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# Neonatal lung ultrasound: From paradox to diagnosis … and beyond

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## 1. Introduction

Any medical student is taught that an ultrasound beam will not penetrate an air-filled organ. Therefore, the echographic exploration of the lungs is not possible.

Yet, there has been an explosion of publications on lung ultrasound in the past ten years (Fig. 1) to create an objective paradox. The explanation, however, is quite simple. Combining images from anatomic structures and artifacts (i.e. reproducible images that have no anatomic equivalent), clinical researchers have created ultrasound profiles. These, in turn, have been validated as diagnostic markers of several important respiratory diseases both in adult and in the developing age [1]. One important assumption is that artifacts appear and change in a reproducible parallel with the air to fluid ratio, spanning from a normally aerated to a fully consolidated lung parenchyma (Fig. 2).

The details of this approach applied to neonatal respiratory medicine are well described in recent reviews [2,3]. The present paper is a brief summary of the key points, an update of the most recent results and a speculation on promising research in neonatal lung ultrasound (LUS).

## 2. Descriptive and functional neonatal lung ultrasound

The original strategy pursued by neonatal clinical investigators was to validate ultrasound profiles describing the main infantile respiratory diagnoses [2,3]. In a series of 124 neonates, Corsini I et al. found that the concordance between LUS and chest X ray (CXR) diagnosis was 91% (95% CI 86–96%). The median time to diagnosis was shorter for LUS (9.5 min, IQR 5–15) than for CXR (50 min, IQR 33–64) ($p < 0.0001$) [4]. In an international study, the recognition of the ultrasound profile typical of tension pneumothorax was achieved with absolute diagnostic accuracy and a successful emergency drainage was performed before the CXR diagnosis in 9/42 cases [5].

Besides making a diagnosis, LUS can be applied to clinical situations evolving over time. These functional applications of neonatal LUS stem from the significant correlation between lung aeration and a reproducible sequence of artifacts (Fig. 2). When the latter is given a score, neonatal LUS becomes a reliable tool to monitor post natal transition [6], the need for non invasive respiratory support [7] and surfactant administration [8].

### 2.1. LUS and surfactant administration

Surfactant remains a keystone in the treatment of neonatal respiratory distress syndrome (RDS). Yet, there is only weak evidence supporting the current European recommendation to administer surfactant when the infant requires an inspired oxygen fraction ($FiO_2$) beyond 0.3 to keep a normal saturation range [9].

LUS offers a solid alternative to the purpose. De Martino L et al. showed in a series of 163 neonates less than 30 weeks of gestational age that LUS score thresholds predicted need for the first surfactant dose (area under the curve = 0.94; 95% CI: 0.90–0.98; $p < 0.0001$) and also the need for surfactant redosing (area under the curve = 0.803; 95% CI: 0.72–0.89; $p < 0.0001$) [10]. In a quality improvement project, Raschetti R et al. compared surfactant administration based on the $FiO_2 = 0.3$ limit with a second period when the LUS score threshold from the previous paper was added to oxygen requirement as an alternative treatment criterion. While the total number of infants receiving surfactant remained unchanged, in the second period a significantly higher number of babies received surfactant within 3 h of life [11]. According to available evidence [12], an early treatment is protective against bronchopulmonary dysplasia (BPD).

Other single center studies have recently confirmed these results. In a series of 45 preterm infants less than 34 weeks gestational age, Vardar G et al. demonstrated that a cut-off LUS score = 4 predicted the need for surfactant with 96% sensitivity and 100% specificity [13]. Describing a single NICU yearly experience, Gregorio-Hernandez R et al. showed that LUS predicted surfactant treatment with an AUC = 0.97 [14]. Similar results (AUC = 0.94) came from the study by Perri A and coworkers on 56 infants less than 31 weeks gestational age [15].

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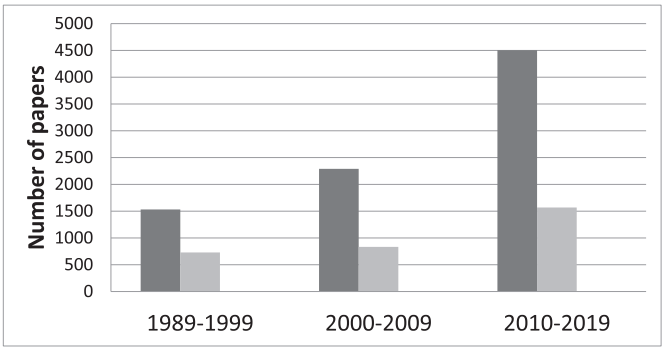


**Fig. 1.** Number of papers retrieved from the PubMed database using "lung ultrasound" (dark grey columns) and "neonate" AND "lung ultrasound" (light grey columns) keywords, respectively.

Recently, Rodriguez Fanjul J et al. published the first RCT on the topic. Fifty-six preterm neonates were randomized to receive surfactant on the basis of a LUS cut-off score and/or $FiO_2 > 0.3$ or on the oxygen requirement alone. The first group received a significantly earlier treatment with a better oxygenation as measured by the $SpO_2/FiO_2$ ratio [16].

### 2.2. LUS and BPD

The most widely accepted definition of BPD consists in oxygen dependency at 36 weeks post menstrual age. As BPD is a significant and often invalidating long term sequel of prematurity, its reliable prediction early in NICU admission would give clinicians time to prepare effective counter measures. Abdelmawla M et al. described a small retrospective cohort where a LUS score = 6 had a remarkable performance (sensitivity = 78% and specificity = 97%; PPV = 95% and NPV = 82%) in predicting BPD [17]. In a cohort of 59 VLBW infants (median PMA = 29 weeks), Alonso-Ojembarrena A et al. showed that a LUS score $\geq 5$ at 2 weeks post-natal age (i.e. PMA = 31 weeks) predicted BPD with an AUC = 0.93 [18]. Similar results were recently published by Oulego-Erroz I and coworkers on 42 preterm infants [19]. A LUS score $\geq 8$ at 7 days of life predicted severe BPD (i.e. $FiO_2 \geq 0.3$ or positive pressure ventilation at 36 weeks PMA) with an AUC = 0.94.

## 3. What lies ahead

Most of the published evidence comes from small, single centers studies with minor protocol variations. There is an objective need for standardization and collaborative studies to render LUS a daily tool in neonatal respiratory medicine [20]. A complementary strategy relies on computer-assisted, big data technology which grants speed of interpretation and generalization of the results. The use of machine learning, deep learning or convoluted neural networks systems has already obtained results comparable to those achieved by expert human operators both in adult and neonatal LUS [21,22].

In summary, researchers have overcome a physical paradox exploiting ultrasound artifacts for clinical purposes. New technologies promise to boost this achievement for routine use in critical care.

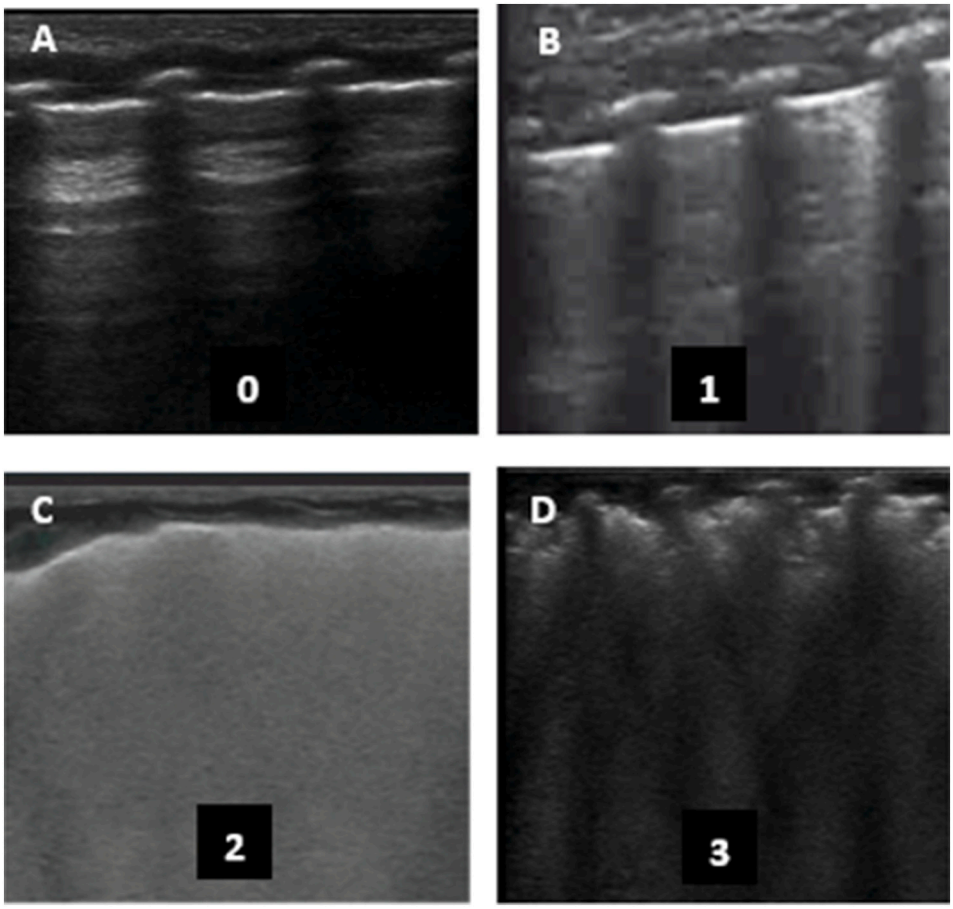


**Fig. 2.** A semiquantitative LUS score reliably parallels lung aeration and oxygenation.
Each lung is divided into 3 areas and for each area a score from 0 to 3 is assigned. Score values correspond to 4 different patterns: (A) horizontal lines (aka A lines) represent the normally aerated lung parenchyma (score 0). A progressively increasing fluid to air ratio (B) is seen as vertical hyperechoic artifacts (aka B lines) (score 1). Confluent and crowded B lines (C) create a "white lung image" (score 2). A minimal air content is visualized as lung echodensity equal to that of the liver (D) called "consolidation areas" (score 3).

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