Lung ultrasound assessment of response to antibiotic therapy in cystic fibrosis exacerbations: a study of two cases

Andressa Oliveira Peixoto[1,2,3,a], Fernando Augusto Lima Marson[1,2,4,5,b],
Tiago Henrique Souza[1,6,c], Andrea de Melo Alexandre Fraga[1,3,d],
José Dirceu Ribeiro[1,3,e]

TO THE EDITOR:

Cystic fibrosis (CF) pulmonary exacerbations (PEx) cause approximately 50% of the decline in lung function.[1] Although there is no consensus, the criteria for defining PEx currently consist of abnormal sputum and/or chest X-ray findings; anorexia; increased cough; dyspnea; fatigue/lethargy; fever; hemoptysis; decreased overall health status; > 10% decrease in FEV_1; and weight loss.[2] However, two questions remain unanswered[1]: how can we improve the treatment of PEx and which imaging techniques can indicate PEx and/or assess pulmonary involvement? Within this context, we can highlight the use of lung ultrasound (LUS), which is a rapid, radiation-free method that is easily reproducible, widely available, and low cost. LUS can be useful for assessing PEx and response to antibiotic therapy. Experimentally, we used LUS before and after antibiotic therapy in two female CF patients who had PEx. The female CF patients had two sweat chloride results ≥ 60 mEq/L and two pathogenic variants in the *CFTR* gene. The following assessments were performed: completion of a clinical/demographic questionnaire; spirometry; chest HRCT on the day of the first LUS was performed; use of the Bhalla CT scoring system; measurement of SpO_2; LUS; and routine sputum culture (Table 1). This study was approved by the local research ethics committee (CAAE no. 64515817.4.0000.54.04).

According to the international recommendation for point-of-care LUS, this test can detect the presence of A-pattern (normal lung sliding and regular pleural line echogenicity with a predominance of A-line artifacts) or B-pattern (presence of at least three B-line artifacts) per lung region.[3,4] In our study, the lung was divided into 12 regions. The physical and anatomical nature of B-lines ("comet tail" artifacts; hyperechoic, vertical lines that mask A-lines originating from the visceral pleura and move with lung sliding) is not fully understood; however, their occurrence is associated with the presence of hydrostatic and/or inflammatory fluid in the lung interstitium.[4] In addition, LUS can identify consolidation (hypoechoic subpleural area with irregular margins and heterogeneous texture, possibly with a hyperechoic image inside and/or B-lines adjacent to its posterior margin or an aspect similar to that of the liver parenchyma) and pleural effusion (anechoic space between the visceral and parietal pleura).[3] Patient 1 (*CFTR* genotype, F508del/G542X) met the following criteria for PEx: increased cough; increased sputum production and change in sputum appearance/consistency; worsening of findings on pulmonary auscultation; and positive routine culture for *Staphylococcus aureus* and *Achromobacter xylosoxidans*. During follow-up, oral antibiotic therapy was prescribed for 15 days. The Shwachman-Kulczycki (SK) score[5] indicated lack of resistance and end-of-day tiredness, but good school attendance (general activity domain); presence of obstructive pulmonary disease, infection, lobular atelectasis, and bronchiectasis (radiological findings domain); weight and height around the 25th percentile, good muscle mass and tone, and well-formed, near-normal stools (nutrition domain); and no cough, normal heart and respiratory rates, clear lungs, and good posture (physical examination domain). In the assessment of PEx, we considered the patient's or caregiver's report of increased cough, increased sputum production, and/or change in sputum appearance/consistency. However, in the SK score,[5] the presence of cough was assessed during the visit, and this information was different from what was reported previously. In summary, the total SK score was 75, classified as "good". LUS assessment showed that, in four lung regions, the pattern changed from B to A after antibiotic therapy, being classified as a mixed pattern at both time points (Table 1).

Patient 2 (*CFTR* genotype, F508del/F508del) met the following criteria for PEx: increased cough; increased sputum production and change in sputum consistency; tiredness; intolerance to physical exertion; weigh loss; decreased SpO_2; and positive routine culture for mucoid and nonmucoid *Pseudomonas aeruginosa*. During

1. Departamento de Pediatria, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas (SP) Brasil.
2. Centro de Investigação em Pediatria, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas (SP) Brasil.
3. Unidade de Urgência e Emergência, Hospital de Clínicas, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas (SP) Brasil.
4. Departamento de Genética Médica e Medicina Genômica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas (SP) Brasil.
5. Programa de Pós-Graduação em Ciências da Saúde, Universidade São Francisco, Bragança Paulista (SP) Brasil.
6. Unidade de Terapia Intensiva Pediátrica, Hospital de Clínicas, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas (SP) Brasil.

a. http://orcid.org/0000-0002-8407-4087; b. http://orcid.org/0000-0003-4955-4234; c. http://orcid.org/0000-0001-6944-0221;
d. http://orcid.org/0000-0003-0999-5350; e. http://orcid.org/0000-0002-3387-5642

follow-up, oral antibiotic therapy was prescribed for 15 days. The SK score[5] indicated lack of resistance and end-of-day tiredness, but good school attendance (general activity domain); presence of obstructive pulmonary disease, infection, lobular atelectasis, and bronchiectasis (radiological findings domain); weight and height below the 3rd percentile, weak muscle tone, reduced muscle mass, mild/moderate abdominal distention, and voluminous, greasy, poorly-formed stools (nutrition domain); frequent cough, usually productive, chest retraction, moderate emphysema, chest deformity, frequent crackles, and digital clubbing (physical examination domain). The total SK score was 45, classified as "moderate". LUS assessment showed that, in one lung region, the pattern changed from B to A after antibiotic therapy, being classified as a mixed pattern at both time points (Table 1).

Both patients were chronically colonized/infected with the aforementioned bacteria and had changes in routine culture results from before to after antibiotic therapy.

The LUS images were examined by a pulmonologist with specific training in LUS interpretation. A second member of the team who specialized in radiology analyzed the LUS findings in a blind fashion. Both professionals scored the LUS images and interpreted the image findings, with identical results. The ultrasound scoring system and the full description of the methods have been published elsewhere.[6]

In reviewing the literature, there is an evident need for a test for assessing antibiotic therapy success in PEx. In addition, there is no consensus regarding the criteria defining the start/end of PEx and the time required for treatment. Furthermore, it is not always possible to identify who will require short-course antibiotic therapy (10-14 days, early responders) or long-course antibiotic therapy (approximately 21 days, late responders).[1,7] Although clinical markers and pulmonary function test results have been used as tools to assess response to treatment, they have limitations and lose specificity as the disease progresses.[1] In this context, our report encourages the applicability of LUS for assessing PEx.

In CF, PEx are markers of disease progression and should be monitored during routine visits. We know that CF patients have experienced an increase in survival despite chronic airway colonization with

Table 1. Data from cystic fibrosis patients and from lung ultrasound assessments before and after antibiotic therapy.

Data	Patient 1		Patient 2	
	Before	After	Before	After
Age, years	22		18	
BMI, kg/m²	23.34		17.41	
SpO₂	95		92	
Comorbidities	PIns		PIns, DM	
CFTR	F508del/G542X		F508del/F508del	
FVC, % predicted	73	74	38	39
FEV₁, % predicted	55	57	42	41
FEV₁/FVC	75	77	99	94
FEF₂₅₋₇₅%,%	24	26	53	46
Bhalla[a]	21		24	
Regions assessed on LUS				
1	A	A	B	A + PI
2	C + PI	C + PI	B + C	B + C
3	B	A	B	B
4	B + PI	B + PI	B	B
5	A + PI	A	B	B
6	B	A	B + C	B + C
7	A	A	B	B
8	B	B	B	B
9	A + PI	A	B + C	B + C
10	B	A	B + PI	B + PI
11	A	A	B	B
12	B	A	B	B
Score[b]	8/36	4/36	18/36	17/36

BMI: body mass index; PIns: pancreatic insufficiency; DM: diabetes mellitus; *CFTR*: cystic fibrosis transmembrane regulator; LUS: lung ultrasound; A: A-pattern; B: B-pattern; PI: pleural irregularity; and C: consolidation. [a]The modified Bhalla CT scoring system was used as in Folescu et al.[10]: the total score for each patient is obtained by summing the scores for each morphological change, which are attributed on the basis of the severity/extent of the abnormality. The total score can range from zero (absence of abnormalities) to 37 (all abnormalities present and severe). [b]The higher the proportion value, the greater the pulmonary involvement in the area, with the presence of consolidation being assigned 2 points and the presence of B-pattern being assigned 1 point. Therefore, the maximum score is 36 points.

bacteria exhibiting increased drug resistance, which culminates in the use of numerous drugs (antibiotics and anti-inflammatory drugs) that require frequent monitoring, since we move toward personalized and precision medicine.[8,9] In this process, LUS could be a tool that accompanies patients in determining their individual response to therapy, without causing complications or exposing patients to radiation.

In summary, LUS could be a useful tool to assess changes due to PEx and response to antibiotic therapy in CF. However, further studies involving a larger sample size are needed in order to confirm our findings, since only one of the two CF patients assessed had distinctly different LUS results before and after antibiotic therapy.

AUTHOR CONTRIBUTION

AOP conceived the project, collected the participant data, and drafted and revised the manuscript; FALM and JDR conceived the study and drafted and revised the manuscript; THS validated the results; and AMAF clinically assessed the study participants and validated the phenotypic findings against reproducibility criteria. All authors read and approved the final version of the article for submission.

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