Primerjava občutljivosti ultrazvoka in rentgenskega slikanja pljuč za diagnosticiranje zunajbolnišnične pljučnice pri otrocih

Comparison of sensitivity of lung ultrasound and chest x-ray imaging for the diagnosis of community-acquired pneumonia in children

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Izvleček

Namen: *Ultrazvok pljuč se šele v zadnjem času uveljavlja kot primerna metoda za diagnosticiranje zunajbolnišnične pljučnice (ZBP) pri otrocih. Ker pa uporabnost ultrazvoka pri različnih vrstah pljučnice še ni dobro raziskana, smo v naši študiji primerjali občutljivost ultrazvoka in rentgenskega slikanja pljuč za diagnosticiranje etiološko različnih vrst ZBP pri otrocih.*

Metode: *Izvedli smo prospektivno študijo, v katero smo vključili 166 otrok, ki so bili hospitalizirani zaradi ZBP. Bolnike smo glede na izvide laboratorijskih in mikrobioloških preiskav razdelili v skupine z bakterijsko (n=80), atipično bakterijsko (n=32) in virusno (n=54) pljučnico. Pri vseh bolnikih smo ob sprejemu opravili ultrazvok pljuč in rentgensko slikanje prsnega koša.*

Rezultati: *Z ultrazvokom pljuč smo prikazali pljučnico pri 161 (97.0%) bolnikih, z rentgenskim slikanjem prsnega koša pa pri 137 (82.5%) bolnikih, (<0.01). Izračunana senzitivnost ultrazvoka je 97.0% (95% CI, 93.1%*

Abstract

Purpose*: Lung ultrasound (LUS) has only recently been considered to be a suitable tool for diagnosing community acquired pneumonia (CAP) in children. Little is known about the usefulness of LUS in different types of pneumonia. Therefore, we analyzed and compared the sensitivity of chest X-ray (CXR) and LUS in different etiological types of CAP in children.*

Methods: *We performed a prospective study in 166 children with CAP, who were admitted to the hospital. The participants were stratified into bacterial (n=80), atypical bacterial (n=32) and viral (n=54) pneumonia subgroups, according to the laboratory and microbiological results. LUS and CXR were performed on all patients at admission.*

Results: *Pneumonia was detected with LUS in 161 (97.0%) participants and with CXR in 137 (82.5%) participants (p<0.01). The sensitivity of LUS was calculated as 97.0% (95% CI, 93.1%–99.0%), and the sensitivity of CXR as 82.5% (95% CI, 75.9%–88.0%), p<0.01. In patients with bac-*

- 99.0%), senzitivnost rentgenograma pljuč pa 82.5% (95% CI, 75.9% - 88.0%), p<0.01. Pri podskupini otrok z bakterijsko pljučnico je bila le-ta z ultrazvokom vidna pri 79 (98.7%) na rentgenogramu pa pri 67 (83.8%) bolnikih (p<0.01). Pri podskupini z atipično bakterijsko pljučnico je bila le-ta vidna z ultrazvokom pri 30 (93.8%), na rentgenogramu pa pri 28 (87.5%) bolnikih (p=0.69). Pri bolnikih z virusno pljučnico je bila le-ta na ultrazvoku vidna pri 52 (96.3%), na rentgenogramu pa pri 42 (77.8%) bolnikih (p<0.01).

Zaključek: *Rezultati naše raziskave potrjujejo, da je ultrazvok pljuč odlična metoda za diagnosticiranje ZBP pri otrocih. Ultrazvok je v primerjavi z rentgenskim slikanjem pljuč vsaj enako občutljiv pri vseh vrstah pljučnice in bo v prihodnosti verjetno postal metoda izbora pri otrocih z ZBP.*

terial CAP, infiltrates were detected with LUS in 79 (98.7%) and with CXR in 67 (83.8%) of cases (p<0.01); in atypical bacterial CAP, with LUS in 30 (93.8%) and with CXR in 28 (87.5%) (p=0.69); and in patients with viral CAP with LUS in 52 (96.3%) and with CXR in 42 (77.8%) (p<0.01).

Conclusion: *We have determined that LUS is an excellent tool for diagnosing CAP in children. LUS is at least as sensitive as CXR in all types of CAP in children and will probably replace it as the investigation of choice in CAP.*

INTRODUCTION

Community-acquired pneumonia (CAP) is the most common cause of death in preschool children in developing countries (1). More than 150 million episodes of childhood pneumonia occur each year in the developing world and more than 2 million of these individuals will die every year. The incidence of clinical pneumonia in children aged less than 5 years in developing countries worldwide is close to 0.29 episodes per child-year (1). The annual incidence of CAP in preschool children in developed countries is around 0.05 episodes per child-year; half of these children need hospitalization and mortality is less than 0.1% (2).

In preschool children, CAP is mostly caused by viruses, followed by bacteria, especially Streptococcus pneumoniae. The atypical bacteria Mycoplasma pneumoniae and Chlamydophila pneumoniae are common causes of CAP in older children and adolescents (3).

There is no pathognomonic symptom or sign of pneumonia. Clinical lung examination in children with bacterial pneumonia is often normal. In viral and atypical pneumonia, crackles and/or wheezes are usually heard on lung auscultation (4). Laboratory results have only a limited role in determination of the etiology of CAP in children. Leukocytosis and increased C-reactive protein (CRP) are characteristic of bacterial CAP; however, the laboratory results in different forms of CAP overlap significantly, and pneumonia caused by adenoviruses or other respiratory viruses can also be associated with increased acute phase reactants (3).

The lower airways are not easy accessible in order to obtain a representative sample for microbiological analysis. Therefore, the diagnosis of CAP in children has long been based on the chest x-ray (CXR). The characteristics of pneumonic infiltrates seen on CXR have, however, a limited role in determining the etiology of CAP. Unilateral alveolar infiltrates in the form of lobar, segmental or round consolidation are to some extent associated with bacterial pneumonia. On the other hand, bilateral interstitial infiltrates are characteristic of viral pneumonia. (5).

CXR is not widely available in the primary care outpatient setting and is associated with a small, but not completely insignificant, radiation dose. The sensitivity of CXR for detecting pneumonia is estimated to be less than 50% when compared with computed tomography (CT) in adult patients (6). The visibility of structures behind the heart shadow is limited with the standard anteroposterior (AP) view. CXR sometimes falls behind the clinical picture and there is a large

interobserver variability in the interpretation. Therefore, CXR cannot be considered a gold standard for establishing the diagnosis of CAP (7, 8).

Lung ultrasound (LUS) has long been considered an inappropriate method for detecting pneumonia, although ultrasound is a widely available, safe, repeatable and bedside imaging method. Ultrasound is superior to CXR in the detection of pleural effusion. In the last few years, several studies have shown LUS to be at least equal to CXR with regard to the sensitivity of detection of CAP. A major limitation of LUS is the lack of standardization and the subjective interpretation of findings (9, 10).

The aim of our study was to compare the sensitivity of LUS and CXR in the detection of pneumonic infiltrates in three main etiological types of CAP in children: bacterial, atypical bacterial and viral. In addition, we compared the ultrasound characteristics of different etiological subtypes of CAP.

We hypothesized that the sensitivity of LUS for detection of CAP in children is at least equal to that of CXR in all types of CAP. In addition, we hypothesized that bilateral infiltrates are more commonly detected with LUS in viral pneumonia when compared with other etiologies.

MATERIALS AND METHODS

We performed a prospective study and included 166 children with CAP, hospitalized in our clinic from October 1, 2014 to September 30, 2017. The age of the participants ranged from 1 month to 18 years. We included all children who were hospitalized in the study period for CAP, detected with CXR and/or LUS. All the studied children were previously healthy and were not born prematurely. We excluded patients with immune deficiency, neurological impairment, developmental delay, chronic lung disease (except asthma) or heart disease, or any other chronic condition which can predispose to pneumonia. We did not exclude patients who had already been treated with antibiotics before admission. Some patients were excluded only after the completion of treatment, when alternative diagnoses were established, therefore we included in the analysis only children with a diagnosis of CAP at discharge from the hospital. In addition, we excluded patients with severe CAP, who required management in the pediatric intensive care unit. The study participants were treated in the same manner as all other children hospitalized because of CAP, with the exception of LUS, which was performed in addition. The study was approved by the Ethics Committee of our institution. All participants or their guardians (for children younger than 16 years) signed an informed consent form according to the World Medical Association Declaration of Helsinki, revised in 2000, Edinburgh.

Venous blood was collected from all participants for the analysis of complete and differential blood count and CRP. Blood culture was performed in patients with suspected bacterial pneumonia. In patients with suspected viral or atypical bacterial pneumonia, we collected nasopharyngeal swabs for the detection of the most common respiratory viruses and three atypical bacteria with a polymerase chain reaction (PCR)-based assay. We tested for the presence of respiratory syncytial virus (RSV), human rhinovirus, human bocavirus (HBoV), influenza A, influenza B, parainfluenza viruses (serotypes 1, 2, 3 and 4), adenovirus, human metapneumovirus (HMPV), enterovirus, coronavirus, Mycoplasma pneumoniae, Bordetella pertussis and Chlamydophila pneumoniae. In a few patients we detected Mycoplasma pneumoniae with PCR from a throat swab. Sputum was collected for bacterial culture in participants older than 5 years with presumed bacterial CAP. All microbiological assays were performed by the National Laboratory of Health, Environment and Food, Maribor, Slovenia.

The participants were stratified into the three groups, based mainly on the microbiological and laboratory results. Patients with detected Mycpolasma pneumoniae or Chlamydophila pneumoniae infection were stratified into the atypical CAP group. Patients with detected viral infection were stratified into the viral CAP group only after the exclusion of bacterial superinfection. Bacterial CAP was considered in patients with large areas of consolidation (>2 cm in diameter) on CXR and/or LUS and leukocytosis (>15,000/mm3), even when viruses were detected in the nasopharyngeal swab. Bacterial CAP was also considered in all patients with a positive blood culture.

The CXR and LUS were performed within 24 hours of admission. A standard anteroposterior (AP) view was used for the CXR. The image was evaluated by a pediatric radiologist. LUS was performed with a Sonosite portable ultrasound machine (SonoSite, Inc. Bothell, Washington, USA) by a pediatric pulmonologist, who was unaware of the results of the CXR, although in few cases CXR was performed before the LUS. A linear probe (13–6 MHz) was used for preschool children. In older children, we also used a curved probe (8–5 MHz). Infants and toddlers were examined in the upright position in the arms of one of their parents, and older patients were seated. LUS was performed according to the technique described by Copetti and Cattarossi (11). Only B-mode was used, and Doppler ultrasound was performed for the evaluation of blood perfusion of the affected lung tissue. Cine loops were obtained and later discussed with another pediatric pulmonologist. Pleural effusion and an increased number of B lines (≥3 per intercostal space) were also recorded. However, only the presence of consolidation (confirmed by another pediatric pulmonologist) was considered a diagnostic criterion for pneumonia in our study. Consolidation was defined as the presence of a hypoechoic or isoechoic (echogenicity similar to liver) area with dynamic air bronchograms and/or the shred sign, in order to distinguish between consolidation and lung collapse (12, 13). We defined the presence of bilateral infiltrates as consolidations which were detected in both lungs simultaneously. LUS was repeated after 48–72 hours in 151 (91.0%) patients, who were still hospitalized at that time. Regression/progression of consolidations in size and number was evaluated. Regarding the regression of consolidations, the participants were stratified at the discretion of the physician who performed LUS into four groups: progression, no regression, regression, complete regression.

Statistical analysis was performed with SPSS 20.0 software (SPSS, Chicago, IL, USA). We compared the clinical characteristics of patients with different types of CAP using the chi-square test (categorical variables) and Analysis of variance (ANOVA) for quantitative variables. The sensitivity of CXR and LUS for the detection of pneumonia and bilateral pneumonic infiltrates was compared with the McNemar test. The association of the type of CAP with the presence of bilateral infiltrates was also analyzed with the chi-square test. Regression (or progression) of infiltrates in association with different types of CAP was analyzed with multinomial logistic regression, adjusting for age and sex. A value of $p<0.05$ was considered statistically significant.

RESULTS

Clinical and demographic characteristics

We included 77 (46.4%) females and 89 (53.6%) males. Their mean age was 4.4 years, with a standard deviation (SD) of 3.7. Pneumonia was caused by atypical bacteria, viruses and bacteria in 32 (19.3%), 54 (32.5%) and 80 (48.2%) patients, respectively.

The demographic, clinical and laboratory characteristics of participants according to the etiology of CAP are presented in Table 1.

Comparison of chest x-ray and lung ultrasound for the detection of pneumonia

Pneumonic infiltrates were detected with CXR in 137 (out of 166) patients and with LUS in 161, as presented in Figure 1. The sensitivity of CXR was calculated as 82.5% (95% CI, 75.9%–88.0%) and the sensitivity of LUS as 97.0% (95% CI, 93.1%–99.0%), $p<0.01$.

When we stratified the participants according to etiology, we detected the infiltrates in patients with bacterial CAP with LUS in 79 (98.7%) participants and with CXR in 67 (83.8%) ($p<0.01$). In atypical bacterial CAP, infiltrates were detected with LUS in 30 (93.8%) and with CXR in 28 (87.5%) ($p=0.69$). In patients with a viral etiology of CAP, infiltrates were detected with LUS in 52 (96.3%) and with CXR in 42 (77.8%) ($p<0.01$).

Among the 39 patients who had bilateral infiltrates detected with at least one imaging method (CXR and/or LUS), the bilateral pneumonic infiltrates were present on LUS in 36 (92.3%) and on CXR in 14 (35.9%) ($p<0.01$). Bilateral pneumonic infiltrates were detected with LUS in 3.8% (n=3), 31.2% (n=10) and 42.6% (n=23) of all patients with bacterial, atypical bacterial and viral pneumonia, respectively ($p<0.01$), as presented in Figure 2.

Table 1: *Demographic, clinical and laboratory characteristics of participants according to the etiology of pneumonia*

Characteristic [n (%)] [1]	Bacterial pneumonia	Atypical bacterial pneumonia	Viral pneumonia	p
Fever[2]	79 (98.8)	26 (81.3)	41 (75.9)	<0.01
URTI[3]	23 (28.8)	20 (62.5)	40 (74.1)	< 0.01
Chest/abdominal pain	41 (51.2)	6 (18.8)	4 (7.4)	< 0.01
Crackles on auscultation	16 (20.0)	27 (84.4)	40 (74.1)	< 0.01
Wheezes on auscultation	4 (5.0)	9 (28.1)	26 (48.1)	< 0.01
Respiratory distress	12 (15.0)	10 (31.2)	32 (59.3)	< 0.01
Diminished breath sounds	22 (27.5)	7 (21.9)	10 (18.5)	0.47
Signs of lung consolidation[4]	17 (21.3)	5 (15.6)	0	< 0.01
Additional oxygen[5]	5 (6.3)	7 (21.9)	21(38.9)	< 0.01
Characteristic (mean ± SD[6])				
Age (years)	3.5 ± 3.0	7.9 ± 3.9	3.4 ± 3.3	< 0.01
WBC7 (×10^9/l)	26.6 ± 18.8	12.7 ± 6,2	15.5 ± 7.0	< 0.01
CRP[8] (mg/dl)	169.1 ± 78.9	47.7 ± 45.0	73.9 ± 67.1	< 0.01

[1] Number of subjects with a particular characteristic (relative proportion in parentheses). [2] Fever was defined as tympanic temperature above 38.0° C anytime during the hospitalization. [3] Presence of signs and/or symptoms of upper respiratory tract infection. [4] Bronchial breathing and/or bronchophony on auscultation. [5] Need of additional oxygen anytime during the hospital stay. [6] Standard deviation. [7] White blood cells. [8] C-reactive protein value in blood.

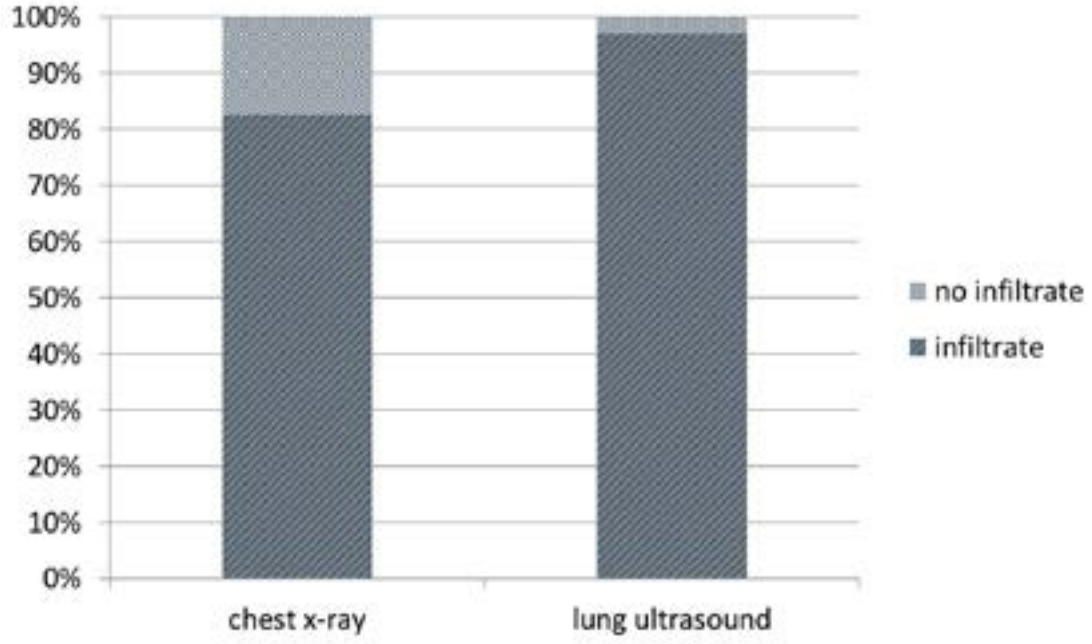

Figure 1. *Comparison of sensitivity between lung ultrasound and chest x-ray for the detection of pneumonia.*

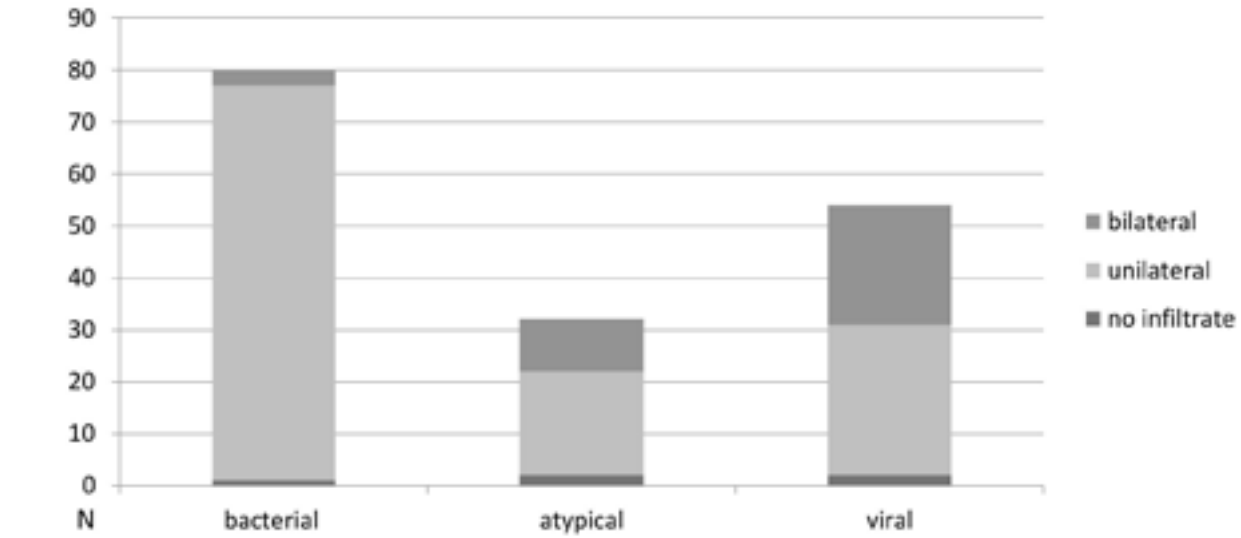

Figure 2. *Location of infiltrates, detected with lung ultrasound in different types of pneumonia (N: number of cases presented on y-axis).*

Follow-up LUS was performed in 151 (91.0%) participants. Progression of pneumonic infiltrate(s) was observed in 2 (1.2%). In 32 (19.3%) participants, the infiltrate(s) remained almost the same. Regression of infiltrate(s) occurred in 102 (61.4%) and complete resolution in 15 (9.0%) patients. The regression or complete resolution of pneumonic infiltrates was detected in 96.1% of all patients with bacterial pneumonia, compared with 80.8 % of all patients with atypical bacterial pneumonia and 45.8 % of those with viral pneumonia (p<0.01), as presented in Figure 3.

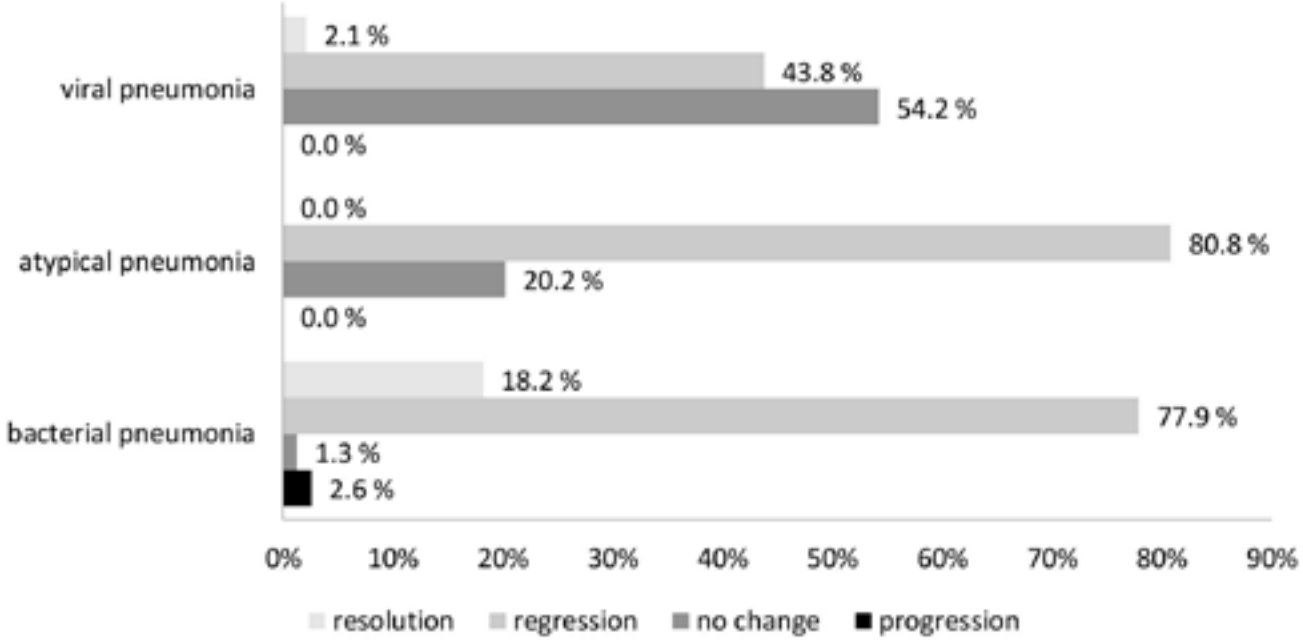

Figure 3. *Course of pneumonic infiltrates according to the etiology: comparison between the lung ultrasound at admission and follow-up.*

DISCUSSION

In our prospective study, we have shown that LUS is a sensitive tool for detecting and evaluating CAP in children. Until recently, LUS was considered inappropriate for diagnosing diseases of the lung parenchyma and was limited to the evaluation of pleural effusion (10). However, the majority of children with CAP do not have pleural effusion. The application of ultrasound in the evaluation of patients with lung consolidation was first described more than 20 years ago (14). Since then, several studies have found LUS to be a consistently accurate and reliable method for the detection of CAP and at least as sensitive as CXR (15, 16). Most studies have confirmed that the sensitivity of LUS for detecting pneumonia in adults is over 90% (17, 18, 19). In children there is no "gold standard" for diagnosing pneumonia, because computed tomography is seldom performed in this age group. Nevertheless, in recent years several studies have shown that LUS is a useful tool for detecting CAP in children, especially when compared with CXR (20). A recently performed meta-analysis also confirmed the high sensitivity (96%) and specificity (93%) of LUS for detecting pneumonia in children (21). In a study similar to ours, Caiulo et al. compared CXR and LUS in 102 hospitalized children with CAP, and only one child with CXR-detected pneumonia had normal LUS, compared with eight children with LUS-detected pneumonia who had normal CXR (22). Our study was performed with a larger sample size and showed similar results. We found that only five children with infiltrates on CXR had no signs of pneumonia on LUS, compared with 34 patients who had LUS-detected pneumonia and normal CXR. The slightly higher percentage of participants with normal LUS in our study can be explained by different ultrasonic criteria for pneumonia, because Caiulo et al. considered an increased number of B lines as a sign of pneumonia (22). In addition, we analyzed the detection of bilateral pneumonic infiltrates as a criterion of sensitivity. Comparing the sensitivity of both diagnostic methods for this outcome, we also found LUS to be superior to CXR, which could be explained by better detection of small infiltrates (mostly in viral CAP) with LUS.

We also evaluated some characteristics of infiltrates, detected with LUS, which could contribute to the etiological definition of pneumonia, such as the presence of pneumonic infiltrates in both lungs and the regression of the infiltrates. Bilateral infiltrates are often present on CXR in viral pneumonia, and sometimes in atypical bacterial pneumonia, but are uncommon in uncomplicated bacterial pneumonia (23). A similar pattern was observed with LUS in our study, where we found bilateral infiltrates in almost half of the patients with viral pneumonia, followed by atypical bacterial pneumonia and in only a few patients with bacterial pneumonia.

To our knowledge, our study is the first to analyze the resolution of pneumonic infiltrates with LUS, although this diagnostic method is obviously more suitable for follow-up than CXR. We observed a much faster regression of pneumonic infiltrates with LUS, compared with studies which analyzed the resolution of pneumonia with CXR. Most studies on the radiographic resolution of pneumonia have been performed in adult populations with CAP and reported that radiographic resolution falls well behind the clinical cure assessed by physicians. Radiographic resolution of CAP occurred in only 30.8% of patients after 10 days of treatment and in 68.4% of patients at follow-up more than 28 days from the beginning of treatment (24). Much less is known about the radiological resolution of CAP in children, because follow-up CXR after CAP is not routinely performed in this age group (3). The rapid resolution of CAP observed with LUS in our study was more in concordance with the clinical course of the disease.

Regarding the etiology of CAP, we observed the fastest resolution in patients with bacterial CAP, followed by atypical bacterial pneumonia and viral pneumonia. Studies performed with CXR in adult patients showed the fastest resolution with atypical bacterial pneumonia caused by Mycoplasma pneumoniae, followed by psittacosis and non-bacteremic pneumococcal pneumonia (24). However, a comparison of both methods for this purpose is difficult, because we performed follow-up examinations after a much shorter time period (two to three days), when compared with a few weeks for CXR-based follow-up cited above. Therefore, additional study with follow-up LUS after 1 or 2 weeks

would be more informative regarding the assessment of the resolution of pneumonia, because the complete course of the disease is much longer than a few days. In addition, we should consider that the resolution of pneumonia does not reflect the natural course of the disease, as antibiotic treatment influences the regression of pneumonia caused by bacteria and atypical bacteria.

Our study has several limitations. There is no gold standard for the diagnosis of CAP in children (25). Therefore, we could only compare the sensitivity of LUS and CXR in children who had infiltrates/consolidation detected with at least one of the imaging methods studied. Second, the stratification of patients according to etiology is not very accurate. The etiology of pneumonia in children is not easy to determine, because we usually do not perform bronchoscopy. The detection of respiratory viruses and atypical bacteria (Mycoplasma pneumoniae, Chlamydophila pneumoniae) in the upper airways does not represent direct proof of lower respiratory tract infection, because prolonged viral shedding or asymptomatic colonization is common in children (26, 27). Methods to detect bacteria in CAP are even less sensitive and specific. Blood culture is positive in less than 5% of children with uncomplicated bacterial CAP and sputum is seldom obtained from preschool children (28, 29). Therefore, our patients were stratified into a group with bacterial pneumonia, according to the laboratory results, the presence of large area(s) of consolidation on CXR and/or LUS, and the absence of atypical bacteria, as described in the Methods section. Third, even with cooperation of another pediatric pulmonologist in the analysis of LUS cine-loops, the problem of interobserver variability in the performance of LUS remains a potential confounder. The same applies to interobserver variability between radiologists in analysing the CXR.

CONCLUSION

In conclusion, we clearly confirmed LUS to be a sensitive tool for detecting CAP in children. We have also shown that LUS can help to establish the etiology of pneumonia and is especially suitable for follow-up. We can agree with studies that showed that LUS can reduce the need for CXR in almost half of children with CAP (30). LUS is harmless, easy to perform and a widely available bedside investigation. Therefore, we predict that LUS will become established as the first-line investigation in children with CAP, and that it will replace CXR for that purpose in the majority of patients. The inclusion of lung ultrasound in the guidelines of CAP management is already warranted. However, better standardization of the investigation is required in the future to diminish the large intra- and interobserver variability of the results.

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