The Usefulness of Lung Ultrasound for the Aetiological Diagnosis of Community-Acquired Pneumonia in Children

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The aetiology of community-acquired pneumonia (CAP) is not easy to establish. As lung ultrasound (LUS) has already proved to be an excellent diagnostic tool for CAP, we analysed its usefulness for discriminating between the aetiologically different types of CAP in children. We included 147 children hospitalized because of CAP. LUS was performed in all patients at admission, and follow-up LUS was performed in most patients. LUS-detected consolidations in viral CAP were significantly smaller, with a median diameter of 15 mm, compared to 20 mm in atypical bacterial CAP (p = 0.05) and 30 mm in bacterial CAP (p < 0.001). Multiple consolidations were detected in 65.4% of patients with viral CAP and in 17.3% of patients with bacterial CAP (p < 0.001). Bilateral consolidations were also more common in viral CAP than in bacterial CAP (51.9% vs. 8.0%, p < 0.001). At follow-up, a regression of consolidations was observed in 96.6% of patients with bacterial CAP and in 33.3% of patients with viral CAP (p < 0.001). We found LUS to be especially suitable for differentiating bacterial CAP from CAP due to other aetiologies. However, LUS must be interpreted in light of clinical and laboratory findings.

Childhood community-acquired pneumonia (CAP) is a common infection of the lower respiratory tract and the single most important cause of mortality in preschool children in the developing world1. In the developed world, CAP is imposing a significant burden of morbidity, with an estimated annual incidence of 14.5 per 10,000 children from 0 to 16 years old5. The diagnosis of CAP in children can be challenging as there is no pathognomonic sign or symptom5.

Respiratory viruses are the most common cause of CAP in preschool children, followed by bacteria, especially Streptococcus pneumoniae. The atypical bacteria Mycoplasma pneumoniae and Chlamydia pneumoniae are common causes of pneumonia in children older than 5 years. The identification of the causal agent is pivotal, especially in children who require hospital admission, as it guides the choice of appropriate treatment. However, the microbial diagnosis of CAP in children is not easy to establish without invasive procedures, which are only rarely performed in this age group5. Pneumonia can be a life-threatening disease if left untreated6. Initially, antibiotic therapy is empirical and influenced by epidemiological, clinical and radiographic findings. Slovenian guidelines recommend a penicillin-based antibiotic as a first-line therapy for non-complicated bacterial CAP7. Children with non-complicated viral CAP need only supportive treatment6.

Clinical features of bacterial pneumonia, atypical bacterial pneumonia or viral pneumonia frequently overlap and cannot be used reliably to distinguish between the various aetiologies8. The same applies to blood tests such as the complete blood count (CBC) with differential and acute phase reactants. Normal white blood cell (WBC) count and low C-reactive protein (CRP) do not exclude bacterial CAP9. On the other hand, a low serum procalcitonin (PCT; < 0.25 ng/ml) was recently found to have a 96% negative predictive value (95% confidence interval [CI], 93–99), 85% sensitivity (95% CI, 76–95), and 45% specificity (95% CI, 40–50) in identifying children without typical bacterial CAP9.

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Chest X-ray (CXR) is not necessary to confirm the diagnosis of CAP in patients with milder disease, who are treated as outpatients and are also associated with a small, albeit not completely negligible, risk of radiation exposure. Although CXR is not considered a ‘gold standard’, it has a high negative predictive value for CAP in children. However, CXR cannot reliably establish the microbial diagnosis of CAP, and the interpretation of radiographic images varies significantly among the observers. Nevertheless, there are some radiographic characteristics that are more often associated with the specific microbial aetiology of CAP. Alveolar infiltrate in the form of lobar, segmental or round consolidation is relatively specific for bacterial pneumonia but lacks sensitivity. Viral pneumonia often presents with bilateral interstitial infiltrates on CXR. A similar form of infiltrates can be observed in atypical bacterial CAP. However, infection with *M. pneumoniae* often radiologically mimics classic bacterial CAP, presenting with alveolar infiltrate or even small pleural effusion.

Lung ultrasound (LUS) seems to be a sufficiently accurate technique for diagnosing pneumonia in the paediatric population with high sensitivity and specificity and may represent an alternative diagnostic tool to CXR. The advantages of LUS are as follows: no ionizing radiation, lower cost, the possibility of follow-up examination, the ability to monitor the effect of therapy, and better patient cooperation. Furthermore, this diagnostic technique is accessible, portable, fast, easy to learn, and can be used immediately as a point-of-care method. LUS has good diagnostic accuracy even when performed by non-experts. By using LUS, it is possible to observe many pathological lung patterns associated with pneumonia, such as consolidation, pleural effusion, and interstitial syndrome. Consolidation, as seen on LUS, is hypoechoic or isoechoic, has a tissue-like structure and represents a loss of lung aeration. Branching, hyperechoic and dynamic air bronchograms detected within the area of consolidation are the hallmark of pneumonia.

Anechoic fluid bronchograms are also characteristic of pneumonic consolidation but are only very seldom encountered without the air bronchograms in children with CAP. Static air bronchograms are more a characteristic of lung collapse but can also be present in pneumonic consolidation. In such cases, it is difficult to distinguish between pneumonia and lung collapse.

Studies using LUS for the identification of bacterial superinfection in patients with viral lower respiratory tract infection (LRTI) have already been performed and considered small subpleural consolidations and/or an increased number of B-lines (interstitial syndrome) as characteristics of viral pneumonia. A similar LUS pattern can also be encountered in viral bronchiolitis. Urbankowska *et al.* found a positive correlation between the size of LUS-detected consolidations and neutrophil count, which implies the association of larger consolidations with bacterial CAP. They also found LUS to be very useful for the follow-up of CAP in children and observed a complete regression of consolidations in 44% of patients after 5–7 days of treatment. However, to the best of our knowledge, our study is the first to investigate the usefulness of LUS in the aetiological diagnosis of all types of CAP simultaneously.

Therefore, the aim of the present study was to find an association between LUS characteristics and the aetiological diagnosis of CAP in the paediatric population. By analogy to the CXR characteristics of different types of CAP, we hypothesize that the aetiologically different types of CAP (bacterial, viral, atypical bacterial) differ in their LUS characteristics. More specifically, the consolidations in bacterial CAP are more likely to be solitary, larger and unilateral than those in the viral and atypical bacterial CAPs, where we expect to find multiple consolidations that are smaller and more often bilateral.

**Participants and Methods**

**Participants.** We performed a prospective study and included 147 children with CAP who were hospitalized in our Department of Pediatrics from October 1, 2014 to September 30, 2018. The age of the patients ranged from 1 month to 16 years. Initially we enrolled all (188) children who were hospitalized in the aforementioned period for CAP and had pneumonic consolidation(s) detected with LUS. LUS was performed in all patients with at least two of the following signs and symptoms: fever (>38 °C), cough, dyspnoea, abnormal auscultatory findings, chest or abdominal pain. LUS was also performed in children with a fever without a localizing sign and leucocytosis (>15 × 10⁹/L). All the studied children were previously healthy and were not born premature. We excluded patients with immune deficiency, neurological impairment, chronic lung (except asthma) or heart disease or any other chronic condition that can predispose individuals to pneumonia. In addition, we excluded patients with severe CAP who required management in the paediatric intensive care unit (ICU). Some patients were excluded only after the completion of treatment, when alternative diagnoses were established or when we were unable to determine the aetiology of CAP. Final number of included patients for subsequent analysis was 147 (Fig. 1). We did not exclude patients who were already treated with antibiotics before admission. There were 12 (9.3%) such patients, 7 (8.2%) of whom were in the bacterial CAP group. The diagnosis of CAP was confirmed according to the British Thoracic Society (BTS) criteria at discharge from the hospital by two senior paediatric pulmonologists.

**Ethical approval and informed consent.** The study was approved by the Ethics Committee of University Medical Centre, Maribor, Slovenia. All methods were performed in accordance with the relevant guidelines and regulations. Legal guardians of all participants signed an informed consent form according to the World Medical Association Declaration of Helsinki, revised in 2000, Edinburgh. There is no identifying information or image in the article.

**Diagnostic investigations.** Venous blood was collected from all participants to obtain complete and differential blood count and CRP levels. PCT levels were determined, and a blood culture was performed in patients with suspected bacterial CAP. We collected nasopharyngeal swabs for the detection of the most common respiratory viruses and three atypical bacteria using polymerase chain reaction (PCR)-based assays from all patients. 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, *M. pneumoniae*, *Bordetella pertussis* and *C. pneumoniae*. We confirmed acute infection with *Mycoplasma pneumoniae* by detecting the specific M class antibody (IgM) in the convalescent phase using enzyme-linked immunosorbent assays (ELISAs)28. All microbiological assays were performed by the National Laboratory of Health, Environment and Food, Maribor, Slovenia.

All 147 patients underwent LUS on the day of admission, followed by CXR in 120 patients. LUS was repeated after 48–72 hours in 111 (75.5%) patients who were still hospitalized at that time. CXR was performed in all patients with uncertain aetiology (e.g. detected viruses and leucocytosis) and at the discretion of the physician. A standard posteroanterior (PA) view was used in the CXR, and the image was evaluated by a paediatric radiologist.

**Lung ultrasound.** LUS was performed with the portable ultrasound machine Sonosite (SonoSite, Inc. Bothell, WA, USA) by a paediatric pulmonologist who was unaware of the clinical and laboratory data and of the CXR results. A linear probe (13–6 MHz) was used in preschool children. In older children, we 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 Cattarossi23. Only the B-mode was used, and Doppler ultrasound was performed for the evaluation of the blood perfusion of the affected lung tissue. Cine loops were obtained and later discussed with another paediatric pulmonologist. Pleural effusion and the increased number of B-lines (≥3 per intercostal space) were also recorded. However, only the presence of consolidation was considered a diagnostic criterion for pneumonia in our study. Pneumonic consolidation was defined as the presence of hypoechoic or isoechoic (echogenicity similar to liver) areas with dynamic air bronchogram and/or shred sign to distinguish between the pneumonic consolidation and lung collapse29,30.

When more than one discrete lung consolidation was detected with LUS simultaneously, we considered the patient to have multiple consolidations for the purpose of statistical analysis, except for the calculation of correlation, where the actual number of consolidations was taken into account. We considered the presence of bilateral consolidations when consolidations were detected with LUS on both lungs simultaneously. The dimensions of each consolidation were measured in the longitudinal, transverse and sagittal axes, and the largest diameter was recorded. At follow-up, the LUS regression/progression of consolidations in size and number was evaluated, and patients were stratified at the discretion of the physician who performed the LUS into four groups: progression, no regression, regression, and complete resolution. In addition, consolidation(s) were measured again as described above.
Stratification of patients. Patients were stratified into the three different groups according to the presumed microbial aetiology (Fig. 1). Patients with detected viral infection were stratified into the viral CAP group only after the exclusion of bacterial superinfection. Bacterial CAP was excluded in all patients with normal serum PCT (<0.25 ng/ml). Bacterial CAP (co-infection or superinfection) was considered in patients with leucocytosis (>15 × 10⁹/L) and alveolar infiltrate(s) on CXR, even when viruses were detected in the nasopharyngeal swab. When no viruses or atypical bacteria were detected, leucocytosis or alveolar infiltrate alone was enough for the stratification into the bacterial CAP group. Bacterial CAP was also considered in all patients with positive blood culture. When no aetiology could be established (negative nasopharyngeal swab, normal WBC count, absence of alveolar infiltrates on CXR), the patient was excluded from the study.

Statistical analysis. Statistical analysis was performed with IBM SPSS 24.0 software (IBM Inc., Chicago, IL, USA). The Mann-Whitney U-test was performed to compare quantitative variables between the different CAP groups and after a Kolmogorov-Smirnov test of normality. The association of the aetiology of CAP with qualitative clinical, CXR and LUS characteristics was analysed using Fisher’s exact or chi-squared test. Risk, positive predictive value (PPV) and negative predictive value (NPV) were calculated for the bacterial CAP. A receiver-operating characteristic (ROC) curve analysis was applied to assess the optimal consolidation size cut-off value for discriminating between the different types of CAP. Correlations between quantitative variables were analysed with Spearman’s rank correlation coefficient, and the agreement between the CXR and LUS regarding the presence of bilateral infiltrates was analysed with Cohen’s kappa coefficient. We considered the strength of the correlation to be very weak (0.0–0.19), weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79) or very strong (0.80–1.0). A comparison of ultrasound characteristics, adjusted for age, sex, and clinical and laboratory characteristics, was performed with logistic regression. The α level for all tests was set to 0.05, and P values are presented for two-tailed tests.

Results

Raw data, including the demographic and clinical characteristics as well as the laboratory, CXR, LUS and microbiological results of patients, are presented in the Supplement (Supplementary dataset).

Demographic, clinical and laboratory characteristics. We included 73 (49.7%) females and 74 (50.3%) males.

Pneumonia was caused by bacteria, atypical bacteria and viruses in 75 (51.0%), 20 (13.6%) and 52 (35.4%) subjects, respectively.

The demographic, clinical and laboratory characteristics of participants according to the aetiology of CAP are presented in Table 1. Blood culture was positive in only 4 patients (5.3% of all subjects with bacterial CAP), and Streptococcus pneumoniae was isolated in all cases.

Chest X-ray. CXR was performed in 120 (81.6%) patients with CAP; pneumonic infiltrates were detected in 92 (76.7%) of them. Infiltrates were detected in 50 (79.4%) of those who underwent CXR patients with bacterial CAP, in 12 (80.0%) patients with atypical bacterial CAP and in 30 (71.4%) patients with viral CAP. The radiological characteristics of patients who had CAP detected with CRX (in addition to LUS) are presented in Table 2.

Lung ultrasound. LUS was performed at admission in all 147 patients; multiple consolidations were detected in 60 (40.8%) and bilateral consolidations in 42 (28.6%) of them. A comparison of LUS characteristics in different types of CAP is presented in Table 3.

The ROC curve analysis (Fig. 2) found that the optimal cut-off for discriminating between the bacterial and viral CAP is a consolidation size of 21 mm, with a sensitivity of 80% and a specificity of 75% for diagnosing bacterial CAP. The area under the ROC curve (AUC) was 0.85 (95% CI 0.79–0.92, p < 0.001). Similarly, the optimal cut-off for discriminating between the bacterial and atypical bacterial CAP is a consolidation size of 21 mm, with a sensitivity of 80% and a specificity of 60% to diagnose bacterial CAP. The area under the ROC curve was 0.68 (95% CI 0.52–0.85, p = 0.012). Regarding the discrimination between atypical bacterial CAP and viral CAP, the AUC was 0.65 (95% CI 0.50–0.80, p = 0.051).

A weak positive correlation was found between the size of the (largest) consolidation and the WBC count (r = 0.28, p < 0.001).

Single consolidation, two consolidations, three consolidations and four (or more) consolidations were detected with LUS in 87 (59.2%), 21 (14.3%), 14 (9.5%) and 25 (17.0%) patients, respectively. A weak to moderate negative correlation was observed between the number of consolidations and the WBC count (r = -0.35, p < 0.001).

A significant agreement was found between the LUS and CXR regarding the presence of bilateral consolidations (κ = 0.45, p < 0.001).

Follow-up LUS was performed in 111 (75.5%) patients, of whom 58, 14 and 39 patients had bacterial, atypical bacterial and viral CAP, respectively. A regression of consolidations was observed in 56 (96.6%), 7 (50.0%) and 13 (33.3%) patients with bacterial, atypical bacterial and viral CAP, respectively. Of these, we found a complete resolution of consolidations in 16 (27.6%), 2 (14.3%) and 1 (2.6%) patient with bacterial, atypical bacterial and viral CAP, respectively. A regression of consolidations was significantly more common in bacterial CAP than in viral CAP (p < 0.001, OR = 56.00 with 95% CI 11.77–266.41) and in bacterial CAP than in atypical bacterial CAP (p < 0.001, OR = 28.00 with 95% CI 4.83–162.25). There was no significant difference in the regression of consolidations between atypical bacterial and viral CAP (p = 0.341, OR = 0.50 with 95% CI 0.15–1.73).

In addition, we analysed the association of LUS characteristics with the aetiology of CAP (viral vs. bacterial) using a regression model to adjust for age, sex, and laboratory characteristics. The regression model was statistically significant (p < 0.001), with 83.6% of the dependent variable variability explained. The accuracy of
the model was 90.9%. The size of the largest consolidation in the model was still significant for bacterial CAP (p < 0.001; OR = 1.13 with 95% CI 1.04–1.23). The presence of bilateral consolidations also remained significant (p = 0.042; OR = 0.05 with 95% CI 0.01–0.86) in favour of a decreased probability for bacterial CAP. When all the clinical characteristics were included in the logistic regression analysis, the regression model remained highly significant (p < 0.001), and the accuracy of the model increased to 93.3%. The size of the consolidation remained significant for bacterial pneumonia (p = 0.041; OR = 1.09 with 95% CI 1.01–1.19).

Discussion

In our prospective study, we have shown that LUS not only is a sensitive tool for detection but also can contribute to the etiological diagnosis of CAP in children.

We found that patients with viral or atypical bacterial CAP were more likely to have multiple consolidations simultaneously detected with LUS than bacterial CAP, where solitary consolidations predominated. In addition, consolidations in patients with viral or atypical bacterial CAP were smaller and more likely bilateral. These findings are in concordance with the studies performed previously with CXR, where large alveolar infiltrates have shown a good positive predictive value for bacterial pneumonia32 and bilateral interstitial infiltrates were a characteristic of viral CAP. Studies of the usefulness of CXR in the microbial diagnosis of CAP were mostly performed more than a decade ago. In recent years, modern PCR-based microbiological diagnostics have allowed more sensitive detection of viruses and atypical bacteria. Therefore, the stratification of patients in our study is probably more accurate.

Several studies have shown that LUS is a useful tool for detecting CAP in children, especially when compared with CXR. A recently performed meta-analysis also confirmed the high sensitivity (96%) and specificity (93%) of LUS for detecting pneumonia in children30.

The potential of LUS to determine the aetiology of acute respiratory failure in adults admitted to the ICU has already been assessed previously, and the Bedside Lung Ultrasound in Emergency (BLUE) protocol has been established, which includes an algorithm according to which a consolidation with air bronchograms and/or focal accumulation of B-lines are associated with pneumonia. This algorithm did not differentiate between the different microbial aetiologies of pneumonia and was later further upgraded for the purpose of differentiating between the viral LRTI and bacterial superinfection in children during the 2009 H1N1 influenza pandemic. In this study,
a bacterial superinfection was considered in all patients in whom lung consolidation with an air bronchogram was detected using LUS. Small subpleural consolidations or confluent B-lines were considered as characteristics of viral pneumonia. Similarly, patients with an alveolar infiltrate on CXR were classified as having bacterial pneumonia, and viral pneumonia was assumed when interstitial infiltrates were detected on CXR. In this way, a high correlation between LUS and CXR was determined. However, the potential of CXR for the microbial diagnosis of CAP is limited, as more than half of patients with interstitial infiltrates on CXR were supposed to have bacterial pneumonia.

Therefore, we have not considered CXR as the “gold standard”, nor have we focused on the comparison between LUS and CXR. Our patients were stratified mainly according to the microbiological results. We considered bacterial co-infection or superinfection only in those patients with proven viral infection who had alveolar infiltrates on CXR and leucocytosis and an increased serum PCT value as described in the Methods section. We considered bacterial co-infection or superinfection only in those patients with proven viral infection who had alveolar infiltrates on CXR and leucocytosis and an increased serum PCT value as described in the Methods section and Fisher’s exact test was used.

**Odds ratio is calculated for bacterial pneumonia (BA and BV) or atypical bacterial pneumonia (AV).**

**Table 2.** Chest X-ray characteristics of patients with different types of pneumonia. *Number of subjects with a particular characteristic (percentage in parentheses). **p value refers to the comparison between bacterial and atypical bacterial CAP (BA), between atypical bacterial and viral CAP (AV) and between bacterial and viral CAP (BV); chi-squared or Fisher’s exact test was used. ***Odds ratio is calculated for bacterial pneumonia (BA and BV) or atypical bacterial pneumonia (AV).****Positive and negative predictive value – calculated for bacterial pneumonia. CAP: community-acquired pneumonia.

| Characteristic [n (%)]** | Bacterial CAP n = 50 | Atypical CAP n = 12 | Viral CAP n = 30 | p value** | Odds ratio (95% confidence interval)*** | Positive predictive value (%)**** | Negative predictive value (%)**** |
|-------------------------|----------------------|---------------------|------------------|-----------|----------------------------------------|-------------------------------|-------------------------------|
| Unilateral infiltrate(s) | 46 (92.0)            | 9 (75.0)            | 20 (66.7)        |           | BA 0.125 AV 0.722 BV 0.006            |                                | 61.3                          | 76.5                          |
|                        |                      |                     |                  |           | BA 3.83 (0.73–20.13) AV 1.50 (0.33–6.80) BV 5.75 (1.61–20.53) |                                |                               |                               |
| Alveolar infiltrate(s)  | 42 (84.0)            | 4 (33.3)            | 10 (33.3)        |           | BA 0.001 AV 1.000 BV < 0.001         |                                | 75.0                          | 77.8                          |
|                        |                      |                     |                  |           | BA 10.50 (2.54–43.36) AV 1.00 (0.24–4.14) BV 10.50 (3.60–30.65) |                                |                               |                               |
| Pleural effusion        | 2 (3.2)              | 2 (13.3)            | 2 (4.8)          |           | BA 0.165 AV 0.281 BV 1.000          |                                | 33.3                          | 46.5                          |
|                        |                      |                     |                  |           | BA 0.21 (0.03–1.65) AV 3.68 (0.39–24.08) BV 0.66 (0.09–4.85) |                                |                               |                               |

**Table 3.** Comparison of ultrasound characteristics of different types of pneumonia. *Number of subjects with a particular characteristic (percentage in parentheses). **p value refers to the comparison between bacterial and atypical bacterial CAP (BA), between atypical bacterial and viral CAP (AV) and between bacterial and viral CAP (BV); chi-squared or Fisher’s exact test was used for the comparison of qualitative variables and Mann-Whitney U-test was used for the comparison of quantitative variables. ***Odds ratio is calculated for bacterial pneumonia (BA and BV) or atypical bacterial pneumonia (AV). ****Positive and negative predictive value – calculated for bacterial pneumonia. CAP: community-acquired pneumonia.

| Characteristic [n (%)]** | Bacterial CAP | Atypical CAP | Viral CAP | p value** | Odds ratio (95% confidence interval)*** | Positive predictive value (%)**** | Negative predictive value (%)**** |
|-------------------------|--------------|--------------|-----------|-----------|----------------------------------------|-------------------------------|-------------------------------|
| Unilateral consolidation | 69 (92.0)    | 11 (55.0)    | 25 (48.1) |           | BA < 0.001 AV 0.793 BV < 0.001         |                                | 65.7                          | 85.7                          |
|                        |              |              |           |           | BA 9.41 (2.80–31.66) AV 1.32 (0.47–3.72) BV 12.42 (4.59–33.62) |                                |                               |                               |
| Solitary consolidation  | 62 (82.7)    | 7 (35.0)     | 18 (34.6) |           | BA < 0.001 AV 1.000 BV < 0.001         |                                | 71.3                          | 78.3                          |
|                        |              |              |           |           | BA 8.86 (2.96–26.51) AV 1.02 (0.35–3.00) BV 9.01 (3.94–20.60) |                                |                               |                               |
| Pleural effusion        | 14 (18.7)    | 3 (15.0)     | 2 (3.8)   |           | BA 1.000 AV 0.127 BV 0.014             |                                | 73.7                          | 52.3                          |
|                        |              |              |           |           | BA 1.30 (0.34–5.06) AV 4.41 (0.68–28.68) BV 5.74 (1.25–26.45) |                                |                               |                               |

**Table 4.** Chest X-ray characteristics of patients with different types of pneumonia. *Number of subjects with a particular characteristic (percentage in parentheses). **p value refers to the comparison between bacterial and atypical bacterial CAP (BA), between atypical bacterial and viral CAP (AV) and between bacterial and viral CAP (BV); chi-squared or Fisher’s exact test was used for the comparison of qualitative variables and Mann-Whitney U-test was used for the comparison of quantitative variables. ***Odds ratio is calculated for bacterial pneumonia (BA and BV) or atypical bacterial pneumonia (AV). ****Positive and negative predictive value – calculated for bacterial pneumonia. CAP: community-acquired pneumonia.
LUS for diagnosing bacterial superinfection in children (up to 2 years old) with acute bronchiolitis and found that bacterial superinfection is very likely when consolidations larger than 1 cm are detected. According to our results, this threshold is relatively low, as we found that the median size of the (largest) consolidations in viral CAP was 15 mm. ROC curve analysis has shown that a cut-off of 21 mm consolidation size, as detected with LUS, yielded an optimal sensitivity of 80% and specificity of 75% for differentiating between the viral and bacterial CAP in the present study. We also included 12 (8.2%) patients who were treated with antibiotics before admission. This treatment could cause some regression of consolidations in the bacterial CAP group even before the first LUS was performed. We assume that the differences in the size of the consolidations between the different types of CAP would be even more significant without those patients.

We detected multiple consolidations with LUS in 40.8% of all patients, which is comparable to the study performed by Caiulo et al., who found multiple consolidations in approximately 30% of patients. In our study, multiple consolidations were detected in only 17.3% of patients with bacterial CAP and were significantly more common (65.4%) in patients with viral CAP. Although Caiulo et al. did not consider the microbial aetiology of CAP, the high percentage of multiple consolidations indicates that they included a substantial proportion of children with viral aetiology. The mean size of the consolidations measured in the study performed by Caiulo et al. was 18 mm, which also supports this presumption, as the value is very close to our results regarding the size of the consolidations in viral CAP. None of the abovementioned studies analysed the position of the consolidations (unilateral vs. bilateral). In our study, LUS-detected, bilateral consolidations were significantly more common in viral CAP (51.9%) than in bacterial CAP (8.0%). These results are in concordance with some of the previous studies using CXR, where bilateral infiltrates were associated with viral pneumonia. The relatively low proportion of bilateral and/or multiple consolidation in bacterial CAP in our study may result from the exclusion of patients with severe cases of bacterial CAP, who are treated in the ICU. In such cases, multiple consolidations are expected to be more common. Therefore, we suggest that LUS findings should always be interpreted in light of other clinical and laboratory findings. In our study, we detected bilateral consolidations with LUS in 28.6% of all patients, compared to 18.5% detected with CXR, which also indicates a higher sensitivity of LUS, although we observed a significant agreement between both imaging diagnostics regarding this issue.

Radiological findings in children with CAP may differ according to the age group. As we included children across a wide age span, we analysed the influence of age on LUS characteristics (results not shown). We found no association except the positive correlation between the age and the size of the consolidations in the subgroup of patients with bacterial CAP. Therefore, we performed regression analysis adjusting for age and still found that the larger size of the consolidation was highly significant for the bacterial CAP.

Pleural effusion, which is considered highly specific for bacterial CAP, was detected with LUS in only 18.7% of our patients with bacterial CAP, which is a significantly higher proportion than that in viral CAP but not significantly different from that in atypical bacterial CAP. Previous studies reported that the prevalence of pleural effusion in adults admitted to the hospital because of CAP was 15–44%. These proportions are comparable to our findings, as bacteria are the most common cause of CAP in adults.

We usually dismissed patients with CAP after 2–3 days of hospitalization, and the follow-up LUS was performed immediately before the dismissal. In our study, a regression of consolidations was observed in 96.6% of patients with bacterial CAP and in 33.3% of patients with viral aetiology. We detected no consolidations (complete resolution) at follow-up in 27.6% of patients with bacterial CAP and in only 2.6% of patients with viral CAP. In bacterial CAP, the median size of the consolidation diminished at follow-up LUS to 14.5 mm (from 30 mm to 14.5 mm).
studies that monitored the resolution of pneumonia with CXR. Radiographic resolution of pneumonia falls well behind the clinical cure assessed by physicians and was observed in only 30.8% of patients after 10 days. Our results confirm that LUS is the preferred imaging method for the follow-up of CAP, as it almost parallels the clinical course. However, compared to the other analysed LUS characteristics (the size, number and position of consolidations), the findings regarding the course of pneumonic consolidations were of minor importance, as we aimed to improve the initial treatment decisions in patients with CAP.

To our knowledge, no other studies have examined the LUS characteristics of atypical bacterial pneumonia so far. According to our results, LUS findings in atypical bacterial pneumonia are similar to those in viral CAP. We observed that the consolidations in atypical bacterial CAP were more likely to be smaller, bilateral and multiple than those in bacterial CAP. With LUS, we detected multiple consolidations in 65.0% and bilateral consolidations in 45.0% of patients with atypical bacterial CAP. Our findings support the results of Bruns et al., where 50% of children with *M. pneumoniae* pneumonia presented with interstitial and bilateral infiltrates on CXR. Considering the detection of bilateral infiltrates in atypical bacterial pneumonia, we found LUS to be superior to CXR for differentiating between atypical and bacterial CAP. Bilateral infiltrates were detected with CXR in only 25.0% of our patients with atypical bacterial CAP, which was not significantly more common than in classic bacterial CAP. We observed a slower regression of consolidations in patients with atypical bacterial CAP than in those with classic bacterial CAP. At follow-up, the regression of consolidations as determined by LUS was observed in only 50% of patients and complete resolution was observed in 14.3%, which is similar to that found in viral CAP and significantly less than we observed in classic bacterial CAP. In contrast to our results, a study performed by Bruns et al. with CXR in adults has shown the fastest resolution in atypical bacterial pneumonia caused by *M. pneumoniae*, followed by psittacosis and pneumococcal pneumonia. However, a comparison of both imaging methods for this purpose is inappropriate because we performed follow-up examinations after a much shorter time period (two to three days) than the interval of a few weeks for CXR-based follow-up performed by Bruns et al. Regarding the differentiation of atypical from viral CAP with LUS, we found that the only difference was the larger size of the (largest) consolidation in patients with atypical bacterial CAP (median 20 mm). However, the patients with atypical bacterial CAP were significantly older (median 7 years) than those with viral CAP (median 2.2 years). According to our results, the combination of school age, the presence of crackles on auscultation, moderately increased WBC count and ultrasonic detection of multiple and/or bilateral consolidations of medium-size indicate an infection with atypical bacteria. The differentiation between the viral and atypical bacterial CAP is less important than the identification of classic bacterial CAP. Infection with *M. pneumoniae* is usually mild and self-limited in otherwise healthy children and can be treated similar to viral LRTI in outpatient settings. As we included only 20 patients with atypical bacterial CAP, larger samples are warranted to ascertain the LUS characteristics of atypical bacterial CAP.

Our results confirm that the epidemiological, clinical and laboratory characteristics are useful in establishing the aetiology of CAP. However, signs that are more specific for bacterial CAP (diminished breath sounds, bronchial breathing) are seldom present and are therefore insensitive. We confirmed that laboratory results are probably more accurate in the aetiologic diagnosis of CAP, but unlike the clinical characteristics, they are useful only when the diagnosis of CAP is already established. LUS in the hands of an experienced clinician can simultaneously detect CAP and add useful information regarding the aetiologic diagnosis. However, the usefulness of LUS is enhanced when used in combination with epidemiological, clinical and laboratory data.

We observed a relatively low sensitivity (77%) of CXR for the detection of pneumonia. However, our results are in accordance with the findings from previous studies that compared the sensitivity of LUS and CXR in children and adults with CAP. A large proportion of bacterial CAPs among our patients probably reflects a low (below 50%) vaccination rate against pneumococci even in preschool children in Slovenia and the inclusion of school-age children in whom viral CAPs are less common. Second, the relatively low proportion of viral CAPs is our conservative approach, as we did not include patients with small subpleural consolidations and/or B-lines detected with LUS as described above. This could also contribute to the similarities in the LUS features of viral and atypical bacterial CAPs in our study.

Our study has several limitations. There is no “gold standard” for the diagnosis of CAP in children, and the differentiation between viral bronchitis bronchiolitis and viral pneumonia is somewhat arbitrary. Moreover, the microbial diagnosis of pneumonia in children is not easy to determine because we usually do not take specimens from the lower airways. The detection of respiratory viruses and atypical bacteria in the upper airways is not a direct proof of lower respiratory tract infection because prolonged viral shedding or asymptomatic colonization is common in children. Furthermore, bacterial CAP often follows viral LRTI, and the viruses are still detectable at that time. Methods to detect bacteria in CAP in children are even less sensitive or specific. Blood culture is positive in less than 10% of children with uncomplicated bacterial CAP. Sputum is seldom obtained from preschool children, and the results are not specific. In addition, even with the cooperation of another paediatric
Data availability

All data have been added to this manuscript and the Supplementary Material section.

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References

1. Rudan, I., Boschi-Pinto, C., Biloglav, Z., Mulholland, K. & Campbell, H. Epidemiology and etiology of childhood pneumonia. Bull. World Health Organ. 86, 408–416 (2008).
2. Harris, M. et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. Thorax 66, 1–23 (2011).
3. Shah, S. N., Bachur, R. G., Simel, D. L. & Neuman, M. I. Does this child have pneumonia? The rational clinical examination systematic review. JAMA 318, 462–471 (2017).
4. Jain, S. et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N. Engl. J. Med. 372, 835–845 (2015).
5. Hammitt, L. L. et al. Addressing the analytic challenges of cross-sectional paediatric pneumonia aetiology data. Clin. Infect. Dis. 64, 197–204 (2017).
6. Bradley, J. S. et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin. Infect. Dis. 53, 25–76 (2011).
7. Cižman, M. Lower and middle respiratory tract infections in How to prescribe antimicrobial drugs in hospital (eds. Čižman, M., Beović, B.) 123–129 (Slovenian Medical Association, 2013).
8. Korppi, M., Don, M., Valent, F. & Canciani, M. The value of clinical features in differentiating between viral, pneumococcal and atypical bacterial pneumonia in children. Acta Pediatr. 97, 943–947 (2008).
9. Stockmann, C. et al. Procalcitonin accurately identifies hospitalized children with low risk of bacterial community-acquired pneumonia. J. Pediatric Infect. Dis. Soc. 7, 46–53 (2018).
10. O’Grady, K. A. F., Torzillo, P. J., Frawley, K. & Chang, A. B. The radiological diagnosis of pneumonia in children. Pneumonia 5, 38, https://doi.org/10.15172/pneu.2014.4/482 (2014).
11. Lipsett, S. C., Monuteaux, M. C., Bachur, R. G., Finn, N. & Neuman, M. I. Negative chest radiography and risk of pneumonia. Pediatrics 142, e20180236, https://doi.org/10.1542/peds.2018-0236 (2018).
12. Elemraid, M. A. et al. Accuracy of the interpretation of chest radiographs for the diagnosis of paediatric pneumonia. PLoS One 9, e100051, https://doi.org/10.1371/journal.pone.0100051 (2014).
13. Korppi, M., Kiekara, O., Heiskanen-Kosma, T. & Soimakallio, S. Comparison of radiological findings and microbial etiology of childhood pneumonia. Acta Paediatr. 82, 360–363 (1993).
14. Nambu, A., Ozawa, K., Kobayashi, N. & Tago, M. Imaging of community-acquired pneumonia: Roles of imaging examinations, imaging diagnosis of specific pathogens and discrimination from noninfectious diseases. World J. Radiol. 6, 779–793 (2014).
15. Hsieh, S. C. et al. Mycoplasma pneumonia: clinical and radiographic features in 39 children. Pediatr. Int. 49, 363–367 (2007).
16. Finnegan, O. C., Fewkes, S. J. & White, R. J. Radiographic appearances of mycoplasma pneumonia. Thorax 36, 469–472 (1981).
17. Alzahrani, S. A., Al-Salmah, M. A., Al-Madani, W. H. & Elbarbary, M. A. Systematic review and meta-analysis for the use of ultrasound versus radiology in diagnosing of pneumonia. Crit. Ultrasound J. 9, 6, https://doi.org/10.1186/s13089-017-0059-y (2017).
18. Orso, D., Ban, A. & Guglielmo, N. Lung ultrasound in diagnosing pneumonia in childhood: a systematic review and meta-analysis. J. Ultrasound 21, 183–195 (2018).
19. Urbankowska, E. et al. Lung ultrasound in the diagnosis and monitoring of community acquired pneumonia in children. Respir. Med. 109, 1207–1212 (2015).
20. Pereda, M. A. et al. Lung Ultrasound for the diagnosis of pneumonia in children: a meta-analysis. Pediatrics 135, 714–722 (2015).
21. Harel-Sterling, M., Diallo, M., Santhirakumaran, S., Maxim, T. & Tessaro, M. Emergency department resource use in pediatric pneumonia: point-of-care lung ultrasonography versus chest radiography. J. Ultrasound Med. 38, 407–414 (2019).
22. Iorio, G. et al. Lung ultrasound in the diagnosis of pneumonia in children: proposal for a new diagnostic algorithm. PeerJ. 3, e1374, https://doi.org/10.7717/peerj.1374 (2015).
23. Copetti, R. & Cattarossi, L. Ultrasound diagnosis of pneumonia in children. Radiol. Med. 113, 190–198 (2008).
24. Musolino, A. M. et al. Lung ultrasound features of children with complicated and noncomplicated community acquired pneumonia: A prospective study. Pediatr. Pulmonol. 54, 1479–1486 (2019).
25. Lichtenstein, D., Mezière, G. & Seitz, J. The dynamic air bronchogram. A lung ultrasound sign of alveolar consolidation ruling out atelectasis. Chest. 135, 1421–1425 (2009).
26. Tsung, J. W., Kessler, D. O. & Shah, V. P. Prospective application of clinician-performed lung ultrasonography during the 2009 H1N1 influenza A pandemic: distinguishing viral from bacterial pneumonia. Crit. Ultrasound J. 4, 16, https://doi.org/10.1186/s12899-012-0041-6 (2012).
27. Bagi, C. et al. Lung ultrasound for the diagnosis of pneumonia in children with acute bronchiolitis. BMC. Pulm. Med. 18, 191, https://doi.org/10.1186/s12890-018-0756-1 (2018).
28. Loens, K. & Ieven, M. Mycoplasma pneumoniae: Current knowledge on nucleic acid amplification techniques and serological diagnostics. Front. Microbiol. 7, 448, https://doi.org/10.3389/fmicb.2016.00448 (2016).
29. Volpicelli, G. Lung sonography. J. Ultrasound Med. 32, 165–171 (2013).
30. Miller, A. Practical approach to lung ultrasound. BIA Education 16, 39–45 (2016).
31. Shuttleworth, D. B. & Charney, E. Leukocyte count in childhood pneumonia. Am. J. Dis. Child. 122, 393–396 (1971).
32. Virkki, R. et al. Differentiation of bacterial and viral pneumonia in children. Thorax 57, 438–441 (2002).
33. Lichtenstein, D. A. & Mezière, G. A. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. Chest 134, 117–125 (2008).
34. Cohen, J. S. et al. The utility of bedside lung ultrasound findings in bronchiolitis. Pediatr. Emerg. Care 33, 97–100 (2017).
35. Basile, V. et al. Lung ultrasound: a useful tool in diagnosis and management of bronchiolitis. BMC. Pediatr. 15, 63, https://doi.org/10.1186/s12887-015-0380-1 (2015).
36. Caiulo, V. et al. Lung ultrasound characteristics of community-acquired pneumonia in hospitalized children. Pediatr. Pulmonol. 48, 280–287 (2013).
37. Wahlgren, H. et al. Radiological findings in children with acute pneumonia: age more important than infectious agent. Acta Radiol. 46, 431–436 (2005).
38. Yang, W., Zhang, B. & Zhang, Z. M. Infectious pleural effusion status and treatment progress. J. Thorac. Dis. 9, 4690–4699 (2017).
39. Bruns, A. H. et al. Pneumonia recovery: discrepancies in perspectives of the radiologist, physician and patient. J. Gen. Intern. Med. 25, 203–206 (2010).
40. Biondi, E. et al. Treatment of mycoplasma pneumonia: a systematic review. Pediatr. Infect. Dis. 33, 1081–1090 (2014).
41. Keali, F. et al. Can lung ultrasound replace chest radiography for the diagnosis of pneumonia in hospitalized children? Respiration 88, 112–115 (2014).
42. Omran, A., Eesai, S., Ibrahim, M. & El-Sharkawy, S. Lung ultrasound in diagnosis and follow up of community acquired pneumonia in infants younger than 1-year old. Clin. Respir. J. 12, 2204–2211 (2018).
43. Ye, X., Xiao, H., Chen, B. & Zhang, S. Accuracy of lung ultrasonography versus chest radiography for the diagnosis of adult community-acquired pneumonia: review of the literature and meta-analysis. PLoS One 10, e0130066, https://doi.org/10.1371/journal.pone.0130066 (2015).
44. Hren, R., Olbrecht, J., Vidmar, A. & Plevnik Kapun, A. Pin83 – Pharmacoeconomic evaluation of public procurement criteria in national pneumococcal vaccine immunization program: Slovenia as a case study. Value Health 21, S254–S255 (2018).
45. Rodrigues, C. M. C. & Groves, H. Community-acquired pneumonia in children: the challenges of microbiological diagnosis. J. Clin. Microbiol. 56, e01318, https://doi.org/10.1128/JCM.01318-17 (2018).
46. McCulloh, R. J. et al. Evaluating the use of blood cultures in the management of children hospitalized for community-acquired pneumonia. PLoS One 10, e0117462, https://doi.org/10.1371/journal.pone.0117462 (2015).
47. Neuman, M. I. et al. Utility of blood culture among children hospitalized with community-acquired pneumonia. Pediatrics 140, e20171013, https://doi.org/10.1542/peds.2017-1013 (2017).
48. Driscoll, A. J. et al. Standardization of laboratory methods for the PERCH study. Clin. Infect. Dis. 64, S245–S252 (2017).

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Author contributions
V.B. and M.T. performed most of the clinical part of the study, including the lung ultrasound; V.B. and B.L. wrote the main text of the manuscript; M.G. and T.B. performed the statistical analysis; and B.L. and T.B. prepared Tables 1–3 and Figures 1–2. All authors reviewed the manuscript.

Competing interests
The authors declare no competing interests.

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