Should the bronchiectasis treatment given to cystic fibrosis patients be extrapolated to those with bronchiectasis from other causes?*

Deve-se extrapolar o tratamento de bronquiectasias em pacientes com fibrose cística para aqueles com bronquiectasias de outras etiologias?

Rodrigo Abensur Athanazio, Samia Zahi Rached, Ciro Rohde, Regina Carvalho Pinto, Frederico Leon Arrabal Fernandes, Rafael Stelmach

Abstract

Objective: To profile the characteristics of adult patients with bronchiectasis, drawing comparisons between cystic fibrosis (CF) patients and those with bronchiectasis from other causes in order to determine whether it is rational to extrapolate the bronchiectasis treatment given to CF patients to those with bronchiectasis from other causes. Methods: A retrospective analysis of the medical charts of 87 patients diagnosed with bronchiectasis and under follow-up treatment at our outpatient clinic. Patients who had tuberculosis (current or previous) were excluded. We evaluated the clinical, functional, and treatment data of the patients. Results: Of the 87 patients with bronchiectasis, 38 (43.7%) had been diagnosed with CF, through determination of sweat sodium and chloride concentrations or through genetic analysis, whereas the disease was due to another etiology in 49 (56.3%), of whom 34 (39.0%) had been diagnosed with idiopathic bronchiectasis. The mean age at diagnosis was lower in the patients with CF than in those without (14.2 vs. 24.2 years; p < 0.05). The prevalence of symptoms (cough, expectoration, hemoptysis, and wheezing) was similar between the groups. Colonization by *Pseudomonas aeruginosa* or *Staphylococcus aureus* was more common in the CF patients (82.4 vs. 29.7% and 64.7 vs. 5.4%, respectively). Conclusions: The causes and clinical manifestations of bronchiectasis are heterogeneous, and it is important to identify the differences. It is crucial that these differences be recognized so that new strategies for the management of patients with bronchiectasis can be developed.

Keywords: Cystic fibrosis; Bronchiectasis/diagnosis; Bronchiectasis/therapy; Respiratory function tests.

* Study carried out in the Pulmonology Division of the Instituto do Coração – InCoR, Heart Institute – Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – HC-FMUSP, University of São Paulo School of Medicine Hospital das Clínicas – São Paulo, Brazil.

Correspondence to: Rodrigo Abensur Athanazio. Disciplina de Pneumologia, Avenida Dr. Enéas de Carvalho Aguiar, 255, 7º andar, Cerqueira César, CEP 05403-000, São Paulo, SP, Brasil.

Tel 55 11 3069-7201. E-mail: rathanazio@yahoo.com.br

Financial support: None.

Submitted: 2 December 2009. Accepted, after review: 5 April 2010.
Introduction

Bronchiectasis is a heterogeneous disease that has multiple etiologies and presentations, characterized by abnormal and permanent dilatations of one or more bronchi. The lesion is part of a continuous process of infection and inflammation, the etiology of which can be congenital or acquired.\(^{[1]}\) It remains in question whether it would not be more accurate to consider bronchiectasis a syndrome, which has recurrent infections, suppuration and hemoptysis as principal characteristics. Bronchiectasis has been considered an orphan disease\(^{[2]}\); however, the development of high-resolution computed tomography has led, in recent years, to the increase in the diagnosis of this disease around the world, including in developed countries.\(^{[3,4]}\)

The factors that influence the evolution of the disease have yet to be well characterized. In addition, its clinical management still lacks consensus and experimental evidence. The etiology most frequently studied is cystic fibrosis (CF), and the literature on its evolution and therapeutic options is extensive. Clinical trials have demonstrated therapeutic benefits with the use of DNase, macrolide antibiotics, and inhaled antibiotic therapy.\(^{[5]}\) The literature is still incipient for the so-called non-CF bronchiectasis, being based on pilot studies or on studies involving small samples.\(^{[6-8]}\)

Although the prevalence of bronchiectasis in Brazil is not well established, it is estimated that it is higher than that found in developed countries. The high incidence of tuberculosis in the country and the inadequate control of respiratory infections in children probably account for this difference.\(^{[9]}\) Because of the difficult access to diagnostic resources in many Brazilian centers, there is an abysmal lack of etiological determination in cases of bronchiectasis that are unrelated to sequelae.\(^{[10]}\)

Although the arsenal of therapeutic strategies for the treatment of the various causes of bronchiectasis is still scarce, a systematic evaluation must be carried out in order to identify the etiology of the disease. The evolution of some causes of bronchiectasis (immunoglobulin deficiencies, atypical mycobacterioses, and allergic bronchopulmonary aspergillosis) can be altered by early diagnosis and specific treatment. However, those causes account for less than 20% of the cases of bronchiectasis.\(^{[11]}\) In clinical practice, most bronchiectasis patients are managed empirically, and most of the practices employed have been extrapolated from the experience with CF patients. The objective of the present study is to profile adult patients with bronchiectasis, drawing comparisons between bronchiectasis in CF patients and bronchiectasis from other causes in order to determine whether it is rational to extrapolate the bronchiectasis treatment given to CF patients to those with bronchiectasis from other causes.

Methods

We carried out a retrospective analysis of the medical charts of adult patients under follow-up treatment at our outpatient clinic. Patients under “current follow-up” were those who had at least one medical appointment in the year before data collection (2008).

The patients included were aged 18-50 years and had a clinical history of cough and/or chronic suppuration, with or without recurrent episodes of pulmonary infection. In addition, it was fundamental to confirm, in tomographic studies, that the internal diameter of the bronchial structure was larger than the diameter of the adjacent pulmonary artery, that there was no gradual decrease in bronchial diameter toward peripheral lung areas, and that there were visible bronchi less than 2 cm from the pleural surface. The exclusion criteria were bronchiectasis caused by mycobacteria, occupational diseases, and other infections in adulthood. Patients whose medical charts described tuberculosis treatment for at least 6 months or bacteriological confirmation on old tests were considered to have sequelae of mycobacterial infection.

The analysis of the medical charts was systematically performed by collecting the information evaluated in the present study. When necessary, childhood records were also analyzed. We collected demographic data (age and gender), data related to diagnosis (age at diagnosis and how the disease was diagnosed), clinical data (follow-up period, symptoms, and treatment at last visit), microbiological data (cultures of sputum samples and bronchoalveolar lavage), and functional data \(\text{SpO}_2\) and spirometry, at beginning of follow-up in adulthood and currently).

At our clinic, the follow-up of patients with bronchiectasis or CF is carried out at quarterly
Should the bronchiectasis treatment given to cystic fibrosis patients be extrapolated to those with bronchiectasis from other causes?

The present study was approved by the human research ethics committee of the institution.

Results

We evaluated 87 patients, 38 (43.7%) of whom had CF. Among the individuals without CF, 34 (39%) had idiopathic bronchiectasis, 4 (4.6%) had bronchiectasis caused by sequelae of a viral infection in childhood, and 3 (3.4%) had bronchiectasis caused by Kartagener syndrome. Table 1 shows all of the diagnoses of the patients included in the study.

Table 1 - Etiologic diagnosis of adult patients with bronchiectasis.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis with cystic fibrosis</td>
<td>38</td>
<td>43.7</td>
</tr>
<tr>
<td>Bronchiectasis without cystic fibrosis</td>
<td>49</td>
<td>56.3</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>34</td>
<td>39.0</td>
</tr>
<tr>
<td>Sequelae due to viral infection in childhood</td>
<td>4</td>
<td>4.6</td>
</tr>
<tr>
<td>Kartagener syndrome</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>Ciliary dyskinesia</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Immunoglobulin A deficiency</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Alpha-1 antitrypsin deficiency</td>
<td>1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

The patients were divided into two groups in order to compare the characteristics of adult CF patients with those of the remaining individuals with bronchiectasis from other causes. The diagnosis of CF was made by determining whether the levels of chloride and sodium in sweat were higher than 60 mmol/L. The remaining diagnoses were made based on clinical history and laboratory tests. Patients in which the clinical history, levels of chloride/sodium in sweat, rheumatologic tests, immunoglobulin levels, and sputum examination results were inconclusive were classified as having “undiagnosed” bronchiectasis.

Since the objective of the study was to profile the current treatment given to bronchiectasis patients (with or without CF) at our clinic, all patients were included in the analysis, even those who had been under follow-up for short periods. We believe that the functional follow-up of patients for less than 6 months is not sufficient to satisfactorily evaluate the evolution of the disease. Therefore, we reanalyzed the database and excluded 5 patients with a follow-up period of less than 6 months.

The statistical analysis was performed with the program Statistical Package for the Social Sciences, version 10.0 (SPSS Inc., Chicago, IL, USA). Results for continuous variables are expressed as mean ± SD when they had normal distribution or as medians and interquartile range when they did not. Results for categorical variables are expressed as relative frequency. The chi-square test was used in order to compare the categorical variables. The means were compared using the Student’s t-test for continuous variables that presented normal distribution; for variables that did not present normal distribution, we used the nonparametric Mann-Whitney test. All tests were two-tailed, and values of p < 0.05 were considered significant.

Table 2 - Clinical and demographic characteristics of adult patients with bronchiectasis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>From cystic fibrosis</th>
<th>From other causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, %</td>
<td>52.6</td>
<td>44.8</td>
</tr>
<tr>
<td>Age, years*</td>
<td>25.2 ± 7.4</td>
<td>37.5 ± 17.3</td>
</tr>
<tr>
<td>Age at diagnosis, years*</td>
<td>14.2 ± 12.5</td>
<td>24.2 ± 12.9</td>
</tr>
<tr>
<td>Follow-up period, months*</td>
<td>21.0 (8.0-48.0)</td>
<td>38.5 (15.5-60.0)</td>
</tr>
<tr>
<td>Symptoms, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>81.5</td>
<td>55.1</td>
</tr>
<tr>
<td>Purulent expectoration</td>
<td>65.7</td>
<td>46.9</td>
</tr>
<tr>
<td>Recent hemoptysis (last 6 months)</td>
<td>10.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Nasal obstruction</td>
<td>26.3</td>
<td>20.4</td>
</tr>
<tr>
<td>Wheezing</td>
<td>23.6</td>
<td>34.6</td>
</tr>
<tr>
<td>Clinical treatment, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled antibiotic treatment*</td>
<td>60.5</td>
<td>-</td>
</tr>
<tr>
<td>Home oxygen therapy*</td>
<td>18.4</td>
<td>6.1</td>
</tr>
<tr>
<td>Bronchodilator</td>
<td>50.0</td>
<td>69.3</td>
</tr>
<tr>
<td>Macrolide*</td>
<td>55.2</td>
<td>20.4</td>
</tr>
<tr>
<td>Inhaled corticosteroid*</td>
<td>18.4</td>
<td>48.9</td>
</tr>
</tbody>
</table>

*p < 0.05. *Values expressed as mean ± SD. *Values expressed as median (interquartile range).
to a greater number of surgical procedures—
lobectomy was performed in 9 (65%) of those 14; 
pneumonectomy was performed in 3 (21%); and 
bilateral lung transplantation was performed in 
2 (14%). This difference was significant between 
the two groups (p = 0.01).

The functional data are shown in Table 3. 
The patients with CF presented significantly 
lower $\text{SpO}_2$, both at the beginning and at the 
end of follow-up. In addition, the patients with 
mucoviscidosis showed a reduction in pulmonary 
function ($\text{FEV}_1$ and $\text{FVC}$) during the follow-up 
period, whereas individuals with non-CF 
bronchiectasis presented slight improvement.

The reanalysis of the database, which led to the 
exclusion of 5 patients whose follow-up period 
was less than 6 months, did not reveal significant 
changes to the results.

Regarding the microbiological profile, 
CF patients presented a higher frequency of 
colonization by $\text{Pseudomonas aeruginosa}$ than 

The clinical and demographic characteristics 
of the patients are shown in Table 2. Most of the 
CF patients were male. The mean age was 25.2 
years. The follow-up period for these patients 
ranged from 2 to 120 months (mean = 33.8 
months), and the age at diagnosis ranged from 
1 to 46 years (mean = 14.2 years). The symptoms 
most commonly found were cough, which was 
present in 81.5% of the cases, and expectoration, 
present in 65.7% of the cases. Nasal obstruction 
was found in 26.3% of the cases, wheezing was 
found in 23.6% of the cases, and hemoptysis in 
the last 6 months was found in only 10.5% of the 
cases. With regard to treatment, 60.5%, 50.0%, 
and 18.4% of the patients used, respectively, 
inhaled antibiotics, long-acting bronchodilators, 
and continuous home oxygen therapy. The group 
of patients with non-CF bronchiectasis was 
composed mostly of females and had a higher 
mean age (37.5 years). The follow-up period of 
these patients ranged from 2 to 154 months 
(mean = 51.3 months), and the age at diagnosis 
ranged from 3 to 45 years (mean = 24.2 years). 
Again, cough was the most prevalent symptom, 
occurring in 55.1% of the patients analyzed. 
Expectoration, wheezing, nasal obstruction, and 
hemoptysis in the last 6 months were found in 
46.9%, 34.6%, 20.4%, and 6.1% of the patients, 
respectively. None of the patients were being 
treated with inhaled antibiotics. Only 6.1% of 
the individuals were receiving home oxygen 
therapy, and 69.3% of the individuals were using 
long-acting bronchodilators.

Of the 38 patients with CF, 2 (5.2%) 
underwent surgical procedures (pneumonectomy 
and bilateral lung transplantation, respectively). 
However, of the 49 individuals with non-CF 
bronchiectasis, 14 (28.5%) were submitted 

Table 3 – Functional characteristics of adult patients with bronchiectasis.  

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>From cystic fibrosis</th>
<th>Bronchiectasis</th>
<th>From other causes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beginning of</td>
<td>End of</td>
<td>Beginning of</td>
</tr>
<tr>
<td></td>
<td>follow-up</td>
<td>follow-up</td>
<td>follow-up</td>
</tr>
<tr>
<td>$\text{SpO}_2$, %</td>
<td>92.5 ± 4.4</td>
<td>92.8 ± 4.9</td>
<td>94.0 ± 4.4</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.5 ± 1.2</td>
<td>2.4 ± 1.0</td>
<td>2.3 ± 0.8</td>
</tr>
<tr>
<td>FVC, % of predicted</td>
<td>64.3 ± 20.2</td>
<td>60.9 ± 22.6</td>
<td>64.0 ± 20.3</td>
</tr>
<tr>
<td>$\text{FEV}_1$, L</td>
<td>1.7 ± 0.9</td>
<td>1.5 ± 0.8</td>
<td>1.4 ± 0.7</td>
</tr>
<tr>
<td>$\text{FEV}_1$, % of predicted</td>
<td>50.8 ± 19.9</td>
<td>46.2 ± 20.8</td>
<td>48.4 ± 21.7</td>
</tr>
<tr>
<td>$\text{FEV}_1$/FVC</td>
<td>0.69 ± 0.15</td>
<td>0.64 ± 0.12</td>
<td>0.61 ± 0.13</td>
</tr>
</tbody>
</table>

*Values expressed as mean ± SD. *p < 0.05 between the two groups.

Figure 1 – Microbiological profile of patients with bronchiectasis from cystic fibrosis and other causes. *p < 0.05 vs. the cystic fibrosis group.
Should the bronchiectasis treatment given to cystic fibrosis patients be extrapolated to those with bronchiectasis from other causes?

did patients of the other group (82.4% vs. 29.7%; p < 0.05). The same was true for the frequency of colonization by \textit{Staphylococcus aureus}(64.7% vs. 5.4%; p < 0.05) and \textit{Burkholderia cepacia} (17.6% vs. 0.0%; p < 0.05; Figure 1).

**Discussion**

In the population studied, 43.7% of the patients were diagnosed with bronchiectasis caused by CF. Most of the remaining cases (56.3%), the diagnoses of which were not associated with CF, had idiopathic causes. When the two groups were compared (bronchiectasis with and without CF) in our sample, CF patients proved to be younger (including the age at diagnosis), to present lower \textit{SpO$_2$}, and to present higher rates of colonization by pathogenic germs. We found no statistically significant differences regarding symptoms and the functional profile, but patients with CF presented a tendency to lose pulmonary function in the follow-up period.

Bronchiectasis “with no diagnosis” have frequently been reported in other studies published, even in studies performed in large centers.\cite{12} Recent studies that attempted to determine the etiology of bronchiectasis in patients with cough, expectoration, and tomographic findings suggestive of bronchiectasis showed that the idiopathic form of the disease occurred in 26–53% of the patients.\cite{13,14} Bronchiectasis caused by viral infections in childhood, humoral immunodeficiency, allergic bronchopulmonary aspergillosis, CF, and aspiration were the diseases most frequently diagnosed after the systematic analysis of these patients. The determination of the underlying disease requires considerable diagnostic effort and, in most cases, does not improve the prognosis or does not alter the clinical condition of the patients. According to one group of authors,\cite{14} although the etiologic diagnosis was made in as many as 74% of the cases referred to a tertiary facility for the treatment of respiratory diseases, the treatment was changed in only 36% of the cases. However, the identification of allergic bronchopulmonary aspergillosis, rheumatoid arthritis, common variable immunodeficiency, aspiration pneumonia, and alpha-1 antitrypsin deficiency allows the initiation of specific treatment and behavioral counseling that can change the course of the disease.\cite{11}

Cough, expectoration, and wheezing were the signs most frequently found in the two subgroups of patients with bronchiectasis, which corroborates the results of another study carried out in Brazil,\cite{10} although the prevalence of symptoms in the latter was even higher: 87.8%, 87.2%, and 68.3%, respectively. Hemoptysis was found in 22.8% of the cases, whereas in our study it was found in 8.0% of the cases. However, the presence of hemoptysis was evaluated only in the last months of our study, with the aim of evaluating the patients at higher risk for developing acute complications. Our patients presented greater pulmonary function involvement, with mean FVC and FEV$_1$ values of 64.7% and 49.0%, whereas in the other study carried out in Brazil\cite{10} the mean FVC and FEV$_1$ values were 81.8% and 67.4%, respectively.

In our cohort, CF patients presented a tendency to worsening of the functional loss over the years and lower \textit{SpO$_2$}. The higher rate of colonization by pathogenic germs can be one of the causes for these results. The colonization by \textit{Pseudomonas} sp. in individuals with CF is related to higher functional loss.\cite{15} Patients with bronchiectasis present better survival rates than patients with CF. The colonization by \textit{Pseudomonas} sp. is an independent factor for mortality in patients with CF and in those with bronchiectasis. The lower rate of colonization by this germ in this group can be one of the reasons for this finding.\cite{16} Another fact that has been well established in the literature is that, in patients with bronchiectasis, the colonization by \textit{Staphylococcus aureus} is related to a higher probability of CF diagnosis.\cite{17}

The mean age at diagnosis in CF individuals was 14 years, which was considered late diagnosis. The lack of specific treatment until this age worsens the prognosis. Various studies in the literature have shown that CF patients diagnosed in adulthood present worse systemic and pulmonary evolution.\cite{18,19} The worse pulmonary function observed in the patients of the present study suggests the possibility of late diagnosis in individuals who presented symptoms since childhood and who, for lack of specialized medical assistance, did not receive specific treatment in a timely manner.

There are still many questions to be answered in the literature, and there is little evidence regarding the treatment of patients with non-CF
bronchiectasis. The use of bronchodilators, the medication most frequently prescribed to our patients, was not based on any clinical trial that confirmed the efficacy of this medication for these patients, as is often seen with most of the other therapeutic options. Although the use of bronchodilators was more common in the group of patients with non-CF bronchiectasis, the difference between the two groups was not statistically significant. The criterion for the use of bronchodilators at our center is principally based on the complaint of dyspnea in patients with obstructive respiratory disorder. In addition, there is no robust evidence to support the use of airway clearance techniques—oscillating pressure devices and hyperosmolar agents—in clinical practice. The use of inhaled corticosteroids is another highly controversial therapy. Despite its potential benefit in terms of reducing the amount of secretion produced in patients with bronchiectasis and improving the quality of life measured by means of questionnaires, the use of inhaled corticosteroids did not reduce the number of exacerbations and the drop in pulmonary function, At our center, the use of inhaled corticosteroids has more individualized indications, such as in patients with good response to the bronchodilator in spirometry and who present a large quantity of pulmonary secretion. The easier access to combined treatment (long-effect bronchodilators + inhaled corticosteroids), as a substitute for the use of bronchodilators in isolation, is also a factor that might have contributed to the higher prevalence of inhaled corticosteroid use in Brazil.

The theory that chronic suppression of a bacterial infection with prolonged antibiotic therapy might change the prognosis in individuals with non-CF bronchiectasis was not confirmed. One systematic review showed a small benefit in terms of reducing the amount of sputum and its purulence, but revealed no impact on major clinical outcomes. In addition, treatment with inhaled antibiotic therapy for Pseudomonas sp. was not found to have any clinical benefits, although it improved microbiological efficacy. Bilateral lung transplantation is a salvage treatment for advanced cases in which there is severe functional limitation. The patients must be intensively monitored to guarantee good nutritional preparation and infection control. The survival rates for this type of transplantation in CF patients and in patients with non-CF bronchiectasis are among the highest when compared with those of individuals submitted to transplantation for other reasons.

The extrapolation of CF treatment to patients with non-CF bronchiectasis presupposes that these patients present similar clinical history, pulmonary function, and natural evolution. The higher colonization by pathogenic germs and the more severe clinical presentation in CF patients raise questions regarding the plausibility of this extrapolation. Despite the limitations that are inherent to a retrospective analysis of medical charts, we observed that patients with bronchiectasis presented a wide spectrum of underlying diseases, with manifestations that can differ greatly, at least between the two principal groups of patients with bronchiectasis. These differences must be considered when individualizing the treatment. A better understanding of the differences between individuals in these highly heterogeneous groups is essential in order to design future therapeutic intervention studies.

References

Should the bronchiectasis treatment given to cystic fibrosis patients be extrapolated to those with bronchiectasis from other causes?


About the authors

Rodrigo Abensur Athanazio
Resident in Pulmonology. Instituto do Coração – InCor, Heart Institute – Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – HC-FMUSP, University of São Paulo School of Medicine Hospital das Clínicas – São Paulo, Brazil.

Samia Zahi Rached
Resident in Pulmonology. Instituto do Coração – InCor, Heart Institute – Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – HC-FMUSP, University of São Paulo School of Medicine Hospital das Clínicas – São Paulo, Brazil.

Ciro Rohde
Medical Student. Faculdade de Medicina da Universidade de São Paulo – FMUSP, University of São Paulo School of Medicine – São Paulo, Brazil.

Regina Carvalho Pinto
Attending Physician, Pulmonology Division of the Instituto do Coração – InCor, Heart Institute – Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – HC-FMUSP, University of São Paulo School of Medicine Hospital das Clínicas – São Paulo, Brazil.

Frederico Leon Arrabal Fernandes
Attending Physician, Pulmonology Division of the Instituto do Coração – InCor, Heart Institute – Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – HC-FMUSP, University of São Paulo School of Medicine Hospital das Clínicas – São Paulo, Brazil.

Rafael Stelmach
Attending Physician, Pulmonology Division of the Instituto do Coração – InCor, Heart Institute – Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – HC-FMUSP, University of São Paulo School of Medicine Hospital das Clínicas – São Paulo, Brazil.