

## High-resolution computed tomography scores in cystic fibrosis patients colonized with *Pseudomonas aeruginosa* or *Staphylococcus aureus*\*

Escore tomográfico em pacientes com fibrose cística colonizados por *Pseudomonas aeruginosa* ou *Staphylococcus aureus*

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### Abstract

**Objective:** To compare HRCT findings in cystic fibrosis (CF) patients chronically colonized with *Pseudomonas aeruginosa* or *Staphylococcus aureus* using the modified Bhalla CT scoring system, as well as to evaluate intraobserver and interobserver reliability of the method. **Methods:** This was a retrospective cross-sectional study involving 41 CF patients, 26 of whom were chronically colonized with *P. aeruginosa* (Pa group), and 15 of whom were colonized with *S. aureus* (Sa group). Two independent radiologists evaluated the HRCT scans of these patients using the modified Bhalla CT scoring system in two different moments. Intraobserver and interobserver reliability was calculated using the intraclass correlation coefficient (ICC). **Results:** There was good intraobserver and interobserver agreement (ICC > 0.8). Scores were higher in the Pa group than in the Sa group for observer 1 (mean, 13.50 ± 3.90; median, 13.5 vs. mean, 5.00 ± 5.28; median, 3.0) and for observer 2 (mean, 11.96 ± 5.07; median, 12.0 vs. mean, 5.07 ± 5.65; median, 5.0). In addition, HRCT findings, such as bronchiectasis, bronchial wall thickening, mucus plugging, generation of bronchial divisions, and mosaic attenuation/perfusion pattern, were more prevalent in the Pa group. **Conclusions:** The modified Bhalla CT scoring system was reproducible and reliable for use in the evaluation of HRCT scans, allowing distinctions to be drawn between the two groups of patients under study. The higher scores in the Pa group provided evidence of greater pulmonary impairment in that group.

**Keywords:** Cystic fibrosis; Tomography; *Staphylococcus aureus*; *Pseudomonas aeruginosa*.

### Resumo

**Objetivo:** Comparar achados de TCAR em pacientes com fibrose cística (FC) colonizados cronicamente por *Pseudomonas aeruginosa* ou *Staphylococcus aureus*, empregando o escore de Bhalla modificado, e avaliar as confiabilidades intraobservador e interobservador do método. **Métodos:** Estudo transversal retrospectivo incluindo 41 pacientes portadores de FC, 26 dos quais colonizados cronicamente por *P. aeruginosa* (grupo Pa) e 15 por *S. aureus* (grupo Sa). Dois radiologistas analisaram independentemente em duas ocasiões, as imagens de TCAR desses pacientes e aplicaram o escore de Bhalla modificado. As confiabilidades intra e interobservador foram avaliadas segundo o coeficiente de correlação intraclasse (CCI). **Resultados:** Houve boa concordância intraobservador e interobservador (CCI > 0,8). Os resultados dos escores do grupo Pa foram mais elevados que os do grupo Sa para o observador 1 (média de 13,50 ± 3,90 e mediana de 13,5 vs. média de 5,0 ± 5,28 e mediana de 3,0) e para o observador 2 (média de 11,96 ± 5,07 e mediana de 12,0 vs. média de 5,07 ± 5,65 e mediana de 5,0). Alterações tomográficas, como bronquiectasias, espessamento das paredes brônquicas, formação de tampões mucosos, comprometimento de gerações de divisões brônquicas e padrão de atenuação em mosaico, foram mais prevalentes no grupo colonizado por *P. aeruginosa*. **Conclusões:** O escore de Bhalla modificado se mostrou reprodutível e confiável para a avaliação de TCAR e permitiu a diferenciação entre os pacientes incluídos nos dois grupos. Escores mais altos no grupo Pa evidenciaram maior comprometimento estrutural pulmonar nesse grupo.

**Descritores:** Fibrose cística; Tomografia; *Staphylococcus aureus*; *Pseudomonas aeruginosa*.

\* Study carried out at the *Instituto Fernandes Figueira, Fundação Oswaldo Cruz* – IFF-FIOCRUZ, Oswaldo Cruz Foundation Fernandes Figueira Institute – and at the Bacteriology Laboratory of the Rio de Janeiro State University Pedro Ernesto University Hospital, Rio de Janeiro, Brazil.

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## Introduction

In patients with cystic fibrosis (CF), chronic bacterial infection is responsible for progressive pulmonary structural damage and respiratory dysfunction, respiratory failure accounting for 95% of the deaths.<sup>(1)</sup> In addition, bacterial infections have an early onset and are associated with a limited number of microorganisms. *Staphylococcus aureus* and *Haemophilus influenzae* are associated with infections in younger patients. Subsequently, *Pseudomonas aeruginosa* colonizes the respiratory tract and, as the disease progresses, produces a polysaccharide designated alginate, characterizing the mucoid phenotype, which is more resistant to the effect of antibiotics. Chronic infection with *P. aeruginosa* has clearly been associated with decreased lung function, worsening of structural damage, higher morbidity, and higher mortality in patients with CF.<sup>(2)</sup> The primary objective of treatment and follow-up strategies in CF patients is to combat infection and progressive lung disease.<sup>(1)</sup>

A set of diagnostic procedures, including respiratory secretion culture, pulmonary function tests, and chest X-rays, has been recommended in order to evaluate respiratory impairment.<sup>(1)</sup> Pulmonary function tests and chest X-rays constitute indirect measurements of lung structure and have low sensitivity for detecting local or early lesions.<sup>(3)</sup> Chest HRCT is an imaging method that is considered specific for early evaluation of involvement of the lung parenchyma, as well as of the proximal and distal airways (bronchial wall thickening, bronchiectasis, mucoid impaction, and lung hyperinflation).<sup>(4)</sup> Reproducible scoring systems can be used in order to quantify CT findings.<sup>(3)</sup> Some studies have reported that magnetic resonance imaging of the chest is an extremely promising imaging method for detecting pulmonary changes in patients with CF; however, a protocol for the use of this method in CF patients has yet to be established.<sup>(5)</sup>

The objective of the present study was to use a CT scoring system to draw comparisons between CF patients chronically colonized with *P. aeruginosa* and those chronically colonized with *S. aureus* in terms of HRCT findings.

## Methods

The study project was approved by the Research Ethics Committee of the Fernandes Figueira Institute, located in the city of Rio

de Janeiro, Brazil (CAAE 0042.0.008.000-07). This was a retrospective cross-sectional study, conducted between January of 2007 and June of 2008, involving CF patients treated at the Pulmonology Section of the Pediatrics Department of the Fernandes Figueira Institute (Oswaldo Cruz Foundation, Brazilian National Ministry of Health), a referral center for CF in children and adolescents.

The criteria for inclusion in the present study were as follows: having met the diagnostic criteria for CF<sup>(6)</sup>; being under regular clinical and laboratory follow-up at the Fernandes Figueira Institute Pulmonology Outpatient Clinic, such follow-up including the collection of respiratory secretion samples, during scheduled appointments, for subsequent culture; and, while clinically stable (without clinical markers of respiratory exacerbation, i.e., increased cough or secretion, changes in secretion appearance, weight loss, or loss of appetite), having undergone HRCT of the chest in accordance with the recommendation and planning of treatment by the team.<sup>(7)</sup>

The patients selected for inclusion in the present study were divided into two groups, on the basis of the results of the microbiological examination of respiratory secretions: Sa, comprising patients whose respiratory secretion was positive for *S. aureus* but who had never been colonized with *P. aeruginosa* or whose respiratory secretion culture results had been negative for *P. aeruginosa* in the last 12 months; and Pa, comprising patients who met the criteria for chronic colonization with *P. aeruginosa* (more than 50% of cultures having been positive for *P. aeruginosa* and having tested negative for other pathogenic bacteria in respiratory secretion for more than 12 months). Demographic and clinical data were collected from the medical charts of the patients under study.

The respiratory secretions were processed in accordance with specific and standardized protocols for the follow-up of patients with CF.<sup>(8)</sup> The microorganisms were initially identified by phenotypic methods and, when necessary, by molecular techniques. We performed PCR, as well as sequencing of the *recA* and *16S rDNA* genes, in the Nonfermenting Gram-Negative Bacilli Laboratory of the Microbiology Department of the Rio de Janeiro State University, located in the city of Rio de Janeiro, Brazil.<sup>(9)</sup>

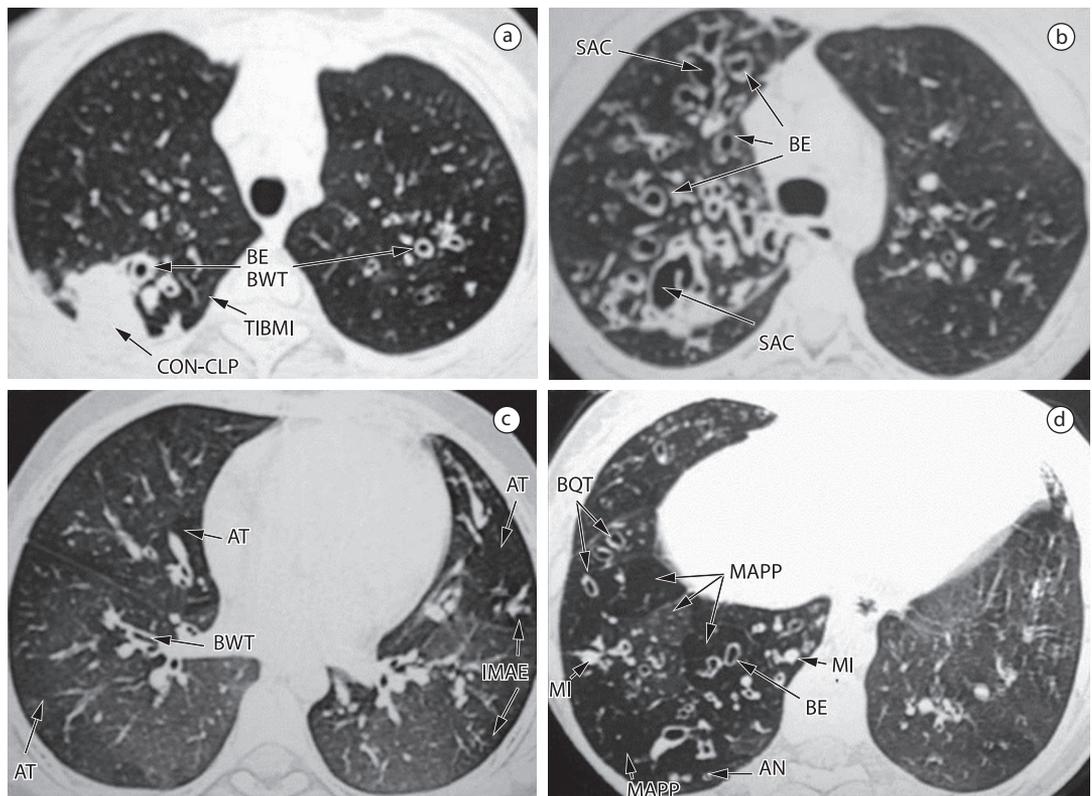
The patients included in the present study underwent radiological evaluation in accordance with the routine of the referral center, which consists of CT scans taken at intervals of at least two years when patients are stable from a respiratory standpoint. All of the HRCT scans were taken without sedation with a ProSpeed-S™ device (General Electric, Milwaukee, WI, USA), as follows: 1-mm slices; 10-mm intervals; 80–100 mA/s; and 120 kV. The images were obtained with a 1,500-HU window and a level of –700 HU, in accordance with the protocol of the radiology department of the institution. We used HRCT scans taken after Pa and Sa group patients had been colonized, and the images were selected in accordance with the inclusion criteria, being initially evaluated by two pediatric radiologists, each with over 10 years of experience.

To define abnormal findings on HRCT scans (Figure 1), we used the criteria established by the Fleischner Society<sup>(10)</sup> and the Illustrated

Brazilian consensus of terms and fundamental patterns in chest CT scans.<sup>(11)</sup> Subsequently, the two independent observers, who were blinded to the clinical and laboratory data, used a CT scoring system to evaluate the images. The same observers performed this procedure again after a mean period of three months.

The CT scoring system used in the present study was a modified Bhalla CT scoring system,<sup>(12)</sup> which is detailed in Chart 1. The total score for each patient was obtained by summing the scores for each morphological change, which were 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).

Using data from the first evaluation, we determined the intraobserver and interobserver reliability for each item on the scoring system by calculating the kappa statistic, categorizing the level of agreement as poor (< 0.20), fair



**Figure 1** – HRCT scans. In A, presence of bronchiectasis (BE), bronchial wall thickening (BWT), tree-in-bud mucoid impaction (TIBMI), and consolidation/collapse (CON-CLP). In B, presence of BE and sacculations (SAC). In C, presence of BWT and air trapping (AT). In D, presence of BE, mucoid impaction (MI), mosaic attenuation/perfusion pattern (MAPP), and acinar nodule (AN).

**Chart 1** – The modified Bhalla CT scoring system.<sup>a</sup>

HRCT scan parameter	Score			
	0	1	2	3
Severity of bronchiectasis	Absent	Luminal diameter slightly greater than that of the adjacent blood vessel	Luminal diameter 2-3 times greater than that of the adjacent blood vessel	Luminal diameter 3 times greater than that of the adjacent blood vessel
Bronchial wall thickening	Absent	Airway wall thickness equal to the diameter of the adjacent blood vessel	Airway wall thickness greater than and up to twice the diameter of the adjacent blood vessel	Airway wall thickness > 2 times the diameter of the adjacent blood vessel
Extent of bronchiectasis (no. of BP segments)	Absent	1-5	6-9	> 9
Extent of mucus plugging (no. of BP segments)	Absent	1-5	6-9	> 9
Sacculations/abscesses (no. of BP segments)	Absent	1-5	6-9	> 9
Generations of bronchial division involved (bronchiectasis/mucous plugging)	Absent	≤ 4th generation	≤ 5th generation	≤ 6th generation and distal
Number of bullae	Absent	Unilateral	Bilateral (≤ 4)	> 4
Emphysema (no. of BP segments)	Absent	1-5	> 5	
Collapse/consolidation	Absent	Subsegmental	Segmental/lobar	
Mosaic attenuation/perfusion pattern <sup>b</sup>	Absent	1-5	> 5	
Air trapping <sup>b</sup>	Absent	1-5	> 5	
Acinar nodule <sup>b</sup>	Absent	Subsegmental/segmental	Lobar	
Intralobular septal thickening <sup>b</sup>	Absent	Subsegmental/segmental	Lobar	Diffuse (> 1 lobe)
Ground-glass infiltrate <sup>b</sup>	Absent	Subsegmental/segmental	Lobar	Diffuse (> 1 lobe)

BP: bronchopulmonary. <sup>a</sup>Adapted from Judge et al.<sup>(12)</sup> <sup>b</sup>Modifications of the original Bhalla CT scoring system.

(0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), or very good (> 0.81).<sup>(13,14)</sup>

In both evaluations, interobserver agreement was measured by the intraclass correlation coefficient (ICC). Intraobserver and interobserver reliability was also evaluated by means of Bland & Altman plots.<sup>(15)</sup>

The two groups of patients under study were compared, in terms of the results of the modified Bhalla CT scoring system, by computing the descriptive statistics for the scores by observer and microbiological group. The statistical analyses were performed with the Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, IL, USA). The results were compared by the Mann-Whitney test, the level of statistical significance being set at  $p < 0.05$ .

We determined the frequency of abnormal findings on the HRCT scans. An abnormality was considered to be present only if the two observers agreed that the corresponding score was different from zero. Otherwise, the abnormality was considered to be absent. Subsequently, we used the chi-square test in order to compare the two groups in terms of the results obtained, the level of statistical significance being set at  $p < 0.05$ .

## Results

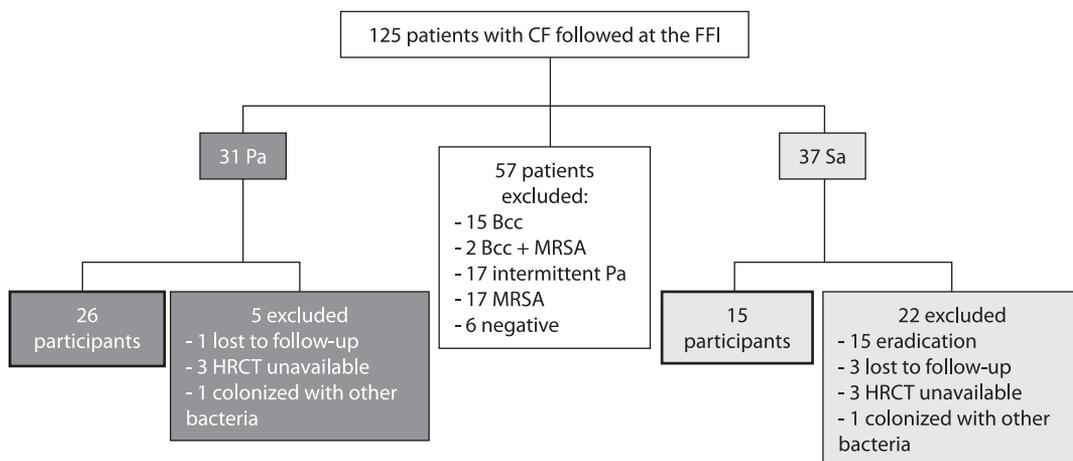
As can be seen in Figure 2, 41 patients met the inclusion criteria and were therefore selected for inclusion in the present study, having been divided into two groups: Sa ( $n = 15$ ) and Pa

(n = 26). Table 1 shows the demographic and microbiological characteristics of the study population.

Intraobserver reliability, as measured by the ICC, was 0.824 for the first observer and 0.892 for the second, values that demonstrate a good level of agreement between the two evaluations. The Bland & Altman plots showed that the difference

between the two evaluations did not increase as the score increased.

The interobserver reliability for the total score, as measured by the ICC, was 0.814, a value that shows a good level of agreement between the observers. The Bland & Altman plots confirmed that and demonstrated that the difference between the two observers did not increase as the score increased. Table 2 shows



**Figure 2** - Flowchart of the process of selection of cystic fibrosis (CF) patients. FFI: Fernandes Figueira Institute; Pa: patients chronically colonized with *Pseudomonas aeruginosa*; Sa: patients colonized with *Staphylococcus aureus*; Bcc: patients colonized with *Burkholderia cepacia* complex bacteria; and MRSA: patients colonized with methicillin-resistant *Staphylococcus aureus*.

**Table 1** - Characteristics of the cystic fibrosis patients colonized with *Staphylococcus aureus* or *Pseudomonas aeruginosa* at the time of HRCT.<sup>a</sup>

Characteristics	Group Sa (n = 15)	Group Pa (n = 26)
Age, years <sup>b</sup>	10	13
Gender, M/F	9/6	9/17
Genetic evaluation, total of patients	7	15
DF508/DF508	1	6
DF508/other	1	3
Others	5	6
Pancreatic insufficiency	6	24
Colonization		
MPa	-	6
MPa + Sa	-	3
MPa + NMPa	-	2
MPa + NMPa + Sa	-	13
MPa + NMPa + Sa + NFGNB	-	2
Sa	11	-
Sa + Sm	2	-
Sa+ NFGNB	2	-

Sa: *Staphylococcus aureus*; Pa: *Pseudomonas aeruginosa*; MPa: mucoid *Pseudomonas aeruginosa*; NMPa: nonmucoid *Pseudomonas aeruginosa*; NFGNB: nonfermenting gram-negative bacilli; and Sm: *Stenotrophomonas maltophilia*.<sup>a</sup>Values expressed as n, except where otherwise indicated. <sup>b</sup>Values expressed as mean.

intraobserver and interobserver reliability results for each parameter in isolation and for the total score. Scores were higher in the Pa group than in the Sa group for observer 1 (mean,  $13.50 \pm 3.90$ ; median, 13.5 vs. mean,  $5.0 \pm 5.28$ ; median, 3.0) and for observer 2 (mean,  $11.96 \pm 5.07$ ; median, 12.0 vs. mean,  $5.07 \pm 5.65$ ; median, 5.0), the difference being statistically significant ( $p < 0.001$ ).

Abnormal HRCT findings, such as bronchiectasis, bronchial wall thickening, mucus plugging, involvement of multiple generations of bronchial division, and mosaic attenuation/perfusion pattern, were more prevalent in the Pa group than in the Sa group, the difference being statistically significant ( $p < 0.05$ ). Air trapping and acinar nodules were more prevalent in the Pa group, and collapse/consolidation was more prevalent in the Sa group. However, those differences were not significant ( $p > 0.05$ ).

## Discussion

Since it was first proposed that a scoring system be created in order to quantify the pulmonary structural damage seen on HRCT scans from patients with CF,<sup>(16)</sup> various scoring systems have been described and shown to be reproducible and comparable. The use of CT scores allows us to standardize the interpretation of the images and quantify the pulmonary changes that indicate disease severity. The HRCT scoring systems employed in cases of CF emphasize the importance of certain morphological changes in the lungs, as well as their anatomical and

pathological substrates. For instance, mucous plugging plays a crucial role in the pathogenesis of bronchiectasis, whereas bronchial wall thickening reflects the presence of chronic or recurrent infection.<sup>(16)</sup> Certain changes, such as bronchiectasis, bronchial wall thickening, and mucous plugging were found on more than 70% of the HRCT scans analyzed in the present study, regardless of the microbiological group. Other studies have reported that those three changes are the most prevalent HRCT findings in patients with CF.<sup>(1,3,17)</sup>

In parallel with the identification of the most prevalent changes, the results of the present study demonstrated that the use of a semiquantitative scoring system to detect pulmonary abnormalities on HRCT scans from patients with CF allows good overall intraobserver and interobserver agreement, demonstrating that the measurements are reproducible and reliable. We found good interobserver agreement for the total score and for three HRCT findings, namely acinar nodule, severity of bronchiectasis, and extent of bronchiectasis. One group of authors<sup>(11)</sup> evaluated CT and spirometric changes in adults with CF. They found good interobserver agreement for the total scores; however, when they analyzed each structural change in isolation, they found that interobserver agreement was good only for mosaic attenuation/perfusion pattern, being poor or moderate for the severity of bronchiectasis, the involvement of multiple generations of bronchial division, and air trapping.

Other authors<sup>(3)</sup> used five different scoring systems in order to evaluate HRCT scans of the

**Table 2** – Intraobserver and interobserver reliability for evaluation and re-evaluation of HRCT parameters and total HRCT score.

Item	Measure of agreement	Agreement		
		Intraobserver		Interobserver
		Observer 1	Observer 2	
Severity of bronchiectasis		0.771	0.668	0.716
Peribronchial thickening		0.645	0.198	0.451
Extent of bronchiectasis		0.815	0.806	0.778
Extent of mucous plugging	Weighted kappa	0.645	0.581	0.578
Generations of bronchial divisions involved		0.690	0.674	0.541
Collapse/consolidation		0.377	0.556	0.391
Mosaic attenuation/perfusion pattern		0.277	0.727	0.407
Air trapping		0.274	0.721	0.375
Acinar nodule		0.511	0.411	0.648
Total score	Intraclass correlation coefficient	0.824	0.892	0.814

chests of children with CF and demonstrated that all of the systems were reproducible ( $ICC \geq 0.74$ ) and caused greater interobserver variability when the score was low (i.e., CT images showing fewer changes and changes that were less severe). We found that the intraobserver reliability for the modified Bhalla CT scoring system was good and remained stable for low and high total scores. The modified Bhalla CT scoring system proved useful even in the less advanced forms of the disease.

In the two microbiological groups under study (Pa and Sa), bronchiectasis, bronchial wall thickening, and mucous plugging were found to be the three most prevalent changes. In addition, the prevalence of each of those three abnormalities was significantly higher in the Pa group (> 80%) than in the Sa group (range, 30-55%). Furthermore, bronchiectasis was found in 96.2% of the patients in the Pa group and in 33.3% of those in the Sa group. This preponderance of irreversible lesions, such as bronchiectasis, is due to a greater structural involvement of the airways in the Pa group, which comprised individuals who were chronically exposed to infection/inflammation.<sup>(17,18)</sup> The presence of bronchiectasis seems to be one of the most important factors in the longitudinal deterioration of pulmonary function in patients with CF.<sup>(12)</sup> A study involving 82 patients with CF and evaluating 12 risk factors for developing irreversible lesions (such as bronchiectasis) found that only colonization with mucoid *P. aeruginosa* was significantly correlated with the presence of bronchiectasis.<sup>(19)</sup> The results of the present study are in agreement with those of the studies cited above. All of the patients who were chronically colonized with *P. aeruginosa* presented with the mucoid phenotype, and HRCT revealed a significantly higher prevalence of bronchiectasis in those patients.

Few studies of CF have investigated the differences between distinct microbiological groups in terms of their CT scores. In one study,<sup>(20)</sup> 25 children with CF were investigated in order to determine whether there were differences between those who were infected with *P. aeruginosa* and those who were not in terms of their CT scores. Chest HRCT scans, taken when the patients were clinically stable, were evaluated by means of a CT scoring system derived from the Bhalla CT scoring system. The results showed that the total scores

were significantly higher in the group of patients infected with *P. aeruginosa*, reinforcing the well-known association between colonization with *P. aeruginosa* and disease progression. Abnormal HRCT findings were also analyzed separately, and certain parameters, such as bronchial wall thickening, severity of bronchiectasis, extent of bronchiectasis, and air trapping, were found to be more prevalent in the group of patients colonized with *P. aeruginosa*. The total scores obtained in the present study were significantly higher in the Pa group than in the Sa group, a result that corroborates the abovementioned data. We also found that bronchiectasis, mucous plugging, involvement of multiple generations of bronchial division, and mosaic attenuation/perfusion pattern were more prevalent in the Pa group.

Although there have been studies investigating the application of various CT scoring systems, a formal recommendation for the routine use of such systems has yet to be made.<sup>(21)</sup> In addition, the use of HRCT scoring systems in patients with CF is time-consuming, and the routine use of such systems in referral centers meets with resistance. However, the present study showed that the modified Bhalla CT scoring system can be used in such patients and allows the discrimination between more severe and less severe involvement on the basis of an important marker of disease progression, namely chronic colonization with *P. aeruginosa*.

Because the life expectancy of patients with CF has increased, there is a need to perform a considerable number of imaging tests. This raises the issue of the doses of radiation involved in such tests. Although the risk of developing neoplasia secondary to exposure to relatively low doses of radiation has yet to be determined, current evidence suggests that the risk is low.<sup>(21)</sup> Within this context, although there is no consensus as to how often CT scans should be taken (principally in infants and preschool children), some referral centers have established that CT scans be taken every two years.<sup>(3)</sup>

In conclusion, higher total scores in the group of patients chronically colonized with *P. aeruginosa*, as well as the presence of bronchiectasis in nearly all of those patients, constitute evidence of the severity of pulmonary impairment in such patients and confirm the association between chronic colonization with *P. aeruginosa* and

the progression of pulmonary structural damage in patients with CF. Such evidence corroborates the premise that chronic colonization with *P. aeruginosa* elicits a stronger inflammatory response and leads to earlier structural damage.

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