain unanswered regarding the diagnosis of neonatal pneumonia. For example, the abovementioned lung ultrasound signs are typically associated with pneumonia, but congenital pneumonia may also present with an alveolar-interstitial pattern, and an irregular pleural line with or without small consolidations [35]. These findings will need to be confirmed in larger studies. Lung POCUS may also be an interesting tool in the diagnosis and management of neonatal ventilator-associated pneumonia (VAP) as described in a recent study by Tusor et al. [36]. The proposed multiparametric score including clinical variables and lung ultrasound findings demonstrates promising predictive values for diagnosis of VAP in neonates with underlying CLD but needs further testing in larger patient populations under prospective, multicenter clinical trial settings.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) remains a major negative outcome of prematurity. BPD is a continuum starting soon after, or even before birth, and potentially continuing throughout infancy as chronic respiratory morbidity. BPD is characterized by its evolutive nature and its variable clinical severity [37]. Lung POCUS can document the evolving changes of BPD that include pleural line abnormalities, areas with B-lines, and consolidations and reflect the non-homogenous nature of the disease. The characteristic lung POCUS finding of BPD is the presence of a thick pleural line with areas of interstitial-alveolar syndrome, in some cases a "white lung" appearance, with or without consolidations [35, 38]. Lung ultraosund can reliably predict progression towards BPD starting shortly after birth (see below).

Neonatal Acute Respiratory Distress Syndrome

ARDS is an acute and life-threatening respiratory disease characterized by extensive lung tissue inflammation, endothelial injury, and secondary surfactant dysfunction that leads to loss of lung aeration [27]. Pediatric (pARDS) and neonatal ARDS (nARDS) share the same biological and pathophysiological aspects as adult ARDS. However, nARDS may have different pathophysiology that presents specifically in the neonatal period, such as MAS, pulmonary hemorrhage, sepsis, perinatal asphyxia, pneumonia, and/or necrotizing enterocolitis [1].

Lung POUS findings show bilateral, irregular, diffuse loss of aeration that may vary from a diffuse interstitial pattern to an irregular alveolar pattern with consolidations, air bronchograms, and atelectasis [1, 39]. The Montreux diagnostic definition of

nARDS officially requires chest radiographic findings defined as "diffuse, bilateral and irregular opacities or infiltrates, or complete opacification of the lungs, which are not fully explained by local effusion, atelectasis, RDS, TTN, or congenital lung anomalies," but lung POCUS is used reliably for the diagnosis of ARDS in adults [40],] and is considered suitable in neonates when sufficient clinical expertise is available for interpretation [41]. Further research is necessary to define the use of lung POCUS in pARDS and nARDS.

Congenital Lung and Airway Malformations

Congenital pulmonary adenomatous malformation (CPAM) and pulmonary sequestration (PS) are usually diagnosed prenatally. Although most of the babies are asymptomatic at birth, some may present with respiratory distress and/or hemodynamic compromise and require critical care and early surgical resection [42]. Chest CT and CT-angiography remain the gold standard for postnatal management of CPAM and PS, but lung POCUS seems promising as an additional bedside tool for diagnosis, follow-up, and management. Several case series show that lung POCUS can be used to confirm lung lesions in infants with an antenatal diagnosis of CPAM [43–45]. The main lung ultrasound findings for CPAM are the presence of single or multiple cystic lesions, with or without consolidation, and have not been described for any other neonatal lung disease [43] (Fig. 5). In PS, the search for evidence of a systemic feeding vessel is essential [45].

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a complex condition with considerable associated mortality and morbidity rates. The congenital defect of the diaphragm leads to herniation of abdominal organs into the thorax and compromise of the ipsilateral as well as contralateral lung leading to lung hypoplasia and pulmonary hypertension. The role of lung POCUS in the

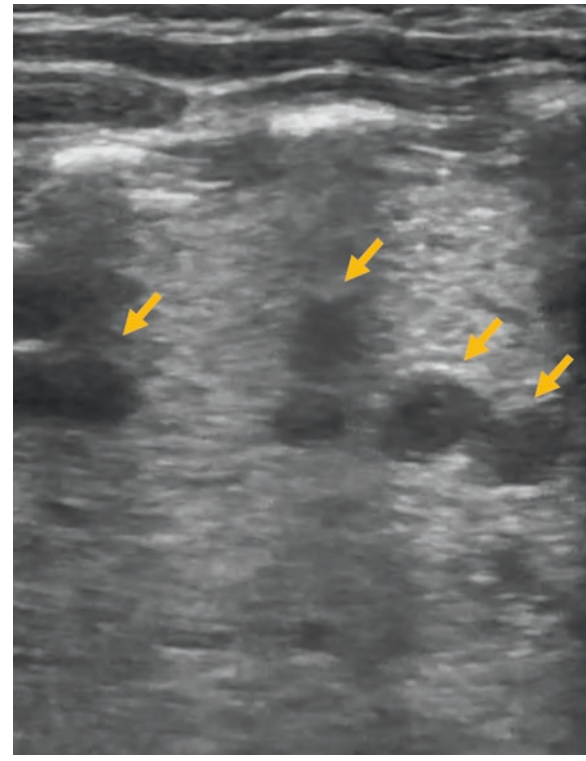

Fig. 5 Congenital pulmonary adenomatous malformation (CPAM). Vertical scan of a CPAM lesion. The presence of one or more cystic lesions (arrows) in the lung parenchyma is characteristic of CPAM and has not been described for other neonatal respiratory diseases

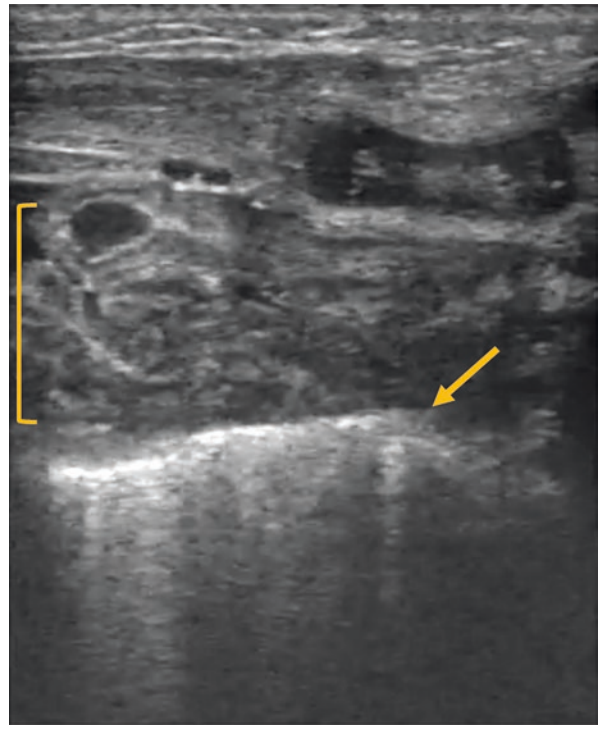

Fig. 6 Congenital diaphragmatic hernia (CDH). Vertical scan of the left anterior chest wall. In this image, loops of small bowel (bracket) are seen above the pleural line (arrow)

diagnosis and management of CDH seems promising but remains to be determined [35, 46]. Postnatal data on lung POCUS findings are scarce and limited to case descriptions. Thoracic ultrasound shows a defect in the diaphragm, with partial absence of the pleural line and absence of A-lines in the affected hemithorax, and the presence of a multilayered area with hyperechoic dynamic content (bowel) with or without abdominal organs in the thoracic cavity [46]. (Fig. 6).

Functional Use of Lung Ultrasound

Lung POCUS is a valuable tool for the diagnosis of the most common respiratory diseases shown in the sections above. In addition, lung POCUS can be used to guide respiratory therapeutic interventions and help in clinical decision-making as shown below.

Lung Ultrasound Scores

Lung POCUS is an excellent tool for the evaluation of loss of lung aeration as it detects the artifacts generated when the fluid/air ratio in the lungs increases. The decrease in aeration leads to an increase in B-lines and/or a progression towards consolidation seen with complete loss of aeration. Multiple quantitative lung aeration scores have been developed based on this concept and are widely used in adult critical medicine to guide ventilation and lung recruitment, as well as for other applications [47, 48]. Quantitative and semi-quantitative LUS are fairly recent techniques in pediatric and neonatal critical care and are based on the same principles as adult scores [1]. The following subsections will discuss a few main applications of LUS in newborn (Fig. 7).

Lung Ultrasound Scores in RDS

The lung in RDS is characterized by a loss of aeration as a result of alveolar collapse due to surfactant deficiency. A quantitative LUS first published by Brat et al. is a simplified version of the adult lung ultrasound aeration scores [7]. The LUS is specifically adapted for newborn and correlates significantly with the quality of available surfactant [19]. Each lung is divided into three

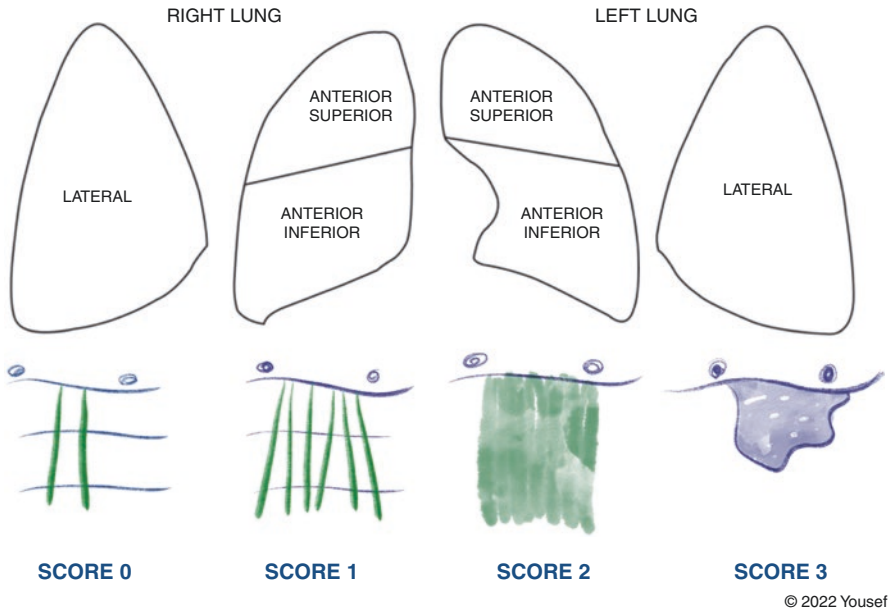

Fig. 7 The LUS score. © 2022 Yousef. All rights reserved with permission. The lung ultrasound score allows for a quantitative evaluation of lung aeration in the newborn. Each lung is divided into three regions. A score of 0–3 is given for each region and added to give a total score of 0–18; 0 is given for <3 B-lines per intercostal space, 1 >3 B-lines per intercostal space, 2 when there are uncountable B-lines and disappearance of A-lines, and 3 is given for consolidation. The LUS is the sum of the regional scores and is inversely correlated with lung aeration

regions (anterior superior and inferior, and lateral) and a score from 0 to 3 is given to each region according to the degree of lung aeration (Fig. 8). The LUS is calculated as the sum of regional scores (maximal score of 18) and shows high accuracy in predicting surfactant need in CPAP-treated preterm and extremely preterm infants [7, 49] with a meta-analytical AUC of 0.952 (95% CI: 0.951–0.953) for LUS cutoff value between 6 and 8, and a higher diagnostic accuracy than chest X-rays [50, 51]. Although most authors use the score described by Brat et al., some include the posterior field in the evaluation for a total of three to six areas of each lung [50].

Another simplified semi-quantitative approach has been proposed to evaluate the loss of aeration and utilizes three basic pattern classifications: Type 1 or white lung (severe alveolo-interstitial pattern), Type 2 or white and black lung (moderate alveolo-interstitial pattern), and Type 3 or black lung (A-line pattern; normal lung) [52]. Both proposed methods show good diagnostic accuracy for the early prediction of the need for surfactant replacement, especially for younger preterm infants compared with late preterm and term infants as shown in two recent meta-analyses [50, 53].

Surfactant administration should ideally be performed within the first 2–3 hours after birth to reduce mortality and morbidity [54]. LUS-guided surfactant replacement (also known as (Echography-guided Surfactant THERapy (ESTHER)) significantly increases the number of patients treated within the optimal 3 hours time frame, reduces oxygen exposure early in life, and improves oxygenation after surfactant dosing, without increasing the use of surfactant or changing cost/benefit ratios [55–57].

Lung Ultrasound Scores in BPD

Early prediction of the respiratory clinical course and progression towards BPD are promising applications of functional lung POCUS in very low birth weight infants. Quantitative LUS allows

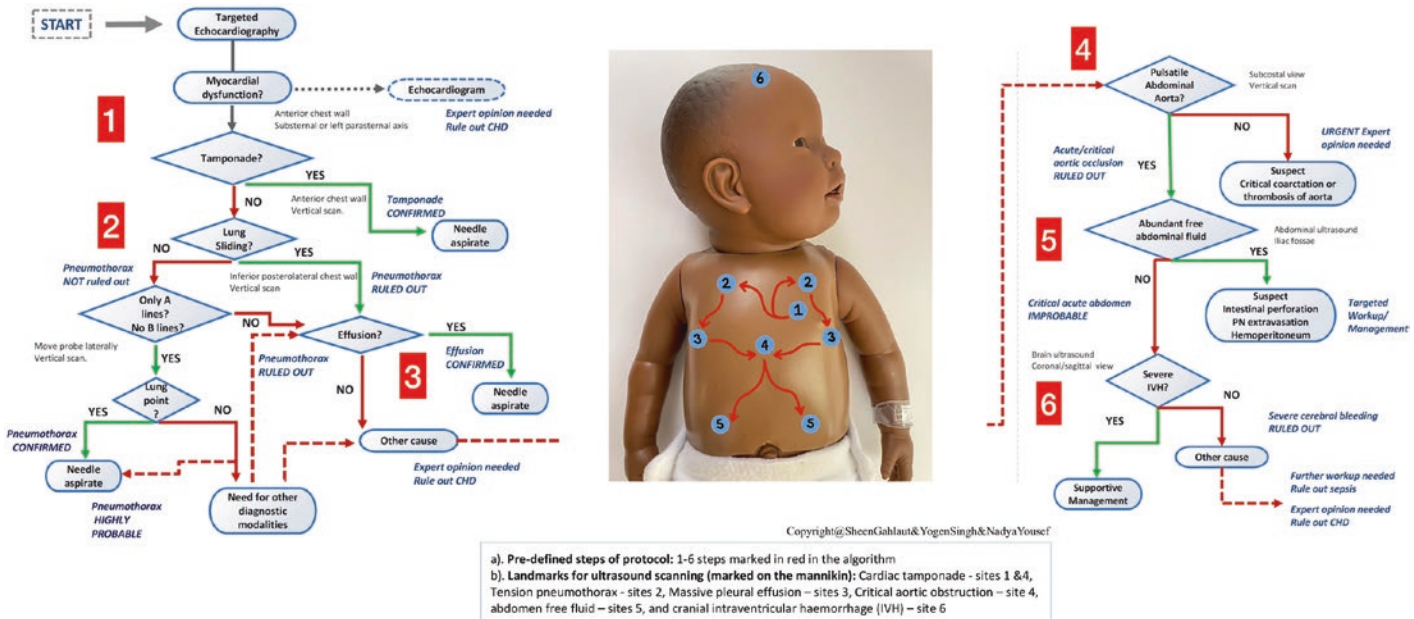

Fig. 8 The SAFE-R ultrasound protocol. © 2021 Gahlaut, Singh and Yousef. All rights reserved with permission. The SAFE-R protocol is specifically designed for the neonatologist faced with a suddenly decompensating NICU infant when no apparent cause is evident. The protocol starts at the upper left with the most urgent intra-thoracic causes: cardiac tamponade, tension pneumothorax, and pleural effusion, then includes extra-thoracic causes at the right hand of the figure with critical aortic occlusion, abdominal complication, and severe intraventricular hemorrhage. An important reminder of the possibility of congenital heart disease (CHD) needing a full echocardiogram by an expert is indicated on both sides of the panel since for the neonatal population this remains an important differential diagnosis. The step-by-step ultrasound protocol uses a single probe, at standardized SAFE points and a simple rule-in/rule-out approach. The decision tree is designed by urgency, and the order of the standardized points allows for a logical and easy use of the ultrasound probe from the thorax to the abdominal aorta, the iliac fossae, and then the head

to monitor changes in lung aeration and lung function in extremely preterm infants over time.

Serial studies in preterm infants demonstrate a significant difference in the trajectory of LUS in infants who later develop BPD and those who do not [58–60]. This difference is observed as early as 1 week after birth. LUS are accurate for early prediction of BPD and moderate to severe BPD, in an average population of preterm infants <32 weeks' gestation as shown in a recent analysis by Pezza et al. [61]. These authors evaluated the use of LUS (the LUS described by Brat et al. and eLUS, an extended LUS including posterior lung regions) for the prediction of progression towards BPD diagnosed at 36 weeks gestational age. Seven studies (1027 neonates) were meta-analyzed. Both LUS and eLUS showed good diagnostic accuracy in predicting BPD at 7 and 14 days after birth (AUC 0.85–0.87; pooled sensitivity, 70–80%; pooled specificity, 80–87%) [61]. There is currently no specific treatment for BPD, but the ability to predict BPD at an early stage may have practical implications for the management of at-risk infants in the future.

Integrating Lung Ultrasound into POCUS Protocols

Targeted emergency ultrasound protocols are widely used in adult medicine in many situations, e.g., dyspnea [62], shock [62, 63], and cardiac arrest [63, 64]. There is a need for specific and adapted ultrasound protocols for the neonatal population. SAFE-R (Sonographic Assessment of liFe-threatening Emergencies—Revised) is the first ultrasound protocol specifically designed for the neonatologist faced with a suddenly decompensating infant in the NICU and aims to help guide initial management and resuscitation efforts [65].

SAFE-R uses standardized ultrasound points and a simple one-probe rule-in/rule-out approach and needs minimal training to perform (Fig. 8). SAFE-R allows for rapid screening for the most common life-threatening complications needing immediate attention, thereby allowing the clinician to quickly initiate treatment, or in the case of a negative screen, to promptly assess for other neonatal conditions such as sepsis, decompensation of metabolic or endocrine disorders, or critical congenital heart disease needing urgent comprehensive echocardiography.

The SAFE-R protocol requires prospective evaluation as have similar adult critical care ultrasound protocols [62]. Although any probe can be used, the optimal probe needs to be determined for each specific study [5]. International collaborative efforts are ongoing to develop and evaluate targeted multiorgan ultrasound protocols.

Conclusion

The integration of lung POCUS into clinical practice promises to transform the field of neonatology. Neonatal lung POCUS has evolved from being a purely descriptive tool for qualitative diagnosis of neonatal respiratory diseases to a functional bedside tool to quantitatively evaluate lung aeration and guide respiratory interventions. The literature on neonatal lung ultrasound has seen a rapid increase in recent years, but there persists a significant knowledge gap compared with adult critical care. Collaborative efforts and multicenter studies using rigorous methodology will hopefully contribute to increase experience and knowledge regarding applications in the coming years.

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