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RESEARCH ARTICLE

Ultrasound Studies on Mycoplasma Bronchopneumonia

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Abstract

Backround Pediatric bronchopneumonia represents a clinical challenge, especially when it comes to the identification of its etiology**.**

Working Hypothesis: We performed a retrospective study on 100 patients admitted to our Pediatric Department. Only patients with bronchopneumonic thickening were selected, discharged with a diagnosis of Community - Acquired Pneumonia (CAP) or bronchopneumonia. The purpose of our study was to identify Mycoplasma Pneumonia based on lung ultrasound (LUS) findings.

Methodology: At least two lung LUS were performed on each patient: on admission and few days after start of therapy, with most patients undergoing a third ultrasound evaluation approximately one week after discharge. These reports were collected for each patient together with clinical and laboratory data. The study population was divided into two groups: patients who tested positive for Mycoplasma pneumoniae (Myc-CAP) and negative ones (non-Myc-CAP). All patients performed serological test for determination of anti-mycoplasma antibodies, and in doubtful cases also molecular test with PCR on pharyngeal exudate.

Results: The results obtained after statistical analysis showed no significant differences in LUS findings between the two groups that could allow a positive differential diagnosis of Myc-CAP without resorting to laboratory testing.

Conclusions: LUS undoubtedly represents a valid and irreplaceable help in the morphological study of pulmonary lesions over the course of disease from the time of admission to follow-up.

Introduction:

Pathologies of respiratory system represent one of the most frequent causes of hospitalization among children. CAP is defined as an acute infection of the lower airways in children who have not resided in a hospital or health care facility in the 14 days preceding the onset of symptoms[1]. CAP is the most important cause of mortality among preschool children in developing countries, while in industrialized countries it imposes a significant burden of morbidity, with an estimated annual incidence of 14.5 per 10,000 children up to 16 years of age[2]. Its etiology can be viral, bacterial (typical or atypical), fungal, parasitic or polymicrobial. In addition, viral CAP is often complicated by bacterial superinfections. Respiratory viruses are the most frequent cause of CAP in preschool years, followed by typical (Streptococcus pneumoniae) and atypical bacteria (Mycoplasma pneumoniae and Chlamydia pneumoniae), which are instead the predominant cause among school-age children. Identifying etiology is necessary to properly manage these patients, however the microbial diagnosis of CAP often requires invasive procedures, due to the overlapping clinical features of bacterial, atypical or viral pneumonia[3]**.** Chest x-ray (CXR), considered until a few years ago the gold standard for the diagnosis of pneumonia, has seen its role progressively reduced[4]. Moreover, even though some radiological findings could be considered pathognomonic to identify the nature of pneumonia[5], no finding can on its own predict reliably its etiology[6]. LUS has been employed in clinical practice for over 20 years now, and it is a fairly sensitive and specific tool for the diagnosis of pneumonia especially in children, whose anatomical features including a thinner chest wall and a smaller surface to be examined, make them the ideal candidate for the procedure[7]. This technique has several advantages compared to conventional chest radiography: it doesn't require Ionizing radiation, it has lower costs, it is more convenient during follow up and/or to monitor the effects of therapy as it can be performed right at patient's bedside. Furthermore, it is fast and easy to learn and, in expert hands, it has good diagnostic accuracy. LUS allows to identify a number of typical pneumonia lesions including alveolar consolidations, pleural effusion and interstitial disease. Alveolar consolidations, which represent non-ventilated areas of the lung parenchyma are hypoechoic and have a tissue-like appearance on LUS. The echographic hallmarks of pneumonia are represented by branched, hyperechoic and dynamic air bronchograms which are often detected in consolidation foci. Fluid bronchograms can also be found, but they are rarely seen in absence of air bronchograms in pediatric CAP[8]. LUS has been used to identify bacterial superinfections in patients with viral lower airways disease. Such studies have described small subpleural consolidations with or without an increase in the number of B lines (interstitial syndrome) as features of viral pneumonia, even though similar findings are commonly found in viral bronchiolitis[9]. Urbankowska[10] has described a positive correlation between the size of consolidations detected on ultrasound and neutrophils count on peripheral blood, which would imply an association between larger consolidation foci and bacterial CAP. The 2019 Vojko[11] study was the first to highlight the usefulness of ultrasounds in the diagnosis of CAP in children, finding a correspondence between echographic features and etiology. In particular the study found that areas of consolidation in bacterial pneumonia are more commonly solitary, larger and unilateral than those found in viral and atypical bacterial CAPs, in which multiple, smaller and often bilateral consolidations generally prevail. Antibiotic therapy of CAP is often empirical and influenced by epidemiological, clinical, laboratory and radiographic findings. Current guidelines recommend the use of a penicillin-class antibiotic as first-line therapy for uncomplicated typical bacterial CAP, while macrolides should be used for atypical pneumonia[12]. Children with uncomplicated forms of viral CAP only require supportive treatment.

Objective of the study

The idea to conduct this study came from daily practice, particularly from the challenge to recognize among all forms of pneumonia, those due to Mycoplasma only by ultrasound images. This study had two main objectives: 1) to establish whether, based on LUS findings alone, it could be possible to reliably predict the

etiology of CAP in pediatric patients [13] ; 2) to evaluate the role of LUS as a follow-up tool in patients recovering from CAP, to better monitor response to therapy and to more accurately establish prognosis.

Study design

We conducted a retrospective study drawing data from medical records of a group of patients admitted to our pediatric hospital operating unit in the period between 1st December 2018 and 31st January 2020. Only those with a discharge diagnosis of "pneumonia" and "bronchopneumonia" were selected. All children underwent pulmonary ultrasounds on admission, during hospitalization and post-discharge. Pneumonia was diagnosed with lung ultrasounds or chest radiography. For each patient, the following data were collected and tabulated: gender, age, length of hospitalization and discharge date, signs, symptoms (dyspnea, cough and fever), LUS findings on admission, during antibiotic therapy and after discharge, administered therapy, serology and/or real-time PCR for Mycoplasma pneumoniae (Fig. 1). No other available microbiological tests (viral swabs, blood cultures) have been considered.

Methods

The study included 100 children with CAP, 44 boys and 56 girls (median age 4 years and 10 months, ranging between 2 months and 15 years) 40% of whom tested positive and 60% tested negative for anti-Mycoplasma IgM. All patients underwent a first LUS within the first 24 hours of hospitalization, a second one after 3-4 days from the start of antibiotic therapy ("ad-interim" LUS) and a third one at the end of therapy[14]. Follow –up of CAP was performed exclusively by LUS. Chest radiographs were not taken into consideration, as they were performed only in 15% of patients and during night shifts or holidays, in the absence of ultrasound operators. Patients were stratified into two different groups based on molecular testing results (Fig. 2). Patients positive for anti-Mycoplasma IgG and IgM were included in the Mycoplasma-CAP group, all other subjects were included in the non-Mycoplasma CAP group (Bacterial/Viral CAPs). In all children with positive serology for Mycoplasma, and in those for whom there was a strong clinical suspicion despite a negative serology, pharyngeal swabs were performed, for the direct detection of Mycoplasma DNA using Polymerase Chain Reaction (PCR). These biological samples were sent and processed in the Virology laboratory belonging to University of Bari. Coronavirus infection was not considered among the differential diagnoses because the subjects were all admitted before February 2020.

Ultrasound examination

All ultrasound examinations were performed with the same GE Logiq 5 device with a 7-12 MHz linear probe. In patients with a thicker chest wall, a 2-5 MHz convex probe was used. The execution technique involved longitudinal and transverse scans of the anterior, lateral and posterior pulmonary fields, taken with the patient in supine, prone and lateral decubitus positions, depending on the area to be examined[15]. Patients were then stratified, based on ultrasound findings into the following groups: no injuries detected; presence of single or multiple consolidation foci with or without air bronchograms; presence of thickened B lines (sign of interstitial disease); mixed alveolar-interstitial involvement; pleural effusion[16]. All patients underwent a second LUS scan ("Ad interim" LUS: i-LUS), to evaluate the evolution of lesions after starting antibiotic therapy. Regression, progression, complete remission or stationary disease were defined based on variation in size and number of the lesions detected on admission. Three outcomes were described based on end of therapy LUS (eot-LUS): stationary disease, residual disease and complete remission, based on the same criteria indicated above. Examinations were performed by four different operators, all trained in lung ultrasound, who alternated according to duty shifts.

Statistical analysis

Statistical analysis was performed using the Vassar Stats: Statistical Computation Website (Poughkeepsie, New York, USA)[17] and the MedCalc software package, version 19. 2. 1 (MedCalc, Ostend,

Belgium)[18]. Continuous variables were expressed as mean or as median with interquartile range (IQR) as appropriate. The categorical variables were presented as absolute frequencies and percentages. Diagnostic reliability of clinical and ultrasound features in discriminating between Mycoplasma-CAP and non-Mycoplasma CAP was assessed by calculating positive predictive values (PPV) and negative predictive values (NPV). Correlation between CAP etiology and clinical and ultrasound qualitative variables was analyzed using the Fisher Exact test or the Chi-square test. Logistic regression was instead used to assess the impact of age on the size of lung lesions. All *p* values were calculated using a two-tailed test, a $p < 0.05$ was judged statistically significant.

COMPARISON OF LUS FINDINGS ON ADMISSION: *MYC-CAP* VS *Non-MYC-CAP*

I LUS

Finding	n° (% of Mycoplasma CAP subjects)	n° (% of non-Mycoplasma CAP subjects)	p value	Odds ratio (95% CI)	PPV	NPV
Single consolidation	30 (75%)	47 (78%)	0,809	0,83 (0,32-2,13)	39%	57%
Multiple consolidations (≥ 2)	4 (10%)	8 (13%)	0,758	0,72 (0,20-2,58)	33%	59%
Interstitiopathy	13 (33%)	18 (30%)	0,828	1,12 (0,47-2,66)	42%	61%
Pleural effusion	6 (15%)	11 (18%)	0,789	0,79 (0,26-2,33)	35%	59%
Larger consolidation	31 (78%)	47 (78%)	1,00	0,95 (0,36-2,50)	40%	59%
Focal consolidation	5 (13%)	11 (18%)	0,580	0,64 (0,20-2,00)	31%	58%

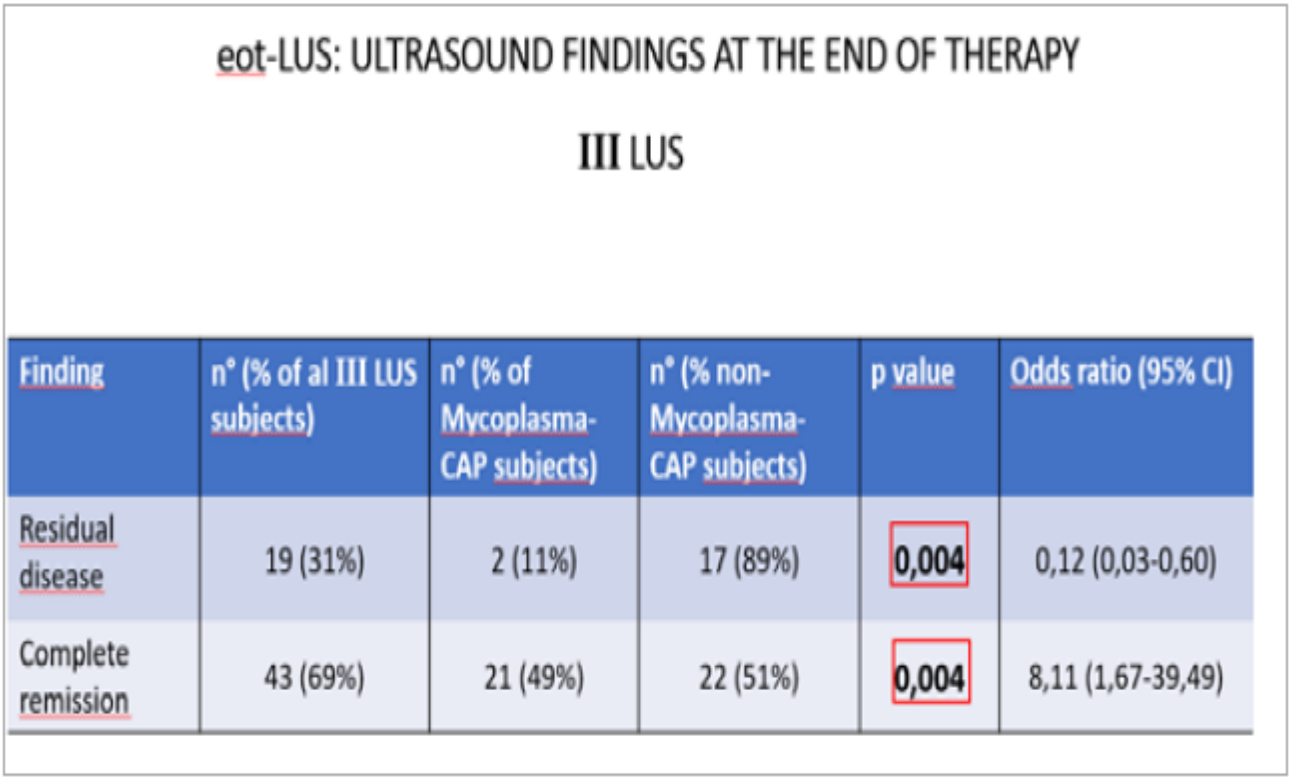
Table 1. Comparison of ultrasound findings detected on admission in the two groups. Frequency of each finding is reported for each group; p values were not significant for all items, thus there is no ecographic feature which would allow to discriminate between Mycoplasma-CAP and non-Mycoplasma CAP.

i-LUS: ULTRASOUND FINDINGS DURING THERAPY

II LUS

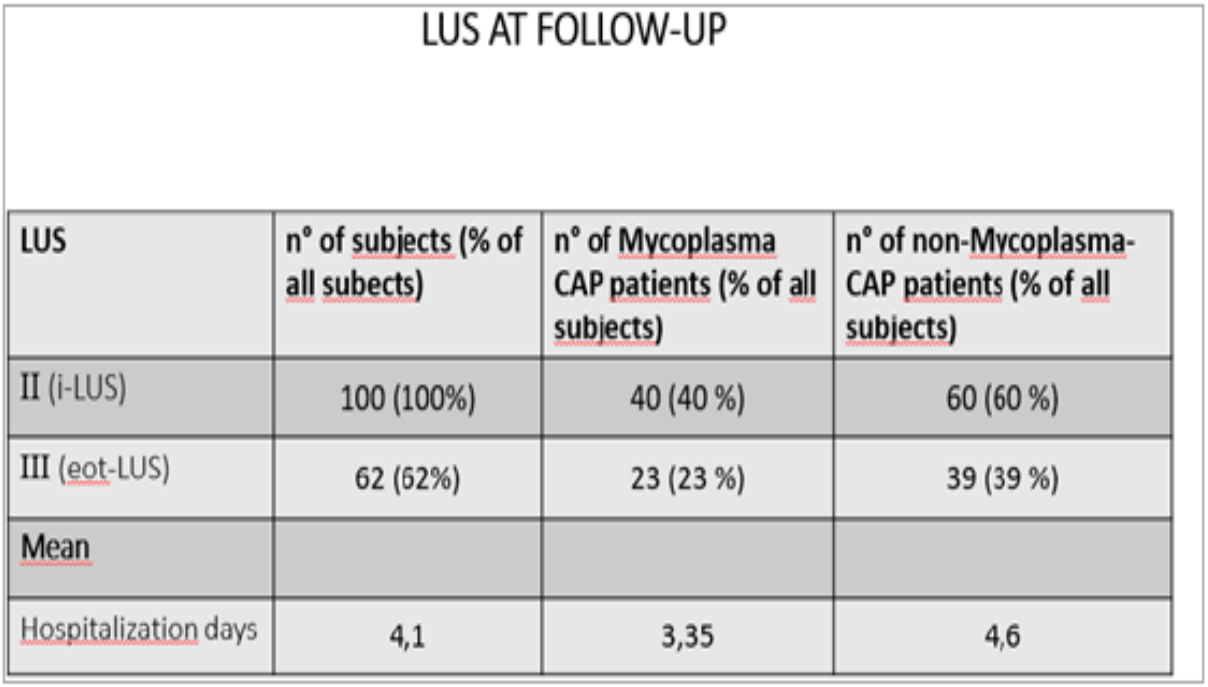
Findings	n° (% of pts who underwent II LUS)	n° (% of all Mycoplasma CAP-patients)	n° (% of all non-Mycoplasma-CAP subjects)	p value	Odds ratio (95% CI)
Progression	4 (4%)	3 (75%)	1 (25%)	0,299	4,78 (0,48-47,28)
Stable disease	3 (3%)	1 (33%)	2 (67%)	1	0,74 (0,07-8,49)
Regression	86 (86%)	32 (37%)	54 (63%)	0,239	0,44 (0,14-1,40)
Complete remission	7 (7%)	4 (57%)	3 (43%)	0,433	2,11 (0,45-9,99)

Table 2. Comparison of ultrasound findings on the "ad-interim" examination in the two groups. The following patterns of disease evolution were described: progression, stable disease, consolidation regression, complete remission. The table shows the frequencies of each pattern in the two groups; p values and Odds ratios are reported for each comparison. No correlation was found between findings oni-LUS and the microbial etiology of pneumonia.



Finding	n° (% of al III LUS subjects)	n° (% of Mycoplasma-CAP subjects)	n° (% non-Mycoplasma-CAP subjects)	p value	Odds ratio (95% CI)
Residual disease	19 (31%)	2 (11%)	17 (89%)	0,004	0,12 (0,03-0,60)
Complete remission	43 (69%)	21 (49%)	22 (51%)	0,004	8,11 (1,67-39,49)

Table 3. Comparison of LUS findings on the third examination ("eot-LUS") in the two groups. Two outcomes were described for each group: "Residual disease" and "Complete remission". The frequency of each outcome in the two groups is reported. A statistically significant difference emerges between the two groups (p = 0. 04): non-Mycoplasma-CAP shows slower resolution of lung consolidations compared to Mycoplasma-CAP.eot-LUS: end of therapy lung ultrasound; 95% CI: 95%.



LUS	n° of subjects (% of all subects)	n° of Mycoplasma CAP patients (% of all subjects)	n° of non-Mycoplasma-CAP patients (% of all subjects)
II (i-LUS)	100 (100%)	40 (40 %)	60 (60 %)
III (eot-LUS)	62 (62%)	23 (23 %)	39 (39 %)
Mean			
Hospitalization days	4,1	3,35	4,6

Table 4. All patients underwent LUS on admission and during therapy. 62% of patients also underwent a third LUS after discharge (eot-LUS). The table also shows the average length of hospitalization in the two groups of patients.

Antibiotic regimen	n°of Mycoplasma CAP patients (% of all Mycoplasma-CAP subjects)	n°of non-Mycoplasma CAP patients (% of all non-Mycoplasma-CAP subjects)
Clarithromycin	3 (8%)	1 (2%)
Amoxicillin + Clavulanic Acid	1 (2%)	2 (3%)
Ceftriaxone	0 (0%)	5 (8%)
Association therapy (macrolide + β-lactam/cephalosporin)	36 (90%)	52 (87%)
Total	40	60

Table 5. The table shows the antibiotic regimens in the two groups of patients with relative frequencies.

AGE	Total number of subjects	n° of focal consolidation	n° of larger consolidation	p value	Odds ratio (95% CI)
Mycoplasma CAP	34	9 (26,47%)	25 (73,53%)	0,2830	0,90 (0,73-1,10)
Non-Mycoplasma CAP	58	23 (39,66%)	35 (60,34%)	0,8731	1,01 (0,86-1,19)

CORRELATION BETWEEN AGE AND SIZE OF LUNG CONSOLIDATIONS

Table 6. Univariate analysis of the effects of age on size of lesions detected in the two groups. The table shows the relationship between age (independent variable) and the size of lesions (dependent variable). No significant correlation was found (p not significant) in either of the two groups.

LINICAL FINDINGS IN PNEUMONIA CAUSED BY DIFFERENT AGENTS

Finding	n°/total cases	Mycoplasma CAP	Non-mycoplasma CAP	p value	Odds ratio (95% CI)	PPV	NPV
Fever	89	37 (42%)	52 (58%)	0,52	1,90 (0,47-7,64)	42%	73%
Dyspnea	27	10 (37%)	17 (63%)	0,82	0,84 (0,34-2,09)	37%	59%
Cough	90	36 (40%)	54 (60%)	1,00	1,00 (0,26-3,79)	40%	60%
Rhonchi	18	6 (33%)	12 (67%)	0,603	0,71 (0,24-2,67)	33%	59%
Rales	56	24 (43%)	32 (57%)	0,543	1,31 (0,58-2,95)	43%	64%
Wheezing	8	2 (25%)	6 (75%)	0,471	0,47 (0,09-2,47)	25%	59%
Diminished breath sounds	16	10 (63%)	6 (37%)	**0,045**	3,00 (0,99-9,07)	63%	64%
Normal findings	17	4 (24%)	13 (76%)	0,18	2,49 (0,75-8,28)	24%	57%
Total							
Number of subjects	100	40 (40%)	60 (60%)				
Males	44	21 (48%)	23 (52%)				
Females	56	19 (34%)	37 (66%)				
Median [IQR]							
Age (years)	4,8 [5,3]	5,6 [6,8]	3,7 [3,6]				

Figure 1. Frequency of clinical findings at onset in the two groups. For each comparison, p value and Odds ratio are reported. PPVs and NPVs were calculated for each item.

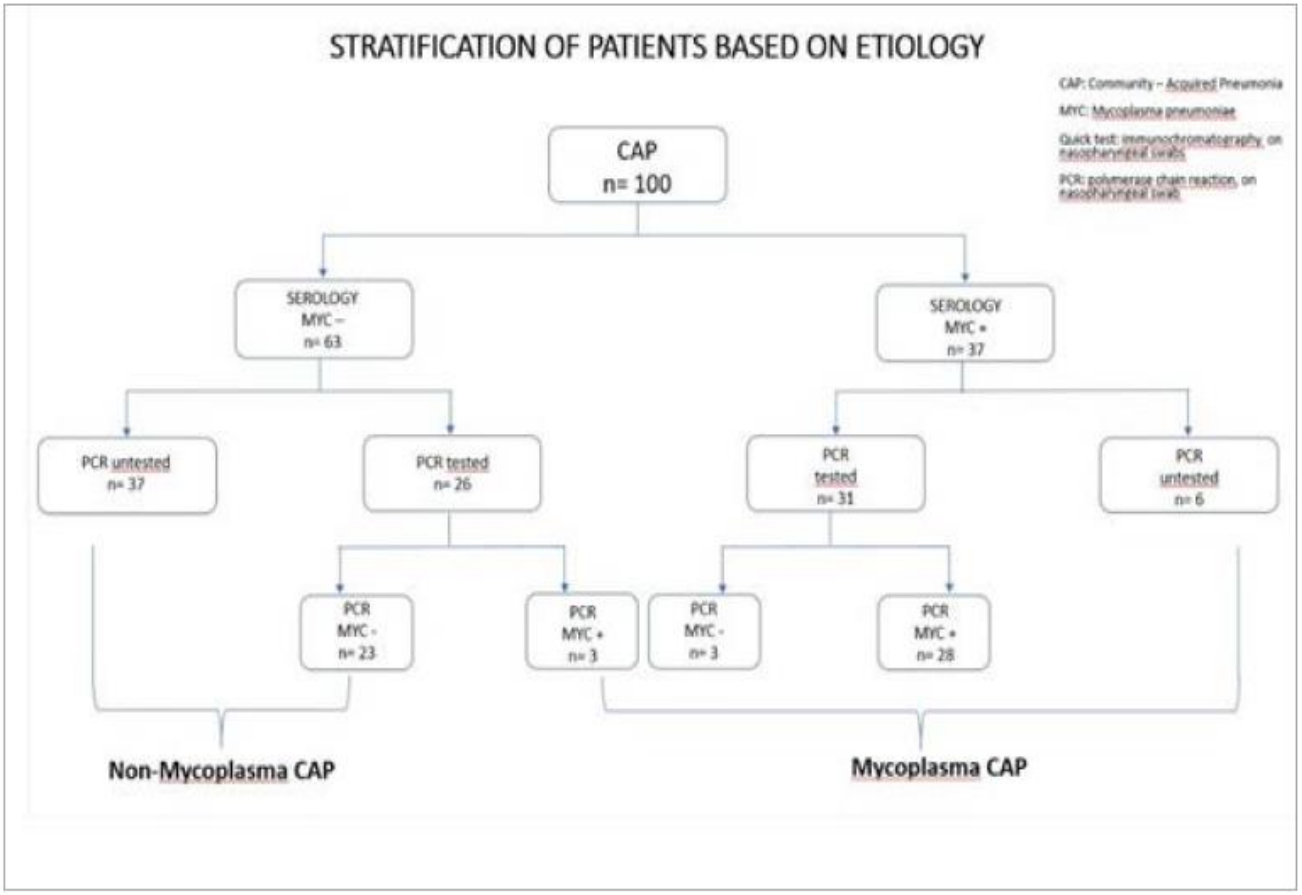


Figure 2. Laboratory diagnosis of pneumonia by serology and PCR. PCR confirmatory testing was performed on all patients with a positive serology and on some patient with negative serology, but with a strong clinical suspicion for Mycoplasma-CAP. On the basis of laboratory results, patients were divided into two groups: Mycoplasma CAP and non-Mycoplasma CAP.

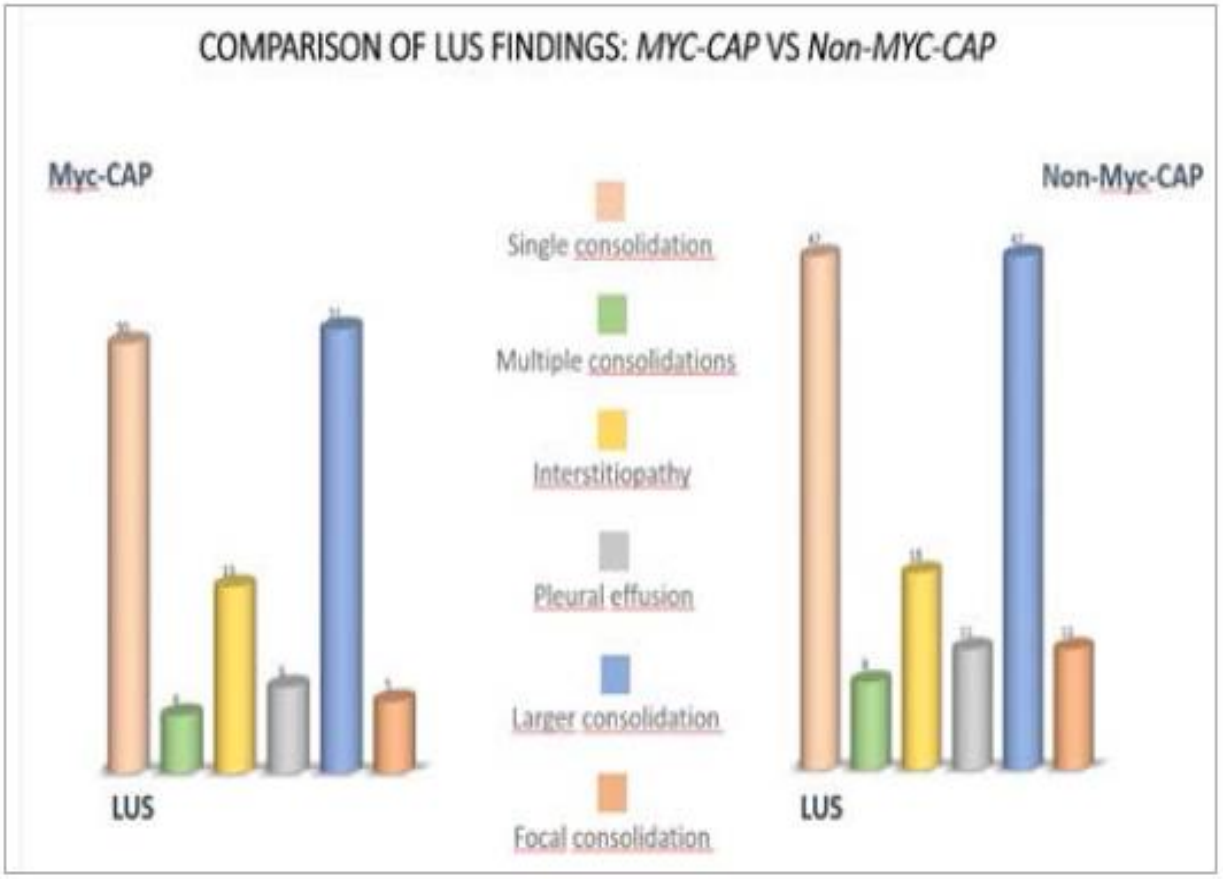


Figure 3. Frequency of ultrasound findings in the two groups. The two graphs show a similar distribution of LUS features.

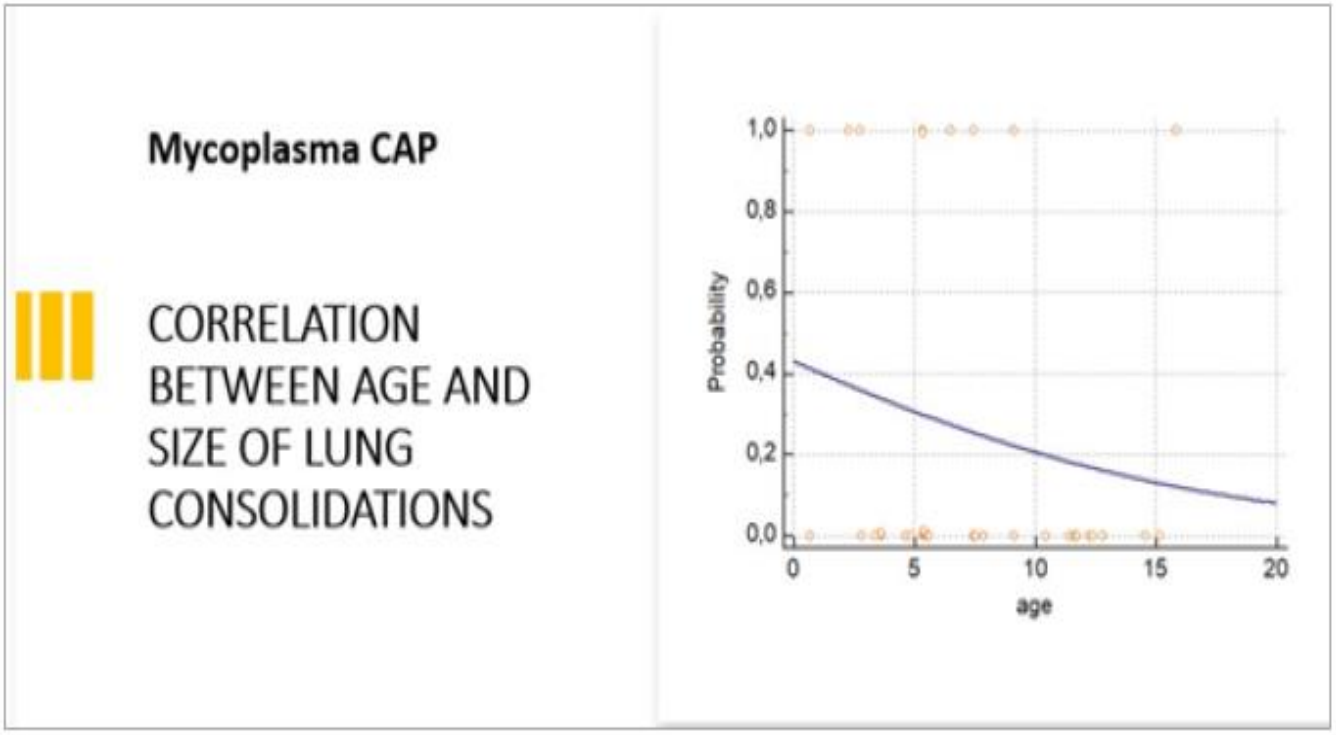


Figure 4. Logistic regression curve representing the correlation between age of patients and the probability of detecting a small lesion (less than one centimeter) in the Mycoplasma CAP. Increasing age, appeared to increase the likelihood of finding a small lesion however this was not significant (p = 0. 2830).

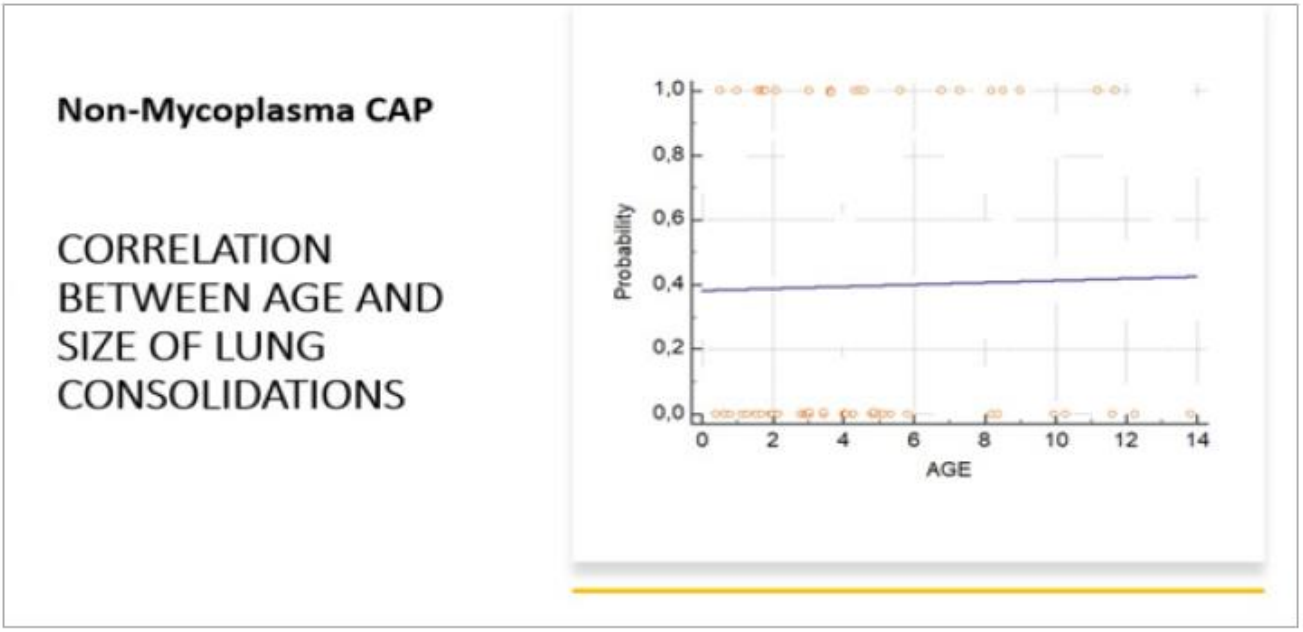


Figure 5. Logistic regression representing the correlation between age and the probability of detecting a small lesion in the non-Mycoplasma CAP. It appears that as age increases, the probability of detecting a small lesion increases slightly, contrary to what was expected. This trend, however, is not statistically significant (p = 0. 8731).

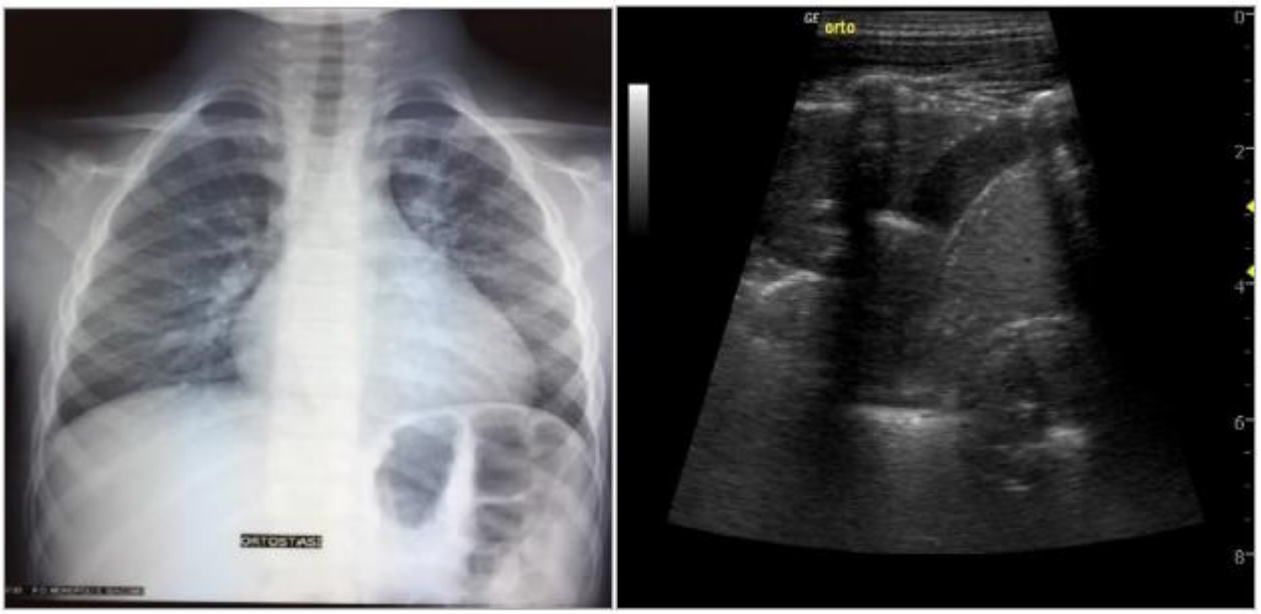


Figure 6. Chest X-ray and LUS of a 5-year-old patient with Mycoplasma-positive CAP with pleural effusion. Pulmonary ultrasounds were performed 24 hours after the chest X-ray. It highlights both the lesion and the pleural effusion, which were not visible on the x-ray film

Results:

The study population was composed of 100 pediatric patients, all suffering from CAP. Of these patients, 40/100 were positive to Mycoplasma pneumonia and 60/100 had a non-Mycoplasma CAP. In all those with positive anti-Mycoplasma IgM, the search for Mycoplasma was confirmed by PCR in all cases.

The prevalence of clinical symptoms at onset is shown in Fig. 1. The most frequent symptoms were represented by cough (90%) and fever (89%) both of which occurred with a slightly greater frequency among patients with non-Mycoplasma pneumonia (respectively 60% vs 40% for cough and 58% vs 42% for fever, in the two different groups). The prevalent finding on clinical examination was represented by

rales (56%), which were almost evenly distributed in the two groups.There was no statistically significant difference in the modality of clinical presentation between the two groups, as shown by a *p*-value well above the threshold value of significance. The only exception to this was the reduction of breath sounds (vesicular murmur) which was significantly more common among patients with Mycoplasma CAP (p = 0.045).

All enrolled children underwent LUS within 24 hours from admission to confirm the clinical suspicion of pneumonia. Ultrasounds showed signs of pneumonia in 99/100 patients. In one patient no lesions were detected at LUS, despite testing positive for Mycoplasma antibodies, probably because LUS was not performed immediately on admission due to the temporary absence of qualified operators. The different clinical pictures found in the first LUS are shown in Table 1. The distribution of ultrasound lesions was almost identical across the two groups (Fig.3). The lesion most commonly detected in both groups was a large (78% of patients in both groups), single (75% of Mycoplasma CAP patients vs 78% of non-Mycoplasma CAP patients) consolidation focus, followed by interstitial disease (33% for Mycoplasma CAP vs 30% for non-Mycoplasma CAP). Also in this case, there was no significant difference in the frequency of ultrasound findings in the two groups to allow an etiological diagnosis. Out of the 40 patients in the Mycoplasma positive group, 36 underwent a macrolide+beta- lactam/cephalosporin antibiotic regimen, while only 3/40 (8%) underwent macrolide monotherapy. The same applies to the non-Mycoplasma CAP group in which 57/60 patients underwent combination therapy, while only 2/60 received beta-lactams monotherapy (Table 5). A second ultrasound (i-LUS), was performed on all 100 patients 3 to 4 days after the beginning of treatment. Regression of consolidations was observed in 86% of cases, while complete remission was observed in 7% of patients; comparative analysis did not show any correlation between ultrasound findings at i-LUS and the etiology of pneumonia (Table 2). At the end of treatment, about a week after discharge, all patients were given an appointment to repeat ultrasound (eot-LUS) but only 62/100 patients returned; 31% of them showed residual disease while 69% had undergone complete remission. From comparative analysis emerges a statistically significant difference in the speed of disease resolution, showing a slower regression of lung consolidations among patients with non-Mycoplasma CAP compared to those with Mycoplasma CAP (p = 0. 04), who underwent earlier remission and were characterized by a significantly shorter hospitalization period (3. 35 days vs 4. 6 days respectively) (Table 3 and 4). Univariate analysis conducted on a total of 92/100 patients (34/40 CAP- Mycoplasma, 58/60 CAP-Bacterial /Viral) to establish any correlation between patient's age and the size of pulmonary lesions (8 patients had to be excluded from univariate analysis: 1 patient had a normal LUS on admission, 7 patients only had interstitial disease; Table 6).

As shown by Figures 4 and 5, the relationship between age and size of lesions appears to be linear in both groups. However, while in Mycoplasma CAP the probability of finding smaller lesions was higher for younger children and decreased progressively with age, the opposite was observed among Mycoplasma negative patients, in whom an increase in age corresponded to a slightly greater probability of finding small lesions. In neither case however statistical significance was reached (p=0,283 vs p=0,873 respectively). It appears therefore that age plays little to no role in determining the size of ultrasound lesions detected (Table 6).

Discussion

With this observational retrospective study, we wanted to investigate the potential diagnostic and prognostic value of lung ultrasounds in a cohort of 100 CAP patients treated with a macrolide + beta-lactam/cephalosporin combination or with monotherapy (amoxicillin or cephalosporin). The most important limitations of our study are its retrospective nature and the impossibility to stratify patients in the non-mycoplasma group according to the specific etiology due to the unavailability of some microbiological and virological tests which would be required (some of which are not routinely performed in our hospital). Other important limitations are represented by the low number of

Mycoplasma-positive patients and the absence of a centralized review of lung ultrasound images.In addition, the operators who performed the ultrasound examination were not blind to clinical symptoms during the examination.

There are two main indications for LUS in pediatric CAP: diagnosis of disease and monitoring of its evolution[19]. The diagnostic precision of LUS in demonstrating involvement of lung parenchyma was amply confirmed by the Urbankowska study[10], which found a sensitivity of 93.4%, a specificity of 100% and a positive predictive value of 100%. In addition, studies have shown that LUS has greater accuracy, compared to conventional chest X-ray, in identifying pleural effusions in complicated cases of pneumonia[20]. In daily practice, LUS is frequently used as a diagnostic tool in children with CAP, but few authors have questioned the validity of its use for differential diagnosis. In a study by Voiko[11], LUS was performed on admission on 147 patients with CAP and a second US examination was performed after discharge on most of them. From this study, it emerges how LUS can give additional information about the etiology of pneumonia in children, helping to differentiate between viral and bacterial CAPs. Moreover, the study found a statistically significant difference in the number ($p < 0.001$) and size ($p < 0.001$) of lung lesions inviral versus bacterial CAP, with bacterial pneumonia showing a faster regression of consolidations compared to viral pneumonia (96. 6% vs 33. 3%).

The aim of our study instead, was to establish whether LUS could be used as a reliable tool to differentiate between Mycoplasma-induced pneumonia from CAP caused by other agents.

We also took into account clinical signs and symptoms on admission, in order to evaluate whether it is possible, based merely on clinical features, to distinguish Mycoplasma pneumonia from bacterial or viral forms, assessing for each item whether there is a difference between the two groups. Statistical analysis shows that there is no statistically significant difference between clinical features on admission between the two groups (Fig 3), with the most frequent symptoms, fever and cough, being evenly distributed between the two. Reduced breath sounds were detected more frequently among patients diagnosed with Mycoplasma pneumonia (63% Mycoplasma-CAP vs 37% non-Mycoplasma-CAP), even though the positive predictive value was not particularly high (PPV 63%). Contrarily, in Vojko's study [11], this latter finding was prevalent among patients with typical bacterial CAP (32% bacterial CAP vs 20% atypical CAP).

However, it should be noted that this outcome could be influenced by bacterial superinfections, which are always a possibility in Mycoplasma CAP[21]. Furthermore, this study, in agreement with ours, shows thatwheezing, a sign that is commonly considered a hallmark of viral CAPs, is not in fact a sensitive indicator of the etiology of pneumonia, whereas a study by Qian, showed a correlation between wheezing and infections by Mycoplasma pneumoniae[22].

Our data show that LUS alone, cannot discriminate between different etiologies of CAP in children. We have found that patients with CAP caused by Mycoplasma or other infectious agents, frequently have the same pattern of parenchymal involvement: a single consolidation (75% Mycoplasma-CAP and 78% non-Mycoplasma CAP) and interstitial disease (33% Mycoplasma-CAP and 30% non-Mycoplasma-CAP). In addition, the size of consolidation foci was not significantly different in the two groups, with a large lesion present in 78% of cases in both groups (Tab. 1). This finding disagrees with previous studies, which showed how large alveolar infiltrates are a feature of typical bacterial CAPs, while in CAPs by atypical pathogens, lesions are smaller and more commonly multiple (65% vs 10% in our study) and are associated with interstitial infiltrate (50%).

Regarding the influence of age on the size of lesions, we have not found a significant association between the two variables (Tab. 6). As discussed before, while lesion size appeared to increase with age in Mycoplasma CAP (fig. 4), and to decrease with age in non-Mycoplasma CAP (fig. 5), p value was not significant in either case. Patients were discharged after an average of 4,1 days and a third LUS (eot-LUS) was performed approximately one week after discharge on 62 patients. In this last

examination a regression of consolidations was observed in 11% of Mycoplasma positive patients and in 89% of cases non-Mycoplasma CAP. Complete resolution was instead detected in 49% of Mycoplasma CAP patients and 51% of non-Mycoplasma CAP underwent complete resolution. These data show a difference in healing times (p = 0. 04) which turned out to be shorter in Mycoplasma CAP, leading to a reduction in the length of hospitalization (Tab. 3). This finding is in contrast with Vojko's 2019 study, in which a slower regression of consolidations was observed in patients with CAP Mycoplasma (50% of patients showed lesion regression and 14. 3% underwent complete resolution), but in accordance with the Bruns' study in which chest radiographyshowed a faster resolution of consolidations in CAP from Mycoplasma compared to pneumococcal pneumonia[23].

The i-LUS, performed 3-4 days after antibiotic treatment, showed disease progression in 4%, stationarity in3% , regression of consolidations in 86% of cases and complete remission in 7% of cases.

In this regard, LUS did not demonstrate a statistically significant difference in the echographic appearance of the two groups, but, nevertheless, proved itself to be an effective mean of monitoring theeffects of therapy. Our study suggests, in accordance with 2018 Balk's meta-analysis[24], that LUS should be the preferred imaging technique for the diagnosis and follow-up of pneumonia in children.From the collected data and subsequent statistical analysis, it is clear that LUS alone does not allow for a differential etiological diagnosis of CAP, for which serology and/or PCR remain the most accurate tools. However, it often orients and supports the diagnostic suspicion by identifying the presence of pneumonia, allowing in the vast majority of cases to avoid radiographic examination. Its role in follow-up as a reliable and safe tool compared to radiological imaging remains confirmed.

Conclusion:

In pathology treatises, pneumonia caused by *Mycoplasma pneumoniae* is described as an interstitial oratypical form of the disease, with chest radiographs showing interstitial infiltrates, usually unilateral and with a predominant involvement of the lower lobe, but that can also be bilateral and/or multilobar, with patients not appearing clinically as ill as the radiographic images would suggest[25]. From an imaging standpoint, Mycoplasma infections result in an "interstitial disease with micronodular lesions, ground glass appearance and enlargement of the lung hila" even though, children over 10 years of age can show signs of lobar involvement, especially in presence of pneumococcal co-infections[26]. The systematic use of pulmonary ultrasounds in pediatric wards has in fact highlighted how pulmonary lesions in Mycoplasma infection are various, often multiple and bilateral and tend to change over time[27]. At least in some cases, this could be attributed to bacterial superinfections. However, what emerges from our study, in addition to the difficulty in identifying a lesion that can be considered pathognomonic of Mycoplasma infection, is that seriated ultrasound scans at different stages of disease allows to monitor the rapid evolution of lesions, which appear to follow a predictable course: at onset they consist of hypoechoic areas of consolidation which shrink over the course of few days, giving way to signs of interstitial disease, before the *restitutio ad integrum*[28].

Rather than being echographically defined by a single pathognomonic ultrasound feature, what truly defines Mycoplasma pneumonia at a sonographic level is therefore the plastic nature of its lesions, a feature that no other imaging technique can highlight.

The definition of *walking pneumonia*[29] used in reference to the relatively mild clinical features of Mycoplasma-CAP, could therefore be replaced at pathological level by the expression *wandering pneumonia*, which is more evocative of the dynamic evolution of lesions detected through ultrasounds evaluation. This feature has an undoubted utility from a clinical standpoint, providing both a therapeutic feedback as well as carrying a predictive value on healing times[30], let alone of reducing the need for exposing patients to ionizing radiation. Our conclusions could therefore be summarized as follows: lung ultrasounds in Mycoplasma pneumonia does not confirm the etiological diagnosis but

supports it, from the initial suspicion to follow-up, allowing to highlight pathological features that couldn't be otherwise explorable with other diagnostic techniques (Fig. 6).

Abbreviations:

CXR (Chest X-ray), CAP (Community Acquired Pneumonia), LUS (Lung Ultra Sound),i-LUS (Ad Interim LUS),eot-LUS (End of therapy LUS), PPV (Positive Predictive Value), NPV (Negative Predictive Value), CI (Confidence Interval), PCR (Polymerase Chain Reaction), MYC (Mycoplasma Pneumoniae)

Declarations:

Ethics approval and consent to participate

Parental or guardian's consent was obtained at the time of admission for all patients enrolled in the study. All enrolled subjects authorized us to collect and process their data, in accordance with Italian Privacy Law (Legislative Decree 196/2003). All clinical data and images reported are anonymous. The study was authorized on the 30th of January 2020, by dr. Antonio Del Vecchio, head of the Department of Pediatric and Maternal Health of our Hospital, in compliance with art. 11 and art. 110, paragraph 1 of the "Italian code of medical Deontology" and has been submitted to and approved by our local ethics committee ("Comitato Etico Indipendente con competenza territoriale per le aziende sanitarie della provincia di Bari". Date of Approval (13/10/2021).

- **Consent for publication:** The publication of the data was authorized by our Hospital.
- **Availability of data and materials:** All the information supporting our conclusions and relevant references are included in the manuscript. There are no datasets related to this work.
- **Competing interests:** The authors declare that they have no competing interests.
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- **Contributions**

CT devised the study concept and design. VB, IL, ES and CT performed lung ultrasound examinations. FL, TD and MF contributed to data acquisition. MP put down analysis and interpretation of the data. The primary literature search was conducted by MR and MS. OI drafted the manuscript. ES critically reviewed and revised the manuscript for intellectual content. All authors reviewed the final version of the manuscript prior to submission and all accept responsibility for the integrity of the research process and findings. All authors read and approved the final manuscript.

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