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Original Research

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Lung Ultrasound in the Diagnosis and Follow-up of Community-Acquired Pneumonia

A Prospective, Multicenter, Diagnostic Accuracy Study

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Background: **The aim of this prospective, multicenter study was to define the accuracy of lung ultrasound (LUS) in the diagnosis of community-acquired pneumonia (CAP).**
Methods: **Three hundred sixty-two patients with suspected CAP were enrolled in 14 European centers. At baseline, history, clinical examination, laboratory testing, and LUS were performed as well as the reference test, which was a radiograph in two planes or a low-dose CT scan in case of inconclusive or negative radiographic but positive LUS findings. In patients with CAP, follow-up between days 5 and 8 and 13 and 16 was scheduled.**
Results: **CAP was confirmed in 229 patients (63.3%). LUS revealed a sensitivity of 93.4% (95% CI, 89.2%-96.3%), specificity of 97.7% (95% CI, 93.4%-99.6%), and likelihood ratios (LRs) of 40.5 (95% CI, 13.2-123.9) for positive and 0.07 (95% CI, 0.04-0.11) for negative results. A combination of auscultation and LUS increased the positive LR to 42.9 (95% CI, 10.8-170.0) and decreased the negative LR to 0.04 (95% CI, 0.02-0.09). We found 97.6% (205 of 211) of patients with CAP showed breath-dependent motion of infiltrates, 86.7% (183 of 211) an air bronchogram, 76.5% (156 of 204) blurred margins, and 54.4% (105 of 193) a basal pleural effusion. During follow-up, median C-reactive protein levels decreased from 137 mg/dL to 6.3 mg/dL at days 13 to 16 as did signs of CAP; median area of lesions decreased from 15.3 cm^2 to 0.2 cm^2 and pleural effusion from 50 mL to 0 mL.**
Conclusions: **LUS is a noninvasive, usually available tool used for high-accuracy diagnosis of CAP. This is especially important if radiography is not available or applicable. About 8% of pneumonic lesions are not detectable by LUS; therefore, an inconspicuous LUS does not exclude pneumonia.**
Trial registry: **ClinicalTrials.gov; No.: NCT00808457; URL: www.clinicaltrials.gov**

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Abbreviations: CAP = community-acquired pneumonia; LR = likelihood ratio; LUS = lung ultrasound

Community-acquired pneumonia (CAP) is the most common disease recorded worldwide, and 2 to 3 million cases are diagnosed annually in the United States. In an appropriate clinical setting, diagnosis of pneumonia is established in the case of a new infiltrate on chest radiograph. However, because of the methodologic limitations of radiography, CT imaging is regarded as the "gold standard," allowing for a diagnosis of pneumonia earlier and with a higher sensitivity and specificity.[1] Limitations of CT imaging include radiation dose, higher cost, and reduced availability.[2]

Lung ultrasound (LUS) represents a new technique used for diagnosing pleural and pulmonary diseases.[3-9] The primary objective of this study was to determine the accuracy of LUS in diagnosing CAP compared with chest radiograph in two planes and, in case of equivocal or negative radiographic but positive LUS results, to low-dose CT scan. Second, the appropriateness of LUS for CAP follow-up was explored.

Materials and Methods

This was an international, multicenter, prospective, observational study in patients with suspected CAP in 14 European centers (two university hospitals, seven hospitals of internal medicine, one hospital of pulmonary medicine, two practices, and two EDs). The institutional review board approved the study protocol (number 2055-06/07), and patients provided written, informed consent before enrollment. This study is reported according to the Standards for the Reporting of Diagnostic Accuracy Studies statement.[10]

Patients

Patients with clinically suspected CAP were enrolled in the study. Suspicion of CAP was raised clinically (fever > 38.0°C, cough, purulent expectoration, dyspnea) and on the basis of typical auscultation findings (rales or bronchial breath sounds).

Patient history regarding comorbidity and risk factors was documented on day 0. Clinical symptoms of pneumonia were assessed on day 0, between days 5 and 8, and between days 13 and 16. Clinical examination at the same time points focused on auscultation. Laboratory testing included C-reactive protein levels and leukocyte counts on day 0 and between days 13 and 16.

Inclusion criteria were patients with suspected CAP able to undergo chest radiography in two planes and age > 18 years. Exclusion criteria were prior systemic antibiotic therapy; hospital-acquired pneumonia, severe immunosuppression, > 24 h between LUS and radiography or low-dose CT scan; radiographic findings known to the sonographer; and pregnancy or lactation.

Lung Ultrasonography

LUS was performed first. Patients in whom a chest radiograph had already been performed at the time of the ultrasound investigation could be enrolled if LUS was performed within 24 h after the radiograph and if the radiographic findings were neither available nor known to the sonographer.

Sonography was conducted using a 5- or 3.5-MHz convex scanner, whereas examination by a 7.5-MHz linear scanner was occasionally performed. Patients were examined posteriorly in a seated position and anteriorly in a supine position. A systematic examination of all intercostal spaces was performed by experienced physicians who have done at least 100 chest ultrasonography procedures.

Sonography was assessed for the number, location, shape, size, and breath-dependent movement of pneumonia. Furthermore, the incidence of necrotic areas, positive air bronchogram, fluid bronchogram, and local and basal pleural effusion was reviewed on day 0, between days 5 and 8, and between days 13 and 16.

Chest Radiography

All patients underwent posteroanterior and lateral chest radiography on day 0 and, if possible, between days 13 and 16. Radiographs were analyzed by independent experts in chest radiology who were unaware of the LUS results.

CT Imaging

In the case of inconclusive radiographic or positive sonography findings and of negative radiographic findings, a low-dose CT scan was performed without contrast medium using 120 kV, 20 to 40 mA, and a reconstructed layer thickness of 4 mm (multislice CT scan; effective radiation dose in the range of 0.4 mSv) or 120 kV, 50 mA, and a reconstructed layer thickness of 5 mm (one-line CT scan; effective radiation dose in the range of 1.2 mSv). If other diagnoses were suspected, a spiral/multislice CT scan with contrast agent was performed. CT scans were analyzed by experts in chest radiology unaware of the sonographic and radiographic results.

Statistical Analysis

The primary objective was to estimate the diagnostic accuracy of LUS as index test (positive, negative, equivocal) compared with radiograph on two planes followed by CT imaging in case of inconclusive or negative radiographic but positive ultrasonography findings as the reference test (negative, positive). A total sample size of 300 patients was considered necessary and feasible to estimate a sensitivity of 80% with a precision (one-half of the 95% CI) of 5.1% if the prevalence of CAP was 80%. According to the study protocol, sensitivity, specificity, and likelihood ratios (LRs) were estimated, excluding equivocal LUS results (primary analysis). All three test categories were included in an analysis of robustness. Exact 95% CIs were calculated for sensitivity and specificity, assuming a binomial distribution. Asymptotic CIs were computed for LR.[11] Baseline characteristics and clinical, sonographic, and laboratory data were displayed by adequate descriptive statistics. Agreement of LUS and radiographic findings was assessed with the κ coefficient. Bland-Altman plots were constructed to compare the extension of pneumonic lesions measured by LUS and radiograph. Data were analyzed using SAS version 9.2 (SAS Institute Inc) statistical software.

Results

Between November 2007 and February 2011, 14 European centers recruited 397 patients. Thirty-five patients were excluded because of violations of inclusion criteria (n = 3) or an equivocal reference test (n = 32) (Fig 1). The remaining 362 patients underwent LUS and radiographic examinations. Sixty-three patients (17.4%) had low-dose CT scans; of them, 46 were according to the study protocol. In the remaining 17 patients, radiographic findings were confirmed by a spiral CT scan, which was performed to exclude other differential diagnoses. Finally, CAP was

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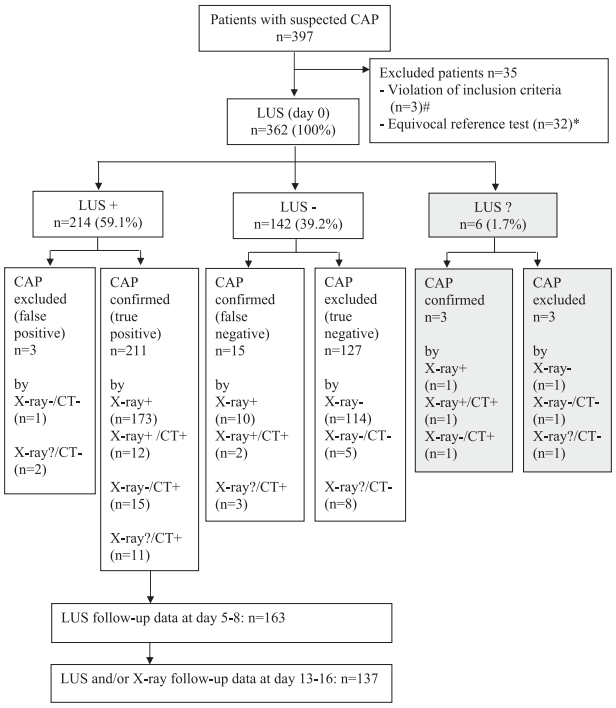

FIGURE 1. Flowchart. #Indicates prior systemic antibiotic therapy (n = 2) and severe immunosuppression (n = 1). *Indicates CT imaging not performed (n = 11), an inconclusive CT scan (n = 10), CT imaging not performed within 24 h (n = 4), > 24 h elapsed between LUS and radiograph (n = 2), inconclusive radiographic and LUS findings (n = 3), radiograph performed but not available (n = 1), and patient refusal of CT imaging (n = 1). CAP = community-acquired pneumonia; LUS = lung ultrasound; − = negative test results; + = positive test results; ? (gray shading) = equivocal test results.

confirmed by the reference test in 229 of 362 patients (63.3%) (Fig 1). The proportion of CAP by center varied between 26.7% and 100%. Follow-up examinations were carried out on patients with sonographically detected CAP between days 5 and 8 (n = 164) and days 13 and 16 (n = 137) (Fig 1).

Baseline Characteristics of the Patients

The patients had a median age of 63.8 years (range, 19-95 years), and men were slightly overrepresented (63.0%). Ninety-five percent were inpatients. The baseline characteristics of the patients are shown in Table 1.

Diagnostic Accuracy of LUS

At baseline, CAP was diagnosed with LUS in 214 patients (59.1%); 142 patients (39.2%) had negative findings, and six patients (1.7%) had equivocal findings (Fig 1, Table 2). Excluding patients with equivocal results, pneumonia was correctly diagnosed with LUS in 211 of 226 patients with confirmed CAP, resulting in a sensitivity of 93.4% (95% CI, 89.2%-96.3%). No signs of pneumonia were found in 127 of 130 patients without CAP, resulting in a specificity of 97.7% (95% CI, 89.2%-96.3%). The LR for negative and positive LUS findings were 0.07 (95% CI, 0.04-0.11) and 40.46 (95% CI, 12.21-123.87), respectively. For the exploration of robustness, patients with equivocal LUS were included in the calculation as a third category. Sensitivity and specificity were marginally reduced to 92.1% (95% CI, 87.8%- 95.3%) and 95.5% (95% CI, 90.4%-98.4%), respectively.

Auscultation typical for CAP was 3.2 times more likely in patients with CAP than in those without CAP (Table 1). A combination of auscultation and LUS findings increased the positive LR to 42.9 (95% CI, 10.8-170.0) and decreased the negative LR to 0.04 (95% CI, 0.02-0.09).

In comparison with LUS, radiography alone revealed 199 positive (55.0%), 138 negative (38.1%), and 25 equivocal (6.9%) findings (Table 2). In patients with unequivocal radiographic results, pneumonia was correctly diagnosed on radiograph in 199 of 215 patients with CAP (92.6%) and correctly ruled out in 122 patients (100%). Because radiographic findings played a part in the final diagnosis, these figures should not be interpreted as sensitivity and specificity. However, in comparing LUS to radiographic findings, 26 cases of LUS-detected CAP were missed

Table 1—*Baseline Characteristics of Patients (Day 0)*

Characteristic	Patients With Pneumonia (n = 229)	Patients Without Pneumonia (n = 133)
Age, y	61.2 (19-91)	65.7 (20-95)
Male sex	133 (58.1)	95 (71.4)
Inpatients	222 (96.9)	122 (91.7)
Symptoms		
Fever	178/227 (78.4)	61/132 (46.2)
Cough	207/228 (90.8)	121/133 (91.0)
Purulent expectoration	119/227 (52.4)	60/133 (45.1)
Dyspnea	159/226 (70.4)	101/132 (76.5)
Thoracic pain	115/212 (54.2)	61/130 (46.9)
Auscultation typical for CAP	158/222 (71.2)	29/129 (22.5)
Duration of symptoms, d	3 (1-30)	4 (1-28)
Comorbidity and risk factors		
COPD	45 (19.7)	61 (45.9)
Pulmonary embolism	5 (2.2)	11 (8.3)
Bronchial carcinoma	4 (1.7)	5 (3.8)
Diabetes mellitus	29 (12.7)	27 (20.3)
Cardiac failure	42 (18.3)	39 (29.3)
Alcohol abuse	17 (7.4)	4 (3.0)
Nicotine abuse	84 (36.7)	44 (31.1)
Aspiration	3 (1.3)	7 (5.3)
Other risk factors	24 (10.5)	37 (27.8)
Laboratory findings, median (IQR)		
C-reactive protein, mg/dL	144 (76.0-229.0)	42.7 (13.7-113.8)
Leukocytes, $\times 10^9$/L	11.7 (8.8-15.2)	9.3 (7.5-12.9)

Data are presented as median (range), n/N (%), and No. (%), unless otherwise indicated. CAP = community-acquired pneumonia; IQR = interquartile range.

Table 2—*Baseline LUS and Radiographic Findings by Final Diagnosis of Pneumonia*

	Patients With Pneumonia				Patients Without Pneumonia			
No.	Radiograph+	Radiograph−	Radiograph?	Total No. (%)	Radiograph+	Radiograph−	Radiograph?	Total No. (%)
LUS+	185	15	11	211 (92.1)	0	1	2	3 (2.3)
LUS−	12	0	3	15 (6.6)	0	119	8	127 (95.4)
LUS?	2	1	0	3 (1.3)	0	2	1	3 (2.3)
Total	199	16	14	229 (100.0)	0	122	11	133 (100.0)

Pneumonia was confirmed by positive radiographic findings or in case of equivocal or negative radiographic and positive LUS findings by positive CT scan findings. LUS = lung ultrasound; − = negative test results; + = positive test results; ? = equivocal test results.

or equivocal by radiograph, whereas radiography detected 14 cases of CAP that were missed by LUS.

Sonomorphology of CAP at Baseline and During Follow-up

Patients with sonographically detected and confirmed pneumonia (n = 211) showed consolidations most frequently on the right side of the lungs (45.5%) and in 15.2%, on both sides of the lungs (Table 3); 22.6% of the patients had more than one lesion at baseline. The shape of the lesions was mostly polygonal (51.2%) or oval (46.3%) with blurred margins (76.5%). Median surface extension of the lesions at baseline was 3.2 cm (interquartile range, 1.7-5.0 cm), and depth was 3.7 cm (interquartile range, 2.2-5.7 cm). Nearly all (97.6%) consolidations revealed breath-dependent motion, 86.7% had an air bronchogram (Fig 2),

Table 3—*Clinical, Sonographic, and Laboratory Findings and Features at Baseline and During Follow-up in Patients With Sonographically Detected and Confirmed Pneumonia*

Clinical, Sonographic, and Laboratory Finding	Day 0 (n = 211)	Days 5-8 (n = 163)	Days 13-16 (n = 137)
No. symptoms[a] per patient	3 (1-5)	1 (0-5)	1 (0-4)
Auscultation typical for CAP	149/204 (73.0)	71/159 (44.7)	18/133 (13.5)
Patients with LUS-detected lesions	211/211 (100.0)	131/162 (80.9)	67/133 (50.4)
Location of pneumonic lesions			
On right side	96/211 (45.5)	59/131 (45.0)	33/67 (49.2)
On left side	83/211 (39.3)	54/131 (41.2)	27/67 (40.3)
On both sides	32/211 (15.2)	18/131 (13.7)	7/67 (10.4)
No. pneumonic lesions	1 (1-7)	1 (0-3)	1 (0-4)
Patients with > 1 lesion	50/211 (22.6)	26/131 (19.8)	11/67 (16.4)
Shape of the largest lesion			
Round	5/203 (2.5)	4/121 (3.3)	1/61 (1.6)
Oval	94/203 (46.3)	61/121 (50.4)	34/61 (54.1)
Polygonal	104/203 (51.2)	56/121 (46.3)	27/61 (44.3)
Margin of the largest lesion			
Sharp	48/204 (23.5)	25/121 (20.7)	11/60 (18.3)
Blurred	156/204 (76.5)	96/121 (79.3)	49/60 (81.7)
Total area of pneumonic lesions, cm^2	15.3 (6.6-36.3)	6.0[b] (1.5-17.1)	0.2[b] (0.0-6.0)
Further sonographical features			
Positive breath-dependent motion	205/210 (97.6)	129/131 (98.5)	65/66 (98.5)
Echopoor necrotic zones within the lesion	2/209 (1.0)	2/131 (1.5)	0/66 (0.0)
Positive air bronchogram	183/211 (86.7)	98/130 (75.4)	47/66 (71.2)
Positive fluid bronchogram	17/211 (8.1)	10/131 (7.6)	4/66 (6.1)
Evidence of local pleural effusion	89/210 (42.4)	57/153 (37.3)	21/99 (21.2)
Evidence of basal pleural effusion	105/193 (54.4)	66/149 (44.3)	28/119 (23.5)
On left side	67/193 (34.7)	44/149 (29.5)	16/119 (13.4)
On right side	69/191 (36.1)	43/149 (28.9)	17/119 (14.3)
Amount of basal pleural effusion, mL			
On left side	50 (30-200)	10 (0-100)[b]	0 (0-0)[b]
On right side	50 (20-150)	10 (0-80)[b]	0 (0-0)[b]
Laboratory findings			
C-reactive protein, mg/dL	137 (76-234)	Not done	6.3 (1.9-20.0)
Leukocytes, $\times 10^9$/L	11.7 (9.0-15.1)	Not done	7.4 (6.0-9.0)

Data are presented as median (range) for No. symptoms per patient and No. pneumonia lesions, n/N (%), or median (IQR). See Table 1 and 2 legends for expansion of abbreviations.

[a]Fever > 38.0°C, cough, purulent expectoration, dyspnea, and thoracic pain.

[b]Defined as zero if present at baseline and disappeared during follow-up.

and only 8.1% showed a fluid bronchogram. A basal pleural effusion was evident in 54.4% at baseline, with a median volume of 50 mL. During follow-up, the median number of symptoms per patient decreased from three to one, median C-reactive protein levels declined from 137 to 6.3 mg/dL, and leukocyte counts decreased from 11.7 to 7.4×10^9/L on days 13 to 16.

Disease remission could also be demonstrated sonographically. The proportion of patients with an air bronchogram decreased from 86.7% to 71.2%

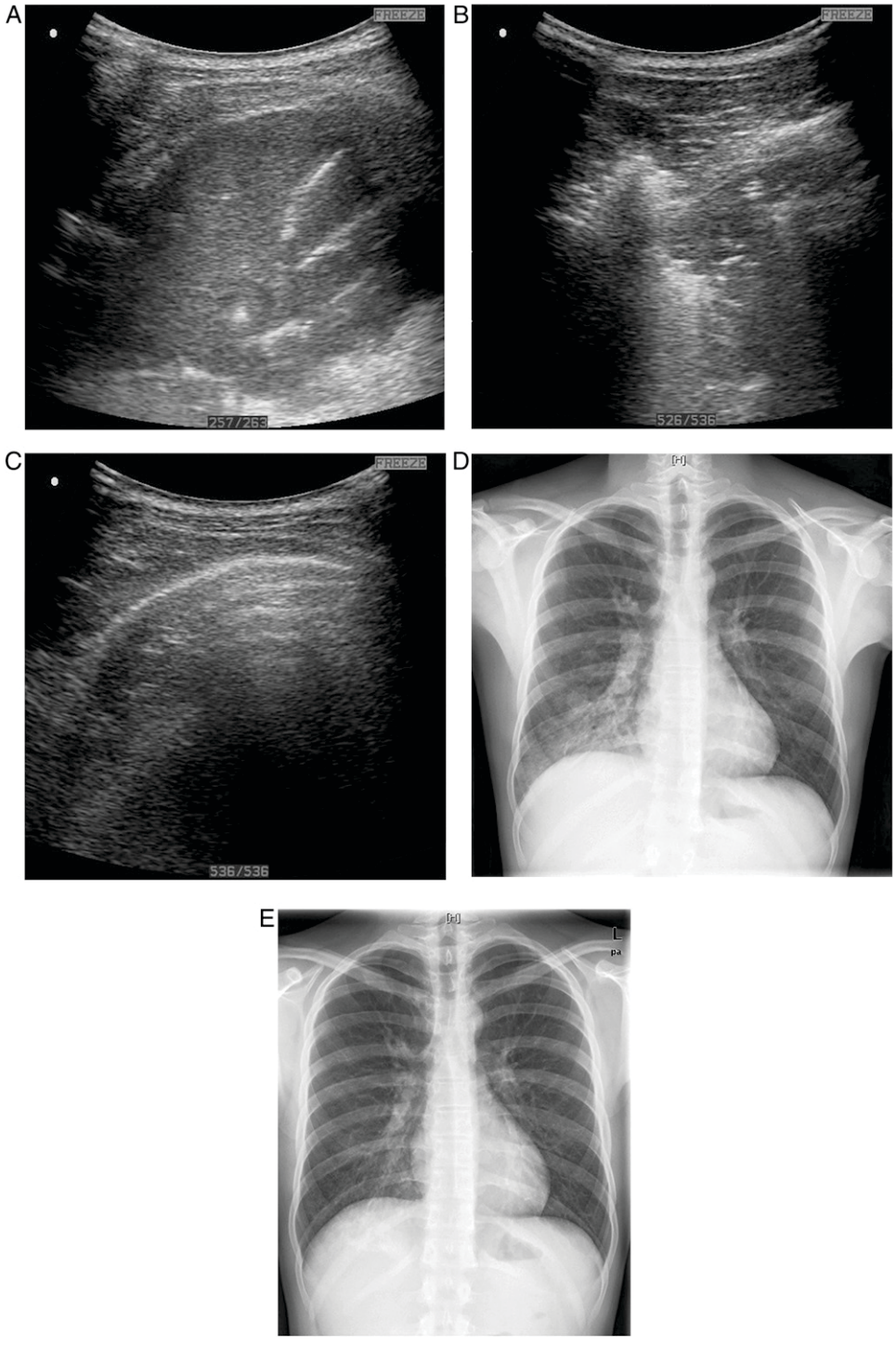

FIGURE 2. Patient with pneumonia caused by *Mycoplasma pneumoniae*. A, Positive air bronchogram reflecting pneumonia on day 0. B, Positive air bronchogram reflecting pneumonia on day 6. C, LUS showing no lesion on day 15. D, Radiograph showing infiltration in the right lower lobe on day 0. E, Radiograph showing postpneumonic residua on day 15. See Figure 1 legend for expansion of abbreviation.

(47 of 66), the area of pneumonic lesions decreased from 15.3 cm^2 to 6.0 cm^2 to 0.2 cm^2, and the median volume of pleural effusion decreased from 50 mL to 0 mL on days 13 to 15 compared with baseline (Table 3). Pneumonic lesions appeared sonographically smaller compared with radiograph. In patients with only one lesion, the measured craniocaudal and ventrodorsal extensions differed, on average, by 1.1 cm and 1.4 cm, respectively. Bigger lesions showed a greater difference.

Concordance Between LUS and Radiographic Findings During Follow-up

In 112 patients with CAP correctly diagnosed with LUS and radiograph at baseline, both examinations were repeated between days 13 and 16. Concordant results were observed in 85 patients (75.6%) (35 negative, 48 positive, two equivocal). Eleven cases of CAP were still diagnosed with LUS but not radiograph. Vice versa, nine cases of CAP were detected by radiograph but were missed by LUS. Seven patients with equivocal radiographic findings had negative results on LUS. A κ of 0.57 (95% CI, 0.43-0.70) was estimated.

Discussion

To our knowledge, this is the first prospective multicenter study dealing with the use of LUS in the diagnosis and follow-up of CAP. These results show an excellent sensitivity of 94% and specificity of 98%, comparable with chest radiograph in two planes. LR >10 and <0.01 are considered to rule in or rule out diagnosis in most circumstances.[12] Combining typical auscultation and positive LUS findings was about 43 times more likely in patients with CAP and provides strong evidence to rule in the disease. Double negative findings were 0.04 times less likely in patients with CAP, which may be used to rule out CAP. These figures refer to patients with clear LUS findings. Patients with equivocal results need to undergo further diagnostic procedures. This applied to 1.7% of patients after LUS and 6.9% after radiograph. However, comparing radiographic and LUS findings in the diagnosis of CAP, it should be mentioned that the chest radiograph missed or was inconclusive in about 7% of the cases detected by LUS.

In about 8% of patients, CAP may not be detected by LUS because ultrasound may only detect lesions reaching the pleura. This is in good accordance with two current studies.[3,13] In the first study, six of 82 patients (7%) did not show subpleural alterations.[3] In the second study, patients with primarily radiograph-confirmed CAP underwent LUS; 28 of 342 patients (8%) had negative LUS and positive radiographic findings.[13] Parlamento et al[14] found only one of 32 patients (3%) with negative ultrasonography and positive radiographic findings. Nevertheless, in the present study, only 66% of the patients underwent radiography in two planes. Another study in children[15] who underwent radiography in one plane also showed a high rate of positive LUS findings. In the present study, CAP was confirmed in about two-thirds of patients, as in the study by Parlamento et al.[14]

CAP was characterized by echopoor lesions with breath-dependent motion, evidence of air bronchogram in about 87%, blurred margins in 75%, and basal effusion in one-half of the patients. In other studies, air bronchogram was detectable in about 70% to 97%,[3,13,16] and a basal effusion was reported in 34% to 61%.[3,13,14,16]

The three false-positive LUS results were retrospectively reviewed and confirmed as false-positive LUS findings. A fluid bronchogram was identified in 17 patients only. This sign reflects airways filled with fluid or secretions following airway obstruction. Differential diagnosis of lung carcinoma should be taken into account in these cases. In only one patient with fluid bronchogram, a lung carcinoma was diagnosed 3 months later.

Necrotic areas within pneumonic lesions were found in only two patients. These echopoor zones within pneumonic infiltrates reflect microabscesses. One patient with microabscess developed empyema. In the other patient, pneumonia showed a complete recovery under antibiotic therapy.

Comparing size of pneumonic lesions on radiograph and LUS, infiltrates were smaller in LUS because sonography can only detect areas directly contacting the pleura. If the lesion becomes broader in central pulmonary regions, it escapes sonographic detection. This finding is in agreement with a study in clinically and radiologically confirmed pneumonia, where the extension of lesions measured sonographically seemed to be smaller than those seen on radiograph in 53 cases (41%).[16]

The present study has several limitations. First, with radiography in two planes, an imperfect reference test was applied to 83% of patients, probably resulting in an overestimated accuracy of LUS. It is possible that small pneumonic infiltrates may escape detection because only 17% of patients underwent CT imaging as the approved gold standard. CT imaging was restricted for ethical as well as financial reasons and with respect to radiation exposure to cases with positive LUS and negative or equivocal radiographic findings. Nevertheless, even in patients with negative LUS and positive radiographic findings, a CT scan would have been preferable. Second, the study was restricted to untreated patients with suspicion of CAP. Patients experiencing hospital-acquired pneumonia and immunodeficiency were excluded because

it is assumed that sonomorphology in these cases may differ. Therefore, these conclusions exclusively refer to CAP. Third, most of the patients were inpatients with CAP. However, it is assumed that the results are comparable to outpatients. Fourth, the investigations were performed in a multicenter setting. Participating investigators had done at least 100 chest ultrasonography procedures. Therefore, the results reflect daily routine practice in experienced hands. Nevertheless, LUS represents a technique with a steep learning curve. Finally, in five centers contributing $\geq$23 patients per center, the prevalence of CAP varied substantially between 39% and 100%. Therefore, predictive values were not reported for the study. They could be calculated for any prevalence from LRs. Furthermore, in centers with small numbers of patients, LUS performed perfectly, which in principle would be expected for methods with high accuracy. However, selection bias could not be ruled out. Excluding those centers with perfect LUS-based diagnoses and small sample sizes, sensitivity changed to 90.8% (95% CI, 85.2%-94.8%) and specificity to 97.4% (95% CI, 92.5%-99.5%).

Conclusions

To our knowledge, this is the first multicenter feasibility study to demonstrate that CAP may be diagnosed and followed up with LUS. The results show an excellent sensitivity and specificity at least comparable with chest radiograph in two planes. In cases with sonographic evidence of pneumonia, the diagnosis can be established. A radiograph or CT scan of the chest is necessary in cases with negative ultrasound results (in about 8% of the patients), if other differential diagnoses are taken into account or if complications occur. LUS offers several different applications, especially if a chest radiograph is not available (in point-of-care ultrasonography, in emergency conditions, on airplanes, in rural regions, in resource-limited settings, in developing countries, in pregnant women, and even in a general practitioner practice) and in immobilized patients in whom only a radiograph in one plane may be taken. Sonographic diagnosis of pneumonia and LUS follow-up allows for rapid therapeutic decisions.

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