Received: 27 October 2019 | Accepted: 6 January 2020

DOI: 10.1002/ppul.24654

ORIGINAL ARTICLE: IMAGING

PEDIATRIC PULMONOLOGY WILEY

# Lung ultrasound—a new diagnostic modality in persistent tachypnea of infancy

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## Abstract

Lung ultrasound (LUS) has been increasingly used in diagnosing and monitoring of various pulmonary diseases in children. The aim of the current study was to evaluate its usefulness in children with persistent tachypnea of infancy (PTI). This was a controlled, prospective, cross-sectional study that included children with PTI and healthy subjects. In patients with PTI, LUS was performed at baseline and then after 6 and 12 months of follow-up. Baseline results of LUS were compared to (a) baseline high-resolution computed tomography (HRCT) images, (b) LUS examinations in control group, and (c) follow-up LUS examinations. Twenty children with PTI were enrolled. B-lines were found in all children with PTI and in 11 (55%) control subjects ($P < .001$). The total number of B-lines, the maximal number of B lines in any intercostal space, the distance between B-lines, and pleural thickness were significantly increased in children with PTI compared to controls. An irregularity of the pleural line was found in all patients with PTI and in none of the healthy children. There were no significant changes in LUS findings in patients with PTI during the study period. The comparison of HRCT indices and LUS findings revealed significant correlations between the mean lung attenuation, skewness, kurtosis and fraction of interstitial pulmonary involvement, and the number of B-lines as well as the pleural line thickness. LUS seems to be a promising diagnostic tool in children with PTI. Its inclusion in the diagnostic work-up may enable to reduce the number of costly, hazardous, and ionizing radiation-based imaging procedures.

KEYWORDS

computed tomography, imaging techniques, neuroendocrine cell hyperplasia of infancy, pediatrics

## 1 | INTRODUCTION

Persistent tachypnea of infancy (PTI) is among the most prevalent chronic interstitial lung diseases (ILD) in infancy. The symptoms of PTI usually start in the 1st year of life and include tachypnea, retraction, crackles, hypoxemia, and failure to thrive in most severe cases. If lung biopsies are taken, neuroendocrine cell hyperplasia of infancy (NEHI), pulmonary interstitial glycogenosis (PIG), or some other histological diagnosis may be found.[1,2] In the majority of patients, PTI is associated with only mild impairment of gas exchange and clinical improvement is observed over time (mainly in NEHI cases).[3,4]

High-resolution computed tomography (HRCT) is a highly sensitive diagnostic method and is currently regarded as a gold-standard imaging technic in children suspected of PTI. The predominant HRCT findings

  

are sharply marked out ground-glass opacities (GGO) localized in the right middle lobe, lingula, paramediastinal and perihilar regions, as well as air trapping.[5] This pattern was previously considered as specific for NEHI,[5] but it has been shown, that it can be also found in other ILD.[1,6,7]

HRCT has some significant limitations, especially in the youngest children. First, the method is associated with relatively high radiation exposure, in particular when repetitive scans are necessary. Second, as young children are incapable of breath-holding and breathing frequency is above 50 breaths per minute, breathing-related artifacts may reduce the quality of HRCT images. Hence, controlled-ventilation computed tomography (CT) under sedation or general anesthesia is often necessary in infants and toddlers.[8] The above limitations highlight the need for other safe and less demanding imaging methods.

Lung ultrasound (LUS) may be an attractive diagnostic alternative to chest radiograph and chest CT scanning in children with various pulmonary diseases, such as pneumonia, transient tachypnea of newborn, or bronchiolitis.[9–12] Its advantages include safety, wide and repetitive accessibility, low costs and, in particular, applicability in the youngest children. Recently, in adults with ILD, the value of LUS has been shown for systemic sclerosis (SSc), rheumatoid arthritis, Sjögren syndrome, and pulmonary fibrosis.[13–19] No cohort studies have been presented for childhood interstitial lung diseases (chILD). The main ultrasound sign of interstitial involvement is the presence of B-lines ("lung comets"), whose origin is from air-fluid interfaces, produced in the lung by adjacent air- and fluid-filled structures.[20,21]

Here, we demonstrate the usefulness of LUS in the initial evaluation and monitoring during follow up of children with PTI.

## 2 | METHODS

### 2.1 | Study design

This was a controlled, prospective, cross-sectional study that included children with PTI hospitalized in our department between January 2014 and December 2016. Children with newly diagnosed PTI, as well as those with previously established PTI diagnosis referred for follow-up evaluation, were enrolled. In all children with PTI, LUS was performed at three time points: at inclusion, after 6 and after 12 months of follow-up. Baseline results of LUS were compared to (a) baseline HRCT images, (b) LUS examinations in healthy, age-matched children constituting a control group, and (c) subsequent LUS examinations in patients with PTI (performed after 6 and 12 months). To take into account a possible impact of time interval between the acquisition of LUS and HRCT images, the relationships between baseline HRCT and LUS were studied in two patient categories: (a) those in whom both examinations were performed within an interval of ≤5 days, and (b) those with time interval between HRCT and LUS longer than 5 days. The study protocol was accepted by Institutional Review Board of Medical University of Warsaw. Informed written consent was obtained from parents or guardians.

### 2.2 | Patients

Diagnosis of PTI was based on (a) clinical signs and symptom (tachypnea defined as respiratory rate >97 percentile of normal range,[22] retractions, crackles, and hypoxemia), (b) typical HRCT findings, including geographically distributed GGOs in different lung regions (the right middle lobe, lingula as well as, perihilar and pericardial region), (c) lung biopsy in patients with ambiguous HRCT findings. Besides HRCT, all patients underwent a full diagnostic work-up to exclude the alternative diagnoses, including the surfactant dysfunction syndromes or significant comorbidities. These included routine blood tests, arterial blood gases, ECG, echocardiography, 24-hour esophageal multichannel intraluminal impedance/pH testing. Importantly, echocardiography revealed no signs of pulmonary hypertension, congenital heart malformation, or impaired cardiac function in any patients from the study group.

The exclusion criteria were as follows: other well-defined chronic lung diseases (eg, asthma), congenital lung malformations, current or recent (within 1 month) lower respiratory tract infections, cardiovascular diseases resulting in heart failure, renal failure that could have resulted in fluid overload.

The control group included age-matched healthy children with no signs and symptoms of respiratory diseases.

### 2.3 | Imaging studies

#### 2.3.1 | High-resolution computed tomography

Baseline chest HRCT was performed in all children with PTI as a part of routine diagnostic process. Computed tomography scanning was done using 16-row multidetector CT scanner (Bright Speed; GE Healthcare, Chicago, IL) and the following settings: 100 kVp, 80 to 150 mAs, pitch: 0.938-0.984. Acquisition of continuous, 0.623-mm thick sections was started at peak inspiration and was performed in the craniocaudal direction. No contrast medium was applied. The HRCT data were reconstructed using a high spatial frequency algorithm (with 1.25 mm interval) and analyzed at a window width of 1300 Hounsfield units (HU) and a window level of −600 HU. Children younger than 5 years underwent HRCT under general anesthesia to obtain high-quality scans free of motion artifacts.

All HRCT images were analyzed using an open-source Osirix software (Pixmeo, Switzerland). The analysis included the quantitative CT indices (CT-QI), which were previously reported as useful in the assessment of ILD: mean lung attenuation, kurtosis, skewness, and fraction of interstitial pulmonary involvement.[23–25] Lung attenuation parameters, that is, mean lung attenuation (the average global attenuation value), kurtosis (representing the peakedness of lung attenuation distribution), and skewness (representing the asymmetry of lung attenuation distribution) were calculated using the method reported by Ariani et al.[23] To assess the severity of lung involvement in patients with PTI, a marker of interstitial changes analogous to previously described in patients with SSc was used.[24] A

fraction of interstitial pulmonary involvement was derived from total and ILD-free lung volumes calculated with predefined CT attenuation thresholds.[24]

### 2.3.2 | Lung ultrasound

LUS was performed at baseline (patients with PTI and controls) and during two follow-up visits (6 and 12 months) in patients with PTI. Each LUS examination was performed by two observers: qualified radiologist (LD) and senior fellow in radiology (EU). Radiologists were informed about the diagnosis but were blinded to the results of HRCT. Both convex and linear probes (3-7 MHz, 5-9 MHz, respectively; Aloka Co, Japan) were used. Sonographic scans were obtained from the anterior and posterior lung areas. Lungs were scanned transversely and longitudinally. Each lung was assessed in four areas: upper posterior (above scapula), lower posterior (below seventh rib), upper anterior (above fourth rib), and lower anterior (below fourth rib). The presence and the number of B-lines in one intercostal space and the regularity of the pleural line were assessed.[26–28] The irregularity of pleural line was defined as the loss of the normal hyperechoic linear pleural contour. The following quantitative ultrasound indices related to B-lines and pleural line were measured: the largest number of B-lines for a particular lung area as well as for all lung areas, the shortest distance between B-lines for a particular lung area (reflecting B-lines density) and the thickness of the pleura.

## 2.4 | Statistical analysis

Data were analyzed using Statistica 12 software package (StatSoft, Inc., Tulsa). The results are presented as medians and interquartile ranges (IQRs). We used the Mann–Whitney *U* test to assess differences between continuous variables and the $\chi^2$ test to assess differences between categorical variables in two different groups. Correlations between HRCT indices of interstitial pulmonary involvement and LUS measurements (ie, number of B-lines, distance between B-lines) were tested using Spearman's rank correlation coefficient. Differences between the number of B-lines, pleural line thickness and the minimal distance between B-lines in subsequent ultrasound studies were tested with the Friedman test. Cochran's Q test was used to assess differences in the presence of B-lines and regularity of pleural line in follow-up LUS examinations. $P < .05$ was considered statistically significant. The Benjamini–Hochberg procedure was applied for multiple testing.

# 3 | RESULTS

## 3.1 | Study group characteristics

Twenty children with PTI (three girls and 17 boys, median age of 19 months [IQR: 8-43]) were enrolled. PTI was diagnosed based on clinical presentation and HRCT images in 17 patients. Lung biopsy was necessary to confirm the diagnosis in three other patients. Baseline characteristics of these patients is presented in Table 1. The same number of children were recruited for the control group. The groups did not differ in age and sex distribution.

## 3.2 | Baseline HRCT findings

By definition, the main HRCT findings in children with PTI were bilateral GGOs, which were demonstrated in all 20 children (100%).

## 3.3 | Baseline LUS findings

B-lines were found in all 20 children (100%) with PTI and in 11 (55%) control subjects ($P < .001$). Three or more B-lines in one intercostal space were found in all PTI children, but only in two (10%) controls ($P < .001$; Table 2). The total number of B-lines in all assessed lung areas, the maximal number of B-lines recorded in any intercostal space and the distance between B-lines (ie, increased B-lines density) differed significantly in children with PTI and controls (Table 2).

An irregularity of the pleural line was found in all children with PTI, whereas pleural line was regular in all healthy children (Figure 1). This was in particular due to the anterior chest wall abnormalities, present in all but one PTI patient. In addition, a significantly higher pleural line thickness was present in children with PTI compared to controls over every assessed area.

**TABLE 1** Demographic data, signs, blood gas analysis, and computed tomography findings in subjects at the inclusion in the study

| | PTI (n = 20) | Controls (n = 20) | PTI vs controls |
|---|---|---|---|
| Demographic data | | | |
| Age (median, IQR), months | 19 (8-43) | 24 (17-50) | NS |
| Sex (female/male); number | 3/17 | 8/12 | NS |
| Abnormal signs, no. (percentage) | | | |
| Underweight | 4 (20) | 0 | NA |
| Growth retardation | 2 (10) | 0 | NA |
| Tachypnea | 13 (65) | 0 | NA |
| Crepitations | 16 (80) | 0 | NA |
| Concomitant disorders, no. (percentage) | | | |
| Gastroesophageal reflux | 10 (50) | 0 | NA |
| Blood gas analysis findings | | | |
| Hypoxemia | 6 (30) | NA | NA |
| Treatment modalities | | | |
| No treatment | 7 (35) | 20 (100) | NA |
| Oxygen therapy | 6 (30) | 0 | NA |
| Bronchodilators | 9 (45) | 0 | NA |
| Inhaled corticosteroids | 8 (40) | 0 | NA |
| Systemic corticosteroids | 1 (5) | 0 | NA |

Abbreviations: IQR, interquartile range; NA, not applicable; NS, not significant; PTI, persistent tachypnea of infancy.

**TABLE 2** Lung ultrasound findings at the inclusion in the study

| | | PTI group (n = 20) | Control group (n = 20) | PTI vs controls |
|---|---|---|---|---|
| Presence of B-lines, no. (percentage) | | | | |
| ≥1 in ≥1 intercostal space | | 20 (100) | 11 (55) | $P < .001^1$ |
| ≥3 in ≥1 intercostal space | | 20 (100) | 2 (10) | $P < .001^1$ |
| B-lines density, mm, median (IQR) | | | | |
| Minimal distance | | 3.5 (3.2-4.1) | 8.4 (7.1-9.1) | $P < .001^2$ |
| Number of B-lines, median (IQR) | | | | |
| **Anterior chest wall** | Right upper area | 4.5 (3-6)[a,b,c,d] | 0 (0-0) | $P < .001^2$ |
| | Left upper area | 5 (3-6)[A,B,C,D] | 0 (0-0) | $P < .001^2$ |
| | Right lower area | 4 (2.5-5.5)[1–3] | 1 (0-2) | $P < .001^2$ |
| | Left lower area | 4 (3-5.5)[I,II,III] | 1 (0-2) | $P < .001^2$ |
| **Posterior chest wall** | Right upper area | 2 (0-3)[a,A,1,I] | 0 (0-0) | $P = .002^2$ |
| | Left upper area | 1 (0-2.5)[b,B,2,II] | 0 (0-0) | $P = .006^2$ |
| | Right lower area | 2 (1.5-3)[c,C,3,III] | 0 (0-0.5) | $P < .001^2$ |
| | Left lower area | 3 (2-4)[d,D] | 0 (0-0.5) | $P < .001^2$ |
| Maximal number | | 5 (4-6.5) | 1 (0-2) | $P < .001^2$ |
| Pleural line thickness, mm, median (IQR) | | | | |
| **Anterior chest wall** | Right upper area | 0.9 (0.9-1)[*,**] | 0.6 (0.5-0.6) | $P < .001^2$ |
| | Left upper area | 0.9 (0.8-1) | 0.5 (0.5-0.6) | $P < .001^2$ |
| | Right lower area | 1 (0.9-1)[#,##] | 0.6 (0.6-0.7) | $P < .001^2$ |
| | Left lower area | 0.9 (0.8-1) | 0.6 (0.5-0.6) | $P < .001^2$ |
| **Posterior chest wall** | Right upper area | 0.8 (0.8-0.9) | 0.6 (0.5-0.7) | $P < .001^2$ |
| | Left upper area | 0.8 (0.8-0.9)[*,#] | 0.6 (0.5-0.6) | $P < .001^2$ |
| | Right lower area | 0.9 (0.8-1) | 0.6 (0.5-0.7) | $P < .001^2$ |
| | Left lower area | 0.8 (0.7-0.9)[*,##] | 0.6 (0.5-0.7) | $P < .001^2$ |

*Note:* [a,b,c,d,A,B,C,D, 1,2,3, I,II,III, *,**,#,##] = significant differences in Friedman test with post-hoc analysis.

Abbreviations: IQR, interquartile range; PTI, persistent tachypnea of infancy.

[1]*P*-value in $\chi^2$ test (PTI vs control group).

[2]*P*-value in the Mann–Whitney *U* test.

## 3.4 | LUS follow-up findings

Twenty (100%) and 17 (85%) patients with PTI underwent LUS follow-up after 6 months and 12 months, respectively. After 6 months, the presence of ≥3 B-lines in ≥1 intercostal space was demonstrated in 19 out of 20 (95%) children. Similarly, LUS examination performed after 12 months showed the presence of ≥3 B-lines in 16 out of 17 cases (94%). There was only one child in whom the lower number of B-lines was found both after 6 and 12 months. The comparison of LUS results at three different time points is presented in Table 3. In fact, there was no significant change in LUS findings in children with PTI during the study period.

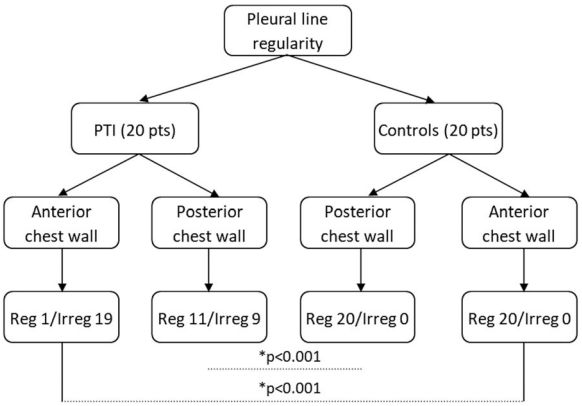


**FIGURE 1** Lung ultrasound (LUS) findings at the inclusion in the study—pleural line regularity

## 3.5 | Correlations of LUS and CT findings

There were 13 patients in whom HRCT and LUS were performed within an interval of 5 days. In these patients, the mean lung attenuation, skewness, and fraction of interstitial pulmonary involvement correlated significantly with the number of B-lines over every assessed area. Kurtosis correlated significantly with the number of B-lines in all but one of the affected areas. There was also a significant correlation between the mean lung attenuation, kurtosis, skewness as well as fraction of interstitial pulmonary involvement and the maximal number of B-lines recorded in one intercostal space. We did not find significant correlations between the minimal distance between B-lines and CT-quantitative indices, except for mean lung attenuation (Table 4). The relationships between CT-quantitative indices and maximal number of B-lines recorded in one intercostal space are presented in Figure 2. Furthermore, significant correlations between CT-quantitative indices and pleural line thickness measured over several areas, especially over the posterior lung area was noted.

In addition, we compared HRCT and LUS findings performed in all 20 children with PTI even if the interval between both imaging examinations was ≥5 days, with the longest period of time 12 months. The same results as those presented for the patients

**TABLE 3** Comparison of LUS results at inclusion in the study and after 6 and 12 months of follow-up

| | Inclusion (n = 20) | 6 mo (n = 20) | 12 mo (n = 17) | Unadjusted *P*-value | Adjusted *P*-value |
|---|---|---|---|---|---|
| Presence of B-lines, no. (%) | | | | | |
| ≥1 in ≥1 ICS | 20 (100) | 19 (95) | 16 (94) | 0.368* | 0.552** |
| ≥3 in ≥1 ICS | 20 (100) | 19 (95) | 16 (94) | 0.368* | 0.552** |
| Pleural line regularity, no. (%) | | | | | |
| Anterior chest wall | | | | | |
| Irregular line | 19 (95) | 20 (100) | 16 (94) | 0.607* | 0.708** |
| Posterior chest wall | | | | | |
| Irregular line | 9 (45) | 4 (20) | 5 (25) | 0.074* | 0.173** |
| Distance between B-lines, mm | | | | | |
| Minimal distance | 3.5 (3.2-4.1) | 3.7 (3.5-3.8) | 3.5 (3-4.2) | 0.168*** | 0.294**** |
| Number of B-lines | | | | | |
| Anterior chest wall | | | | | |
| URL | 4.5 (4-6) | 3 (2-5) | 4 (3-5) | 0.014*** | 0.172**** |
| ULL | 5 (3-6) | 4 (3-5) | 4 (3-5) | 0.071*** | 0.186**** |
| LRL | 4 (2-5) | 3.5 (2-4) | 3 (3-4) | 0.066*** | 0.198**** |
| LLL | 4 (3-5) | 4 (3-4) | 4 (3-5) | 0.510*** | 0.669**** |
| Posterior chest wall | | | | | |
| URL | 2 (0-3) | 1 (0-2) | 1 (0-2) | 0.828*** | 0.915**** |
| ULL | 1 (0-2.5) | 0.5 (0-2) | 0 (0-1) | 0.531*** | 0.656**** |
| LRL | 2 (1.5-3) | 3 (1-3.5) | 2 (0-2) | 0.103*** | 0.216**** |
| LLL | 3 (2-4) | 2 (1-3) | 2 (0-2) | 0.003*** | 0.063**** |
| Pleural line thickness, mm | | | | | |
| Anterior chest wall | | | | | |
| URL | 0.9 (0.9-1) | 0.8 (0.8-1) | 0.9 (0.8-0.9) | 0.006*** | 0.063**** |
| ULL | 0.9 (0.8-1) | 0.9 (0.8-1) | 0.8 (0.7-0.9) | 0.378*** | 0.529**** |
| LRL | 1 (0.9-1) | 0.9 (0.8-1) | 0.9 (0.8-0.9) | 0.019*** | 0.080**** |
| LLL | 0.9 (0.8-1) | 0.9 (0.8-1) | 0.8 (0.8-0.9) | 0.116*** | 0.221**** |
| Posterior chest wall | | | | | |
| URL | 0.8 (0.8-0.9) | 0.8 (0.7-0.8) | 0.8 (0.6-0.8) | 0.010*** | 0.070**** |
| ULL | 0.8 (0.8-0.9) | 0.8 (0.7-0.8) | 0.8 (0.6-0.8) | 0.194*** | 0.313**** |
| LRL | 0.9 (0.8-1) | 0.8 (0.8-0.9) | 0.8 (0.6-0.8) | 0.014*** | 0.074**** |
| LLL | 0.8 (0.7-0.9) | 0.8 (0.7-0.9) | 0.8 (0.6-0.8) | 0.049*** | 0.172**** |

*Note:* Data are presented as medians (IQR) if not otherwise specified.

Abbreviations: ICS, intercostal space; URL, upper area of right lung; ULL, upper area of left lung; LRL, lower area of right lung; LLL, lower area of left lung; LUS, lung ultrasound.

*unadjusted *P*-value in Cochran's Q test, comparison between measurements at three different time points.

***P*-value adjusted with the use of the Benjamini–Hochberg procedure.

****unadjusted *P*-value in Friedman test, comparison between measurements at three different time points.

*****P*-value adjusted with the use of the Benjamini–Hochberg procedure.

with the ≤5 days interval between HRCT and LUS were found (data not shown).

### 3.6 | Relationship between tachypnea and HRCT as well as LUS findings

Comparison of LUS and CT findings in patients with tachypnea and children with normal respiratory rate is presented in Table 5. No significant differences in the number of B-lines between PTI patients with and without tachypnea was found. However, significantly higher median of the mean lung attenuation and fraction of interstitial pulmonary involvement were demonstrated in tachypneic PTI children. We also observed significantly lower kurtosis and skewness in children with tachypnea compared to those with normal respiratory rate. Those differences were significant both, when LUS and CT were performed with an interval of ≤5 days (Table 5) as well as when the results of all children were included (data not shown). These data demonstrate a stability of LUS findings, independent of current clinical findings in a chronic disease course.

## 4 | DISCUSSION

As ILDs in children are a diagnostic challenge, the introduction of a new noninvasive, nonionizing radiation, and easily repetitive imaging method seems to be an unmet need. Here, we evaluated the usefulness of LUS as a diagnostic tool in a relatively large, single center, well defined, single disease cohort of children with ILD. We selected PTI as a rare, but nevertheless the most frequent chILD in infancy and childhood. Different LUS signs evaluated at baseline as well as during 1-year follow up period and computer-derived

**TABLE 4** Correlations between computed tomography quantitative indices and quantitative LUS parameters

| | | Mean lung attenuation | | | Kurtosis | | | Skewness | | | Fraction of interstitial lung involvement | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | R | *P* | $P^{adj}$ | R | *P* | $P^{adj}$ | R | *P* | $P^{adj}$ | R | *P* | $P^{adj}$ |
| **Minimal distance between B-lines, mm** | | −0.62 | .025 | .034 | 0.54 | .054 | .088 | 0.44 | .124 | .148 | −0.5 | .079 | .102 |
| **Number of B-lines** | | | | | | | | | | | | | |
| Maximal number | | 0.81 | .001 | .003 | −0.66 | .014 | .030 | −0.75 | .003 | .008 | 0.8 | .001 | .003 |
| Anterior chest wall | URL | 0.85 | <.001 | .002 | −0.78 | .002 | .006 | −0.85 | <.001 | .005 | 0.83 | <.001 | .003 |
| | ULL | 0.76 | .003 | .006 | −0.68 | .010 | .026 | −0.77 | .002 | .006 | 0.74 | .004 | .009 |
| | LRL | 0.82 | .001 | .004 | −0.69 | .009 | .027 | −0.66 | .014 | .021 | 0.79 | .001 | .004 |
| | LLL | 0.79 | .001 | .003 | −0.59 | .033 | .059 | −0.67 | .011 | .019 | 0.8 | .001 | .003 |
| Posterior chest wall | URL | 0.71 | .006 | .013 | −0.81 | .001 | .004 | −0.80 | .001 | .004 | 0.64 | .019 | .032 |
| | ULL | 0.81 | .001 | .003 | −0.81 | .001 | .005 | −0.71 | .006 | .012 | 0.84 | <.001 | .003 |
| | LRL | 0.89 | <.001 | .001 | −0.83 | <.001 | .004 | −0.83 | <.001 | .003 | 0.86 | .001 | .004 |
| | LLL | 0.8 | .001 | .003 | −0.89 | <.001 | .001 | −0.82 | .001 | .003 | 0.81 | .001 | .003 |
| **Pleural line thickness, mm** | | | | | | | | | | | | | |
| Anterior chest wall | URL | 0.41 | .155 | .164 | −0.23 | .454 | .545 | −0.54 | .055 | .076 | 0.34 | .245 | .276 |
| | ULL | 0.57 | .039 | .051 | −0.41 | .159 | .220 | −0.69 | .009 | .016 | 0.49 | .088 | .106 |
| | LRL | 0.62 | .023 | .034 | −0.23 | .456 | .513 | −0.39 | .180 | .202 | 0.52 | .067 | .093 |
| | LLL | 0.44 | .137 | .154 | −0.16 | .605 | .605 | −0.36 | .224 | .237 | 0.33 | .273 | .290 |
| Posterior chest wall | URL | 0.69 | .009 | .015 | −0.49 | .089 | .134 | −0.75 | .003 | .009 | 0.65 | .017 | .033 |
| | ULL | 0.56 | .044 | .053 | −0.29 | .327 | .421 | −0.54 | .059 | .076 | 0.56 | .046 | .068 |
| | LRL | 0.67 | .012 | .020 | −0.66 | .014 | .028 | −0.84 | <.001 | .003 | 0.64 | .018 | .032 |
| | LLL | 0.19 | .535 | .535 | −0.19 | .516 | .547 | 0 | .993 | .993 | 0.2 | .504 | .504 |

*Note:* NS, not significant; $P^{adj}$: *P*-value adjusted with the use of the Benjamini–Hochberg procedure; R: Spearman's rank correlation coefficient.
Abbreviations: LLL, lower area of left lung; LRL, lower area of right lung; LUS, lung ultrasound; ULL, upper area of left lung; URL, upper area of right lung.

quantitative HRCT indices were used to compare the images and their diagnostic yield.

The principal finding of our study is that LUS could serve as highly sensitive but nonspecific adjunctive imaging modality in children with PTI. We found that B-lines number, B-lines density, as well as pleural thickness were significantly augmented in children with PTI compared to controls. These LUS findings correlated with HRCT quantitative indices (ie, mean lung attenuation, kurtosis, skewness, fraction of interstitial pulmonary involvement).

The main LUS finding in children with PTI were B-lines. B-lines are the most common LUS abnormalities in pulmonary diseases, but this sign is highly nonspecific. Increased number of B-lines has been reported i.a. in pulmonary edema, respiratory tract infections (pneumonia, bronchiolitis), lung injury, and atelectasis.[9–12] Sparse B-lines could be found in healthy subjects,[29] and this was also shown in the present study. The second most common finding, that is, pleural line thickening and irregularity, have been reported in different lung and pleural diseases like pleuritis, pleural tumors, pleural adhesions, pneumoconiosis, and fibrothorax.[30,31] As B-lines and pleural line abnormalities are nonspecific findings, LUS could not replace HRCT in initial PTI diagnostic work-up. However, the results of LUS performed initially in addition to HRCT, could serve as a reference point for further disease monitoring. Although we did not find significant differences in LUS indices between the baseline and follow-up examinations we suppose that the duration of follow-up could have been too short to reveal a resolution of changes. In the recently published papers, clinical and radiological improvement in PTI children was observed after 13 to 39 months,[32,33] thus, longer observation may be required to demonstrate the resolution of LUS abnormalities. The only child in whom lower number of B-lines was

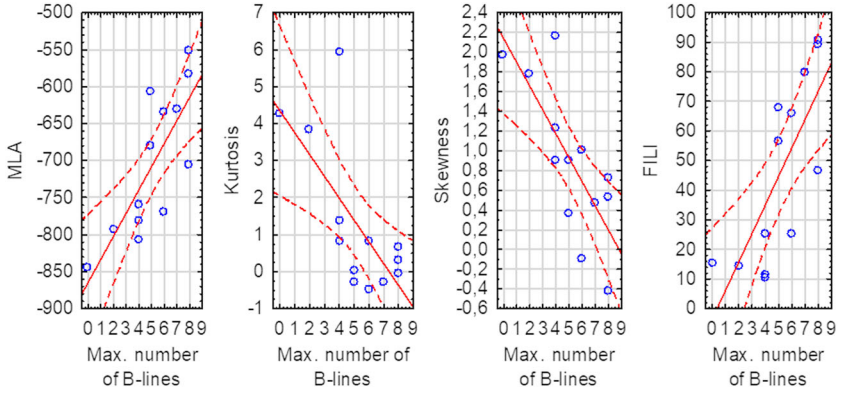


**FIGURE 2** Relationships between computed tomography-derived quantitative indices and maximal number of B-lines recorded in one intercostal space in LUS. LUS, lung ultrasound [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 5** LUS and computed tomography-derived quantitative parameters in PTI children with tachypnea vs non tachypnea

| **Lung ultrasound—number of B-lines (20 children with PTI)** | | | | | |
|---|---|---|---|---|---|
| | | **Tachypnea (n) = 13** | **No tachypnea (n) = 7** | ***P*** | $P^{adj}$ |
| Anterior chest wall | URL | 5 (4-6) | 4 (3-4) | .157 | .252 |
| | ULL | 5 (4-6) | 3 (3-6) | .115 | .229 |
| | LRL | 5 (4-6) | 3 (1-4) | .081 | .216 |
| | LLL | 4 (3-6) | 3 (2-4) | .183 | .244 |
| Posterior chest wall | URL | 2 (2-4) | 0 (0-0) | .011 | .089 |
| | ULL | 2 (0-3) | 0 (0-0) | .030 | .119 |
| | LRL | 3 (2-4) | 2 (1-2) | .115 | .229 |
| | LLL | 3 (2-4) | 2 (2-3) | .183 | .244 |
| **Computed tomography-derived quantitative indices (13 PTI patients with CT performed ≤5 d from study inclusion)** | | | | | |
| | | **Tachypnea, n = 9** | **No tachypnea, n = 4** | ***P*** | $P^{adj}$ |
| Mean lung attenuation, HU | | −634 (−706 to −607) | −800 (−826 to −780) | .006 | .022 |
| Kurtosis | | 0.04 (−0.28 to 0.67) | 4.05 (2.33-5.09) | .011 | .022 |
| Skewness | | 0.53 (0.37 – 0.9) | 1.87 (1.39-2.07) | .006 | .022 |
| Fraction of interstitial lung involvement, % | | 65.8 (46.7-79.9) | 14.9 (13.1-20.4) | .050 | .067 |

*Note:* Data are presented as medians (IQR). $P^{adj}$, *P*-value adjusted with the use of the Benjamini–Hochberg procedure.
Abbreviations: CT, computed tomography; HU, Hounsfield unit; LLL, lower area of left lung; LRL, lower area of right lung; LUS, lung ultrasound; PTI, persistent tachypnea of infancy; ULL, upper area of left lung; URL, upper area of right lung.

found in follow-up LUS examination presented with mild initial symptoms and significant clinical improvement was observed over time.

There is a growing body of evidence supporting LUS as a diagnostic method in different lung diseases.[9–20] Unfortunately, there have been no studies on the usefulness of LUS in PTI and other chILD. As NEHI, which is the most common form of PTI, is characterized by neuroendocrine cells accumulation in the distal airways, it is commonly associated with small airway obstruction and air-trapping. Hence, LUS in NEHI can also be compared with ultrasound images in bronchiolitis. In this context, the results of the current study are concordant with previously published papers that reported an increased number of B-lines in 65.4% to 72% of children with bronchiolitis.[12,34] Moreover, the relationship between the number of B-lines and severity of the disease was demonstrated by Basile et al.[35] Contrary to our observation on the relative durability of this sign, a significant regression of the number of B lines within 12 days was reported in children with bronchiolitis.[34] This can be explained by different etiology and clinical course of this two entities.

The role of LUS and B-lines was also studied in adults with different ILD. A very high sensitivity (100%) and negative predictive value (100%) of the increased number of B-lines was reported in patients with SSc. The authors suggested that LUS is very sensitive diagnostic tool even in patients with early stage SSc.[14] In rheumatoid arthritis-associated lung disease, LUS was also proved to be a reliable diagnostic method.[15] Moazedi-Fuerst et al[15] found B-lines and pleural abnormalities in 28% nonsymptomatic patients with rheumatoid arthritis. In 89% of them ILD was confirmed by HRCT. Likewise, Hasan et al[17] observed the presence of diffuse B-lines in a group of 61 adult patients with different ILD (i.a. hypersensitivity pneumonitis and sarcoidosis).

Another hallmarks of PTI found in our study were pleural line irregularity and increased pleural thickness. Albeit the difference between pleural thickness in PTI patients and control group was statistically significant ($P < .001$) in all assessed lung areas, it was smaller than one half of the millimeter (0.2-0.4 mm). Thus, from the clinical standpoint, the difference can be probably construed as negligible. Pleural line irregularity was present in all patients with PTI and in none of the healthy children. Pleural line abnormalities were also present in children with bronchiolitis[34] and pleural line irregularity was proved as useful sign for evaluation of ILD related to SSc and antisynthetase syndrome.[28] Similarly, increased pleural thickness was demonstrated in patients with connective tissue disease-associated ILD and in patients with pulmonary fibrosis.[18,19]

The important aim point of our study was comparison of the results of LUS, HRCT, and clinical findings in ILD. There are only sparse data, especially in pediatric population, on this topic. In our study, the highest number of B-lines was seen over the anterior chest wall. It is consistent with the predilection sites of GGO in children with PTI. Significant correlations between the results of LUS and HRCT-derived quantitative indices revealed in our study can be compared in some ways to the findings of Martelius et al.[36] The authors analyzed the results of LUS in 60 children referred for chest HRCT (regardless of the diagnosis). They found that the number of B-lines seen on LUS increased consistently with the growing extent of parenchymal changes on CT.[36] Increased number of B-lines was also shown to be a sensitive marker of ILD and to correlate significantly with HRCT scores in rheumatoid arthritis and patients with SSc.[37,38] In addition, the distance between each of two adjacent B-lines was shown to correlate with the extent of the ILD on chest HRCT assessed by semiquantitative Warrick score, as well as with the results of pulmonary function tests.[17]

We are aware of some limitations of our study. First, since LUS was performed by person who was not blinded to the diagnosis of PTI, it could lead to a bias in LUS interpretation. Second, although each LUS was performed by two radiologists, they were not the independent observers but collaborated closely during both LUS examinations and image analyses. Thus, only one result of each measurement reached as a consensus between the two radiologists was included in the final analysis. In consequence, we could not assess an interobserver agreement pertaining to the LUS measurements. Third, as PTI is a very rare disease, we were able to include only 20 patients and this could be associated with suboptimal power of statistical analysis. Moreover, the resolution of pulmonary alterations in PTI is slow, 12-months follow-up could have been too short to reliably assess the potential of LUS as a monitoring tool. Fourth, we realize that the specificity of LUS findings needs to be established. This requires further studies which include not only children with PTI but also with other diseases, i.a. bronchiolitis and bronchiolitis obliterans.

To conclude, the increased number of B-lines and enhanced pleural thickness were found in children with PTI. Both of these LUS signs correlated significantly with HRCT findings. Thus, LUS seems to be a useful diagnostic tool in children with PTI. Its inclusion in the diagnostic work-up may enable to reduce the number of costly, hazardous, and ionizing radiation-based imaging procedures.

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**How to cite this article:** Urbankowska E, Urbankowski T, Drobczyński Ł, et al. Lung ultrasound—a new diagnostic modality in persistent tachypnea of infancy. *Pediatric Pulmonology*. 2020;1–9. https://doi.org/10.1002/ppul.24654