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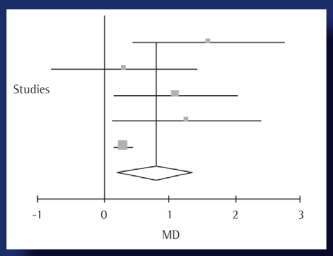
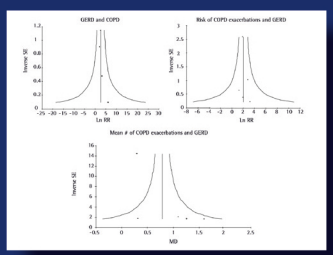
Highlight

Exacerbation of COPD and gastroesophageal reflux





Editorial: Jadwiga A. Wedzicha

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Sumário/Contents

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Sumário/Contents

Is gastro-oesophageal reflux associated with COPD exacerbations?

O refluxo gastroesofágico está associado a exacerbações da DPOC?

Jadwiga A. Wedzicha

COPD is an important long-term condition associated with considerable disability, with a large unmet need for novel therapeutic approaches. The course of COPD is characterized by episodes of respiratory symptom worsening termed exacerbations,[1] and these events are now known to affect health status and disease progression and to be a major factor in the need for hospital admission and readmission.[2] These COPD exacerbations are costly to healthcare services worldwide, and, although a number of pharmacological therapies alone or in combination prevent COPD exacerbations, reductions in exacerbation rates of only about 25% have been observed.[3,4] Thus, novel additional approaches targeting specific pathophysiological mechanisms are essential for COPD patients.

Although exacerbations generally increase in frequency with increasing disease severity, approximately 22% of the patients with moderate COPD in one observational study (FEV_1 = 50-80% of the predicted value) were found to be particularly susceptible to COPD exacerbations and have two or more treated events per year despite usual therapy.[5] These frequent exacerbators have been shown to have a relatively stable exacerbation frequency phenotype, and the number of exacerbations in one year predicts the number of events that are likely to occur in subsequent years.

A number of studies have highlighted the importance of gastro-oesophageal reflux (GOR) as a co-morbidity in COPD.[6-8] This is not unsurprisng as GOR symptoms are common with increasing age in the population. That same observational study also showed that the presence of gastro-oesophageal reflux (GOR) was related to exacerbation frequency in COPD with the frequent exacerbators having a greater chance of developing GOR symptoms.[5] In that study, the prevalence of self-reported GOR was at 27%, and this was similar to the prevalence in other studies in COPD. However, it is known that self-reported GOR may under-estimate the true prevalence as GOR may occur in the absence of symptoms and validated questionnaires need to be used to assess GORD in COPD.

In the present issue of the Brazilian Journal of Pulmonology, Sakae and colleagues present an interesting paper in which they have performed a systematic review and meta-analysis on the relationships between GOR symptoms and exacerbation frequency.[9] The review confirmed the association between exacerbations and GOR and showed that the risk of having a COPD exacerbation was seven times higher in GOR patients than in those without GOR. Furthermore, the authors also showed that patients with COPD have a significantly higher prevalence of GOR than those without COPD, emphasising that GOR is an important and common co-morbidity in COPD.

GOR is a complex condition and may involve both acid and non-acid reflux, including gaseous reflux. The various forms of reflux arise through transient relaxation of the lower oesophageal sphincter, delayed gastric emptying, and increased intra-abdominal pressure. These processes are more likely in COPD patients who are elderly and present with lung hyper-inflation, coughing, use of abdominal muscles, anticholinergic medication use, and altered autonomic tone. Patients with COPD have evidence of lower airway bacterial colonisation,[10] which is now known to increase airway inflammation and affects exacerbation susceptibility. It is possible that airway reflux may increase airway bacterial load in the lower airways with an increase in airway inflammation and, thus, an increase in susceptibility to frequent exacerbations.

Anti-reflux therapy in pulmonary fibrosis has been shown to be independently associated with prolonged survival.[11] However, a study in asthma showed no significant effect of the proton-pump inhibitor esomeprazole on poorly controlled asthma, though there was evidence of considerable asymptomatic GOR in asthmatic patients[12] and in COPD patients.

Sasaki and colleagues reported that the proton-pump inhibitor lansoprazole reduced

exacerbation frequency, though this was in a 12-month, single-blind randomised study involving only 100 patients.[13] Thus, there is a need for further well-designed studies of the therapy for GOR in COPD that are adequately powered for exacerbation reduction and with an appropriate intervention targeting the various types of reflux.

We now know that COPD is associated with complex co-morbidities and that GOR is common in COPD and is associated with a higher exacerbation frequency. Thus, GOR symptoms need to be recognised in COPD, as these patients will be most at risk of future exacerbations and their consequences. Further studies are now required to evaluate what the best intervention is to reduce GOR in COPD patients so that we can more effectively prevent exacerbations in these patients and improve their quality of life.

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Exacerbations of COPD and symptoms of gastroesophageal reflux: a systematic review and meta-analysis*,**

Exacerbações de DPOC e sintomas de refluxo gastroesofágico: revisão sistemática e meta-análise

Thiago Mamôru Sakae, Márcia Margaret Menezes Pizzichini, Paulo José Zimermann Teixeira, Rosemeri Maurici da Silva, Daisson José Trevisol, Emilio Pizzichini

Abstract

Objective: To examine the relationship between gastroesophageal reflux (GER) and COPD exacerbations. **Methods:** We conducted a systematic search of various electronic databases for articles published up through December of 2012. Studies considered eligible for inclusion were those dealing with COPD, COPD exacerbations, and GER; comparing at least two groups (COPD vs. controls or GER vs. controls); and describing relative risks (RRs) and prevalence ratios—or ORs and their respective 95% CIs (or presenting enough data to allow further calculations) for the association between GER and COPD—as well as exacerbation rates. Using a standardized form, we extracted data related to the study design; criteria for GER diagnosis; age, gender, and number of participants; randomization method; severity scores; methods of evaluating GER symptoms; criteria for defining exacerbations; exacerbation rates (hospitalizations, ER visits, unscheduled clinic visits, prednisone use, and antibiotic use); GER symptoms in COPD group vs. controls; mean number of COPD exacerbations (with symptoms vs. without symptoms); annual frequency of exacerbations; GER treatment; and severity of airflow obstruction. **Results:** Overall, GER was clearly identified as a risk factor for COPD exacerbations (RR = 7.57; 95% CI: 3.84-14.94), with an increased mean number of exacerbations per year (mean difference: 0.79; 95% CI: 0.22-1.36). The prevalence of GER was significantly higher in patients with COPD than in those without (RR = 13.06; 95% CI: 3.64-46.87; $p < 0.001$). **Conclusions:** GER is a risk factor for COPD exacerbations. The role of GER in COPD management should be studied in greater detail.

Keywords: Pulmonary disease, chronic obstructive; Gastroesophageal reflux; Meta-analysis; Risk factors; Evidence-based medicine.

Resumo

Objetivo: Examinar a relação entre refluxo gastroesofágico (RGE) e exacerbações da DPOC. **Métodos:** Foi realizada uma revisão sistemática de artigos publicados até dezembro de 2012 utilizando várias bases de dados. Os critérios de elegibilidade incluíram estudos sobre DPOC, exacerbações da DPOC e RGE que comparavam ao menos dois grupos (DPOC vs. controle ou RGE vs. controle) e descrevendo riscos relativos (RRs), razões de prevalência ou ORs e respectivos IC95% (ou com dados que permitissem o seu cálculo) para a associação entre RGE e DPOC, assim como taxas de exacerbações. Os dados foram coletados com um formulário padronizado que incluía o tipo de estudo; critérios para diagnóstico de RGE; idade e gênero dos participantes; número de participantes; método de randomização; escores de gravidade; métodos de avaliação dos sintomas de RGE; critérios de definição de exacerbação; taxa de exacerbações (hospitalizações, visitas à emergência, consultas não programadas, uso de prednisona e uso de antibióticos); sintomas de RGE no grupo DPOC vs. controles; média de exacerbações da DPOC (com sintomas vs. sem sintomas); frequência anual de exacerbações; tratamento para RGE; e gravidade da obstrução. **Resultados:** O RGE foi claramente identificado como um fator de risco para exacerbações da DPOC (RR = 7,57; IC95%: 3,84-14,94), com um aumento na média de exacerbações por ano (diferença média: 0,79; IC95%: 0,22-1,36). Houve uma prevalência significativamente maior de RGE em pacientes com DPOC do que naqueles sem DPOC (RR = 13,06; IC95%: 3,64-46,87; $p < 0,001$). **Conclusões:** O RGE é um fator de risco para exacerbações da DPOC. O papel do RGE no manejo da DPOC deve ser mais profundamente investigado.

Descritores: Doença pulmonar obstrutiva crônica; Refluxo gastroesofágico; Metanálise; Fatores de risco; Medicina baseada em evidências.

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Introduction

Exacerbations of COPD are critical events in the natural history and management of the disease because they are related to the worsening of quality of life,[1,2] accelerated decline in lung function,[1,2] hospital admissions,[2-5] increased risk of death,[1,3,5] and high use of health care resources.[1,3,4] Despite the negative impact of exacerbations on the natural course of the disease, little is known about their causes.[2,5]

Recent studies have suggested that the main determinants for COPD exacerbations are a previous history of exacerbations,[2,4] a low level of physical activity,[4] the severity of the disease,[2,4,5] and the presence of comorbidities, such as gastroesophageal reflux (GER), congestive heart failure, coronary artery disease, and chronic renal/liver failure.[4,6-8] However, the role of GER in this setting remains unclear.

Roughly one-half of the adult population in industrialized countries has a personal experience of GER symptoms, and 20-30% suffer from GER disease (GERD).[9] Presumably, GERD is the most common disease of the digestive tract[9,10] and has been shown to worsen asthma control, due to esophagobronchial reflex,[11,12] and to heighten bronchial reactivity.[11,13,14] In addition, GERD is a determinant of microaspiration.[14,15] It has also been reported that GER is accompanied by neutrophilic airway inflammation,[16] and COPD has the same type of inflammation,[17] which in turn could be increased by this association. Moreover, microaspiration of gastric contents or bronchospasm induced by the vagus nerve due to the irritation of the esophagus caused by the gastric acid might contribute to the association between GER and pulmonary disease/symptoms.[4,15,18]

The association between GER and COPD exacerbation remains unclear.[15,19] One explanation is that GER acts as a collaborating factor of COPD exacerbations by increasing airway inflammation. Therefore, the aim of this meta-analysis was to evaluate the impact of GER on COPD exacerbations.

Methods

We conducted a systematic search of the Medline (PubMed, from 1966 to December 2012), EMBASE (from 1974 to December 2012), the Cochrane Controlled Trials Register (1960-2007), and LILACS (from 1982 to December 2012) databases. We created three groups of keywords, using the connectors "OR" and "AND" within each group and between groups, respectively. We used the following keywords in the first group: "COPD", "chronic bronchitis", and "emphysema". For the explanatory variable, the second group comprised the terms "GERD", "GORD", "GOR" "gastroesophageal reflux", "gastro esophageal reflux", "gastroesophageal reflux disease", "gastro esophageal reflux disease", "gastrooesophageal reflux", "gastro oesophageal reflux", "gastrooesophageal reflux disease", "gastro oesophageal reflux disease", "laryngopharyngeal reflux", and "swallowing". The third group of keywords was used in order to restrict the study design: "cohort", "prospective", "retrospective", "clinical trial", "cross sectional", or "case-control". The bibliographic references of all of the selected articles were also searched, even if they had not been identified by the database search.

Eligibility criteria

Eligibility criteria for the selection of articles were as follows: articles published in English, Spanish, or Portuguese; articles involving patients with COPD (defined by the Global Initiative for Chronic Obstructive Lung Disease criteria),[1] emphysema, or chronic bronchitis; articles reporting the rate of COPD exacerbations, defined by the number of hospitalizations, emergency room visits, and unscheduled clinic visits, as well as by the need for prednisone course/antibiotics or the use of the criteria described by Anthonisen et al.[20]; articles comparing at least two groups (COPD vs. control, or GER vs. control); articles describing the relative risk, prevalence ratio, or odds ratios for the association between GER and COPD with the corresponding 95% CIs or with sufficient data to allow further calculations; and articles reporting exacerbations rates with corresponding 95% CIs or enough data to allow further calculations. No limitations were set for age or for the definition of GER.

Two reviewers screened the titles and abstracts of the identified citations independently and independently acquired the full text of any article that either one judged potentially eligible. The reviewers independently applied the eligibility criteria to the methods section of potentially eligible trials. Disagreements were solved by discussions with a third reviewer.

Data abstraction

Data abstraction was performed independently by two reviewers, using a protocol adapted from the study by Vandenbroucke et al.[21]

Data collection and analysis

The data were analyzed with freeware MIX, version 1.7.[22] We pooled the included studies to yield the risk ratio (RR) or odds ratio for COPD exacerbations and mean number of exacerbations per year with their respective 95% CIs or standard errors.

Selection of reviews

Data extraction and management

The data were extracted using a standardized form, including type of study design; criteria for GER diagnosis (pH monitoring or questionnaires); age and gender of participants; number of participants; randomization method; severity score (i.e., COPD classification); evaluation methods of GER symptoms; definition criteria for exacerbations; rate of exacerbations (hospitalizations, ER visits, unscheduled clinic visits, prednisone use, and antibiotics use); GER symptoms in COPD group vs. controls; mean number of COPD exacerbations (with symptoms vs. without symptoms); annual frequency of exacerbations; GER treatment; and severity of airflow obstruction.

Assessment of methodological quality of included reviews

Data synthesis

We presented all point estimates as RR or as mean ± SE. We used forest plots in order to display the results. The selected trials were combined with freeware MIX.[22] For dichotomous variables, we calculated a fixed-effect RR and the respective 95% CIs for individual studies.

We calculated the mean difference (MD) with 95% CI for continuous variables. When standard deviations (SD) were reported, they were used in order to calculate SE using the following formula:

$$SD = SE \times \text{sqrt}(N) \quad (1)$$

If SDs were unavailable for continuous variables, we analyzed them by transforming 95% CIs into SEs according to the following formula:

$$SE = (\text{upper limit of 95\% CI} - \text{lower limit of 95\% CI}) \div (1.96 \times 2) \quad (2)$$

In addition, OR was adapted to the relative risk using the following formula[23]:

$$\text{Relative risk} = \frac{OR}{(1 - Po) + (Po \times OR)} \quad (3)$$

where Po is the observed prevalence.

We quantified inconsistencies among the pooled estimates using the following formula:

$$I^2 = [(Q - df)/Q] \times 100\% \quad (4)$$

where Q is chi-square, and df is its degrees of freedom.

This illustrates the percentage of the variability, which, in effect, reveals estimates resulting from heterogeneity rather than from a sampling error.[24] If heterogeneity was found, we used a random-effects model. We performed sensitivity analyses by comparing random-effects and fixed-effect models. Potential for publication bias was assessed using the Egger test and funnel plots.

Results

The electronic database searches identified a total of 543 articles. We excluded 507 articles upon review of the titles and abstracts. The review of titles yielded 36 articles that were further examined. Among the remaining 36 articles, some were further excluded due to the following causes: missing information on COPD, GER, or exacerbations[25-32]; review articles[6,12,15,33-37]; lack of adequate data for the meta-analysis[18,28,38-42]; and inclusion/exclusion criteria that made the study unrepresentative of the population.[43] After that, a review of the abstracts and the full texts yielded 11 articles that appeared to fulfill the inclusion criteria. Of the 11 articles, 7 met the inclusion criteria and were included in the analysis (Figure 1).[4,19,44-48] The characteristics of the studies included in the meta-analysis are presented in Table 1. No unpublished or ongoing studies were included.

Increased risk of COPD exacerbations in GER patients

An elevated risk of COPD exacerbations in GER patients was researched by calculating the

RR of COPD exacerbations between patients with and without GER. We found that GER patients showed a risk of having an exacerbation seven times higher than did those without GER (RR = 7.57; 95% CI: 3.84-14.94; z = 5.83; $t^2 = 0.0$; p < 0.0001). We used a fixed-effect model, justified by the low heterogeneity (Q = 1.07; $I^2 = 0.0$; p = 0.89) of the studies (Figure 2). The analysis included 341 patients from all studies.

We further examined the increase in the number of COPD exacerbations in GER patients. In that analysis, we used a random-effects model because of the high heterogeneity (Q = 9.95; p < 0.04; $I^2 = 59.8\%$) instead of a fixed-effect model. Patients with GER showed a higher number of exacerbations per year (MD = 0.79; 95% CI: 0.22-1.36; z = 2.69; $t^2 = 0.23$; p < 0.007) than did those without GER (Figure 3). The analysis included 2,418 patients from all studies.

Association between GER and COPD

In order to determine the association between GER and COPD, we used a fixed-effect model (Q = 0.39; p = 0.94). The pooled analysis found a significantly higher prevalence of GER in COPD patients than in those without COPD (RR = 13.06; 95% CI: 3.64-46.87; z = 3.94; $t^2 = 0.0$; p < 0.001; Figure 4). The analysis included 476 patients from all studies.

Discussion

The present systematic review with meta-analysis showed that GER is a risk factor for COPD exacerbations based on the higher risk for exacerbations and the increased number of exacerbations per year in these patients. In addition, our analyses showed a significant association between GER symptoms and COPD diagnosis. This association is corroborated by the increased frequency of exacerbations per year in patients with GER.

This is the first meta-analysis investigating GER as a risk factor for COPD exacerbations. The major issues about the effect of GER in COPD exacerbations are how exacerbations are determined or defined and whether such determinations are carried out prospectively or retrospectively. Recent retrospective studies[47,48] suggested that GER symptoms were associated with exacerbations; however, in those studies, the subjects were asked to report the number of exacerbations that had occurred during the previous year, which was an approach that could result in a recall bias. To solve this type of problem, other studies[19,45] utilized a prospective questionnaire-based data collection system that allowed us to identify exacerbations according to a more reliable definition of COPD exacerbation, such as the modified criteria by Anthonisen et al.[20] The prospective analyses of Terada et al.[19] and Hurst et al.[4] presented the most reliable information about exacerbations and were the most influential studies on the forest plots about the risk of COPD exacerbations associated with GER (Figure 5).

When less rigid criteria for the definition of an exacerbation were used, we found an increase in the frequency of exacerbations among GER patients. We conducted a preliminary analysis including studies with less rigid criteria,[40,41,48] which demonstrated a similar tendency of the risk of exacerbations (RR = 7.68), a similar increase in the frequency of exacerbations (mean increase = 1,02 per year) among GER patients, and a similar increased risk of GER associated with COPD (RR = 2.82) when compared with the results found in our final analysis (data not shown). Although only one study[44] utilized pH monitoring as the gold standard for the diagnosis of GER, the risk of exacerbations and GER in subjects with COPD demonstrated a good homogeneity across the studies.

Exacerbations of COPD are an important outcome in the natural history of the disease,[29,49-52] not only because they pose a considerable economic burden,[53] but, more importantly, because repeated COPD exacerbations can deteriorate health-related quality of life, accelerate the progression of the disease,[50-52] and lead to premature death.[3,50,52]

Over time, COPD exacerbations become more frequent and more severe, and this is associated with increasing functional impairment.[52] Risk factors for repeated exacerbations include low pre-treatment FEV_1,[4,49,51] increased use of bronchodilators or corticosteroids,[4,48] previous exacerbations (more than two in the last two years),[4,49] prior use of antibiotics,[4,51] and presence of comorbid conditions.[4,29]

Studies have reported in-hospital mortality rates of 11-24%[17] and of 35.6%[50] after two years. Patients with frequent exacerbations had the highest mortality rates (p < 0.001), with a risk of death 4.3 times greater than that for patients requiring no hospital management.[51] Thus, the

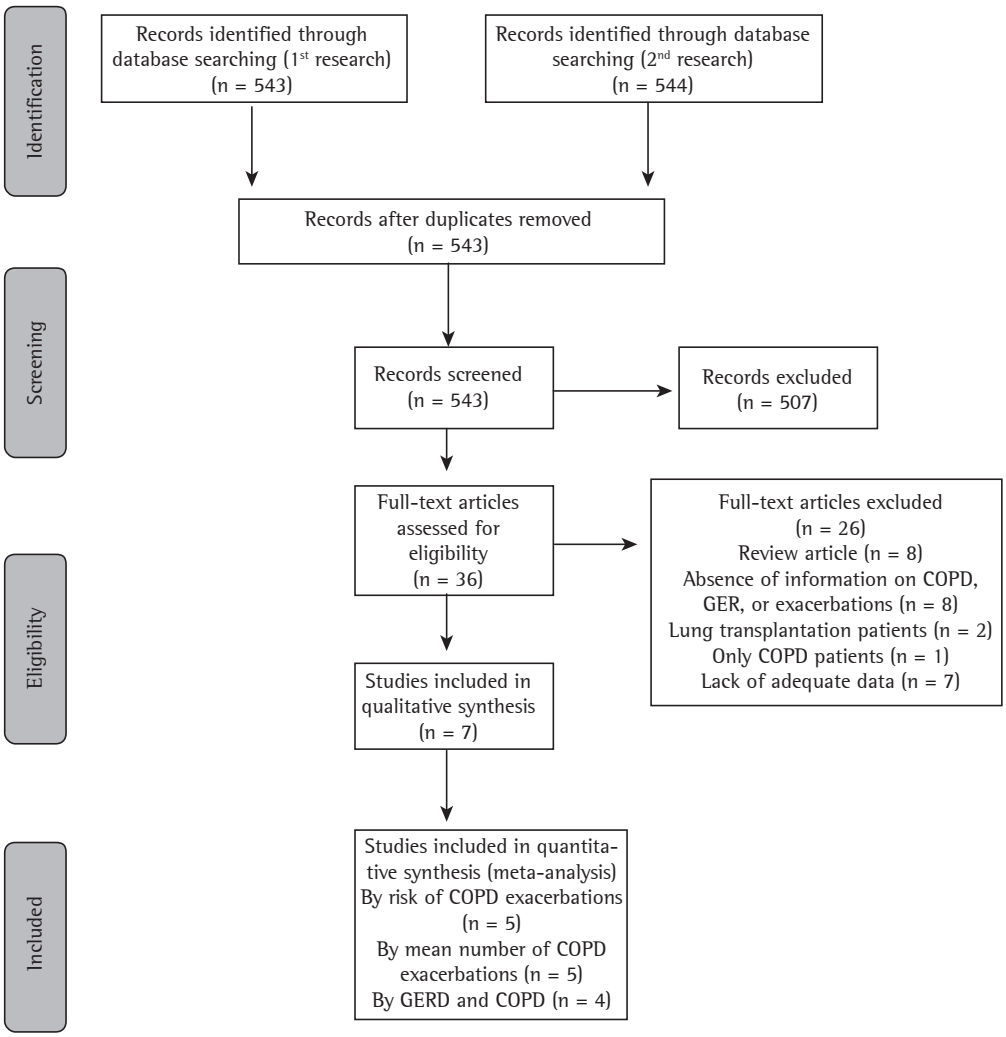

Figure 1 - Flowchart of study selection. GER(D): gastroesophageal reflux (disease).

exacerbation itself might be a significant factor associated with increased mortality in COPD patients; however, the severity of the underlying disease might influence the patient outcome. Some studies[4,19,45,47,48] demonstrated an increase in the number of exacerbations per year related to GER, but its independent association with GER, using adequately controlled multivariate analysis, is yet to be tested.[25]

Another issue is the lack of a gold standard or of objective measurements in order to diagnose GER in the different studies, which makes it difficult to select studies and homogenize the data regarding the diagnosis of GER. The lack of a gold standard can overestimate or underestimate GER in some populations or samples. Respiratory patients frequently experience chest discomfort that can be confused with reflux symptoms, primarily pyrosis, leading to an overestimation of reflux symptoms. According to Sweet et al.,[6] the typical reflux symptoms (heartburn, regurgitation, and dysphagia), have a limited correlation with objectively measured reflux, reaching a sensitivity of 89.5% and a specificity of only 47.1%. These data make studies based on symptom questionnaires inaccurate when compared with those based on more specific tests, such as 24-h pH monitoring and esophageal scintigraphy.[30] In our meta-analysis, 6 of the 7 studies included were based on questionnaires, and, therefore, all of the conclusions should be inferred from GER symptoms as a risk factor, since there was

no diagnostic confirmation of GER. However, the impact of studies based on questionnaires might underestimate this association. The only study[44] included in the present meta-analysis that had objective criteria demonstrated the strongest association between GER symptoms and COPD exacerbations. Prospective studies must be designed in order to identify GER objectively and to demonstrate the impact of GER treatment on COPD exacerbations.

A subanalysis of COPD patients receiving antireflux therapy[47] has shown that the number of COPD exacerbations per year in those patients who had controlled or non-symptomatic GER tended to decrease. In a randomized controlled trial, Sasaki et al.[25] showed that the treatment with lansoprazole

Table 1 - Characteristics of the seven studies included in the present meta-analysis.

Study	Characteristics of the study	Results	Comments
Hurst et al.[4]	Population-based cohort study; 2,138 COPD patients; stages 2 to 4 according to GOLD criteria; females/males: 35%/65%; mean age = 63 years; self-reported symptoms and history of GER or heartburn.	Mean number of COPD exacerbations: GER group = 1.41 per person per year; no GER group = 1.11 per person per year; risk of exacerbations in first year: OR =1.69 (95% CI: 1.38-2.06).	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study.
Terada et al.[45]	Population sample; 67 COPD patients and 19 controls; both genders.	Number of exacerbations: COPD group = 2.82 (95% CI: 1.92-3.72) per year; controls = 1.56 (95% CI: 0,92-2.19) per year; GER risk for COPD exacerbations: RR = 6.24 (95% CI: 0.90-43.34); in the multivariate analysis, abnormal swallowing reflex was associated with ≥ 3 exacerbations per year; p = 0,01).	Abnormal swallowing reflex: COPD (22/67), controls (1/19; p = 0.02).
Eryuksel et al.[48]	29 COPD patients (ATS criteria); LPR criteria: reflux symptoms index by Belafsky et al., reflux finding score (Belafsky et al.) and indirect laryngoscope.	13/29 patients with LPR (44%); number of exacerbations in the last year: GER (or LPR) = 1.38 ± 1.5; no GER (or no LPR) = 1.06 ± 1.06.	COPD symptom score: patients were asked about the severity of dyspnea, cough, wheezing, and the frequency of use of short-acting β_2 agonist during the last month. Definition of COPD exacerbation: any worsening of dyspnea, increase in the amount of sputum, or change in the color of sputum during the previous year. The frequency of exacerbations in each subject was retrospectively collected. At baseline, the groups were similar in terms of the incidences of antibiotic use (p = 0.652), steroid use (p = 0.267), ER visits (p = 0.677), outpatient visits (p = 0.620), hospitalizations (p = 0.448), and number of exacerbations (p = 0.52) during the last year.

Table 1 - Continued...

Study	Characteristics of the study	Results	Comments
Terada et al.[19]	Prospective and retrospective study; 82 COPD patients and 40 matched controls; moderate to severe COPD (GOLD criteria); symptoms evaluated by questionnaire (FSSG), surveyed for 6 months; exacerbations defined according to criteria by Anthonisen et al.[20]	Simple analysis: GER symptoms vs COPD exacerbation: RR = 1.93 ($p < 0.01$); mean number of COPD exacerbations (retrospective - previous year): with GER symptoms: 1.73 ± 1.58; without GER symptoms: 0.70 ± 1.20. Additional 6 months surveyed: GER symptoms were also significantly associated with annual frequency; the frequency was 2.6 ± 2.0 in subjects with GER symptoms and 1.5 ± 1.7 in subjects without such symptoms ($p = 0.048$). GERD symptoms were significantly related to frequent (≥ 3 episodes per year) exacerbations (RR = 2.18; 95% CI: 1.10-5.70; $p = 0.046$). GER symptoms vs. COPD: RR = 2.15 (95% CI: 0.88-5.25).	GER symptoms: 22/82 (COPD), 5/40 (controls). Frequency of exacerbations associated with FSSG score ($p = 0.03$; $r = 0.24$). EBC pH was significantly lower in subjects with GER symptoms than in subjects without GER symptoms (6.47 ± 1.22 vs. 7.17 ± 1.05; $p = 0.02$) in COPD patients and in controls (6.34 ± 1.22 vs. 7.22 ± 0.53; $p = 0.03$). Multiple regression: association between GERD symptoms and occurrence of exacerbations (RR = 6.55).
Rascon-Aguillar et al.[47]	GER definition: heartburn and/or acid regurgitation weekly. Patients with COPD: FEV_1/FVC ratio < 70%; 91 patients: 5 lost to follow-up, 1 twice; total: 86 patients (32 GER+, 54 GER–) GER+ = 37% of the sample.	Exacerbations/year (GER+ vs. GER– groups) = 3.2 ± 3.1; SE = 0.548 vs. 1.6 ± 1.6; SE = 0,21 ($p = 0.02$; RR = 2.0; SE = 2.60). Patients who had weekly GER symptoms had significantly more hospitalizations due to COPD than did those without weekly GER symptoms ($p = 0.007$). All types of exacerbations were also significantly increased in the weekly GER group with the exception of prednisone use, which showed only an increased numerical trend.	A subanalysis of the patients receiving antireflux therapy demonstrated that the number of COPD exacerbations in the patients who were receiving PPIs and had controlled or non-symptomatic GER had a mean of 1.6 ± 0.9 exacerbations/year compared with symptomatic GER group receiving PPIs (3.7 ± 3.3 exacerbations/year; $p = 0.09$), indicating a trend toward a higher number of yearly exacerbations.
Phulpoto et al.[46]	Prospective case-control study; 100 COPD patients, 150 controls.	Patients with GER: COPD group, 25%; controls, 9.33%; $p = 0.001$. GER and COPD: RR = 2.68 (95% CI: 1.47-4.90).	GER symptoms vs. reduced FEV_1 (25% vs. 0%; $p = 0.001$).
Casanova et al.[44]	42 COPD male patients, 16 volunteers; 24-h pH monitoring for GERD diagnosis.	GER: 26/42 COPD patients (62%) and 3/16 controls (19%); RR = 3.30 (95% CI: 1.16-9.41).	58% presented with any GER symptoms; decreased saturation coincided with esophageal acidity in 40% in the GER group.

GOLD: Global Initiative for Chronic Obstructive Lung Disease; GER(D): gastroesophageal reflux (disease); LPR: laryngopharyngeal reflux; ATS: American Thoracic Society; FSSG: frequency scale for the symptoms of gastroesophageal reflux disease; EBC: exhaled breath condensate; and PPIs: proton pump inhibitors.

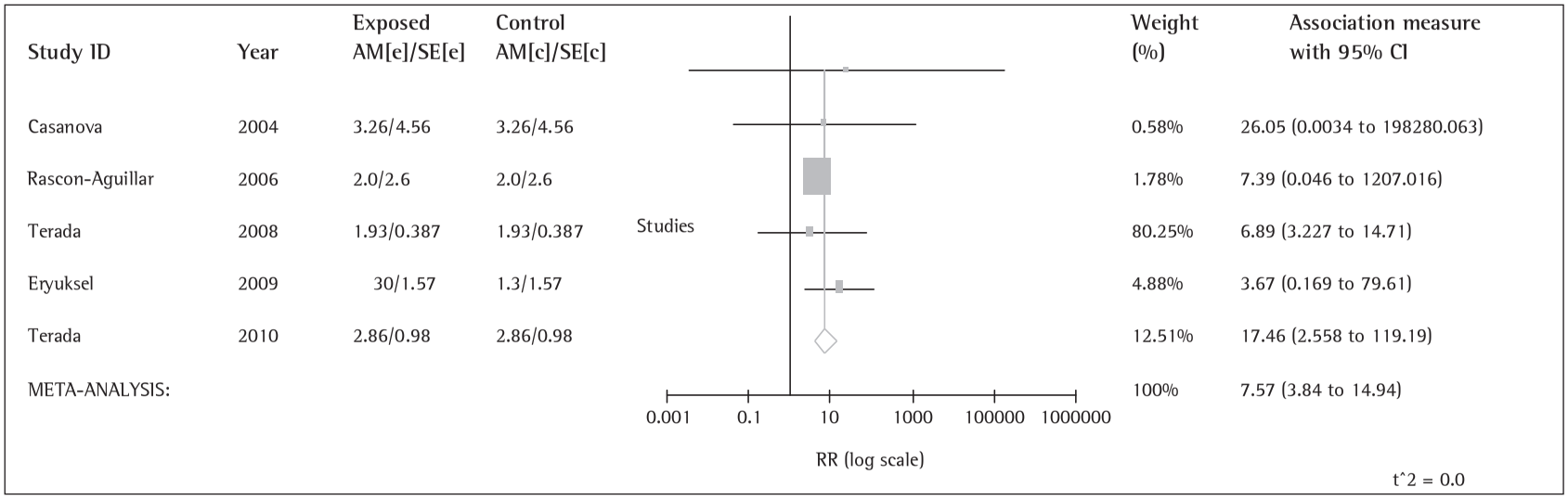

Figure 2 - Risk of COPD exacerbations according to gastroesophageal reflux. RR: relative risk.

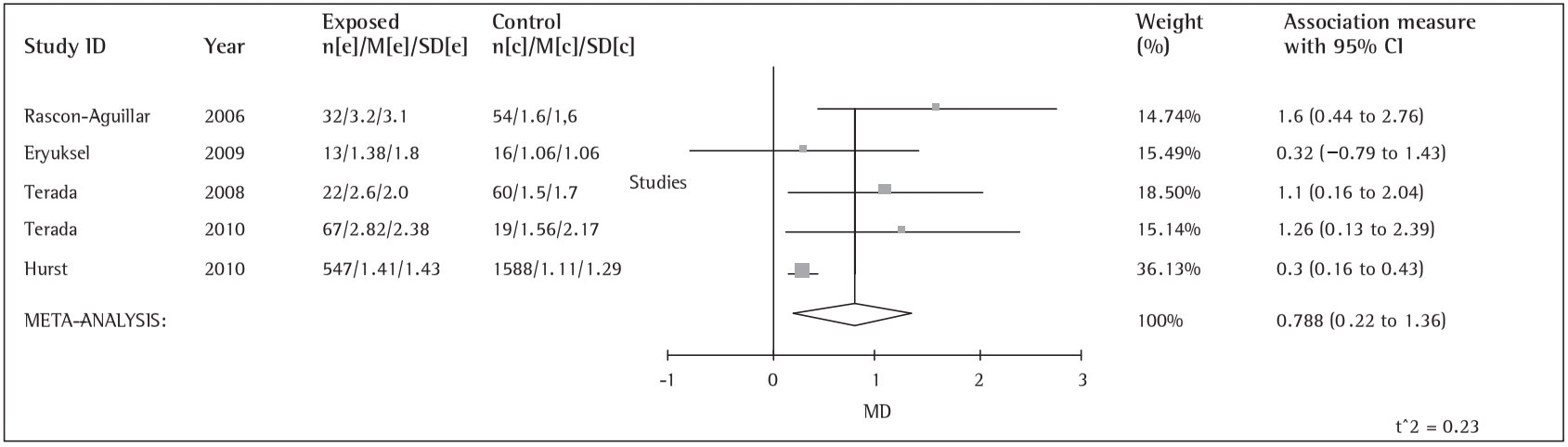

Figure 3 - Mean number of COPD exacerbations associated with gastroesophageal reflux. MD: mean difference.

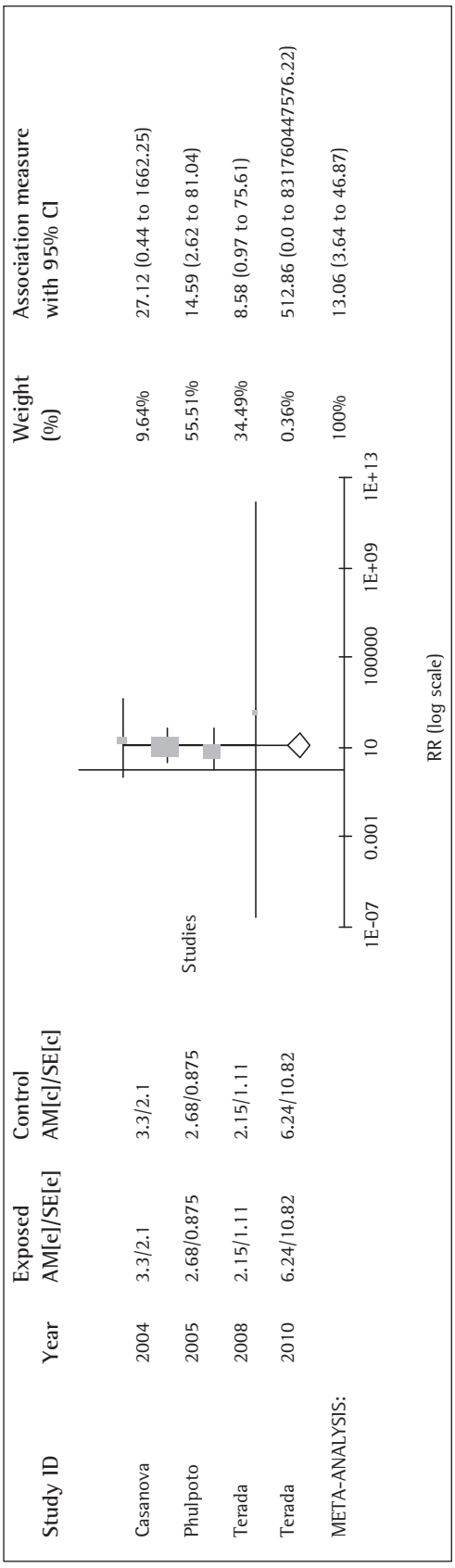

Figure 4 - Risk of gastroesophageal reflux associated with COPD. RR: relative risk.

(15 mg/day) in COPD patients without GER was capable to avoid COPD exacerbations in 77% of the patients (OR = 0.23). Those results must be seen with caution. Some authors[9,10] are skeptical about such data, since the association between asthma and GER is apparently stronger[14,16] than is the association between COPD and GER. In addition, intensive acid suppression in asthma patients, a population more likely to experience acid reflux, with esomeprazole (40 mg bid) did not reduce the number of exacerbations.[11,13] Clinically, silent acid reflux is not a reliable predictor of the success of antireflux treatment in asthma patients.[10]

The reason for such an association is unclear. The most common explanation is that the aspiration of reflux, either acid or not, increases airway inflammation and leads to an increased risk of exacerbations. However, the occurrence of chronic bronchitis clinically increases the risk of COPD exacerbations. A comparative analysis of COPD patients with and without chronic bronchitis, corrected for smoking status, body mass index, medication use, and pulmonary function, would be a much stronger argument for the presence or absence of a role played by GER in COPD exacerbations than would the present analysis. However, the differentiation between chronic bronchitis and emphysema was not performed in the studies included here.[2] We can speculate that there is a higher risk of COPD exacerbations or of GER in COPD patients with a history of chronic bronchitis.

Alternatively, it has been suggested by a number of investigators[26,28,34,47,54,55] that the association between GER and a wide range of respiratory diseases is best explained by the diseases causing or contributing to GER. There are various plausible hypotheses supporting this explanation. First, the high prevalence of hiatus hernia is due to chronic cough associated with different lung diseases.[26,39] Although there is not a perfect correlation between hiatus hernia and reflux, reflux is more likely to occur in the presence of larger hiatus hernia.[10] The diaphragm contributes to reduce the esophageal function, and any alteration between the two will affect its function. Second, bronchodilators also relax gastrointestinal smooth muscles and can facilitate reflux, and some drugs, such as theophylline, increase the production of gastric acid and, consequently, can cause acid reflux.[18,27,38,48]

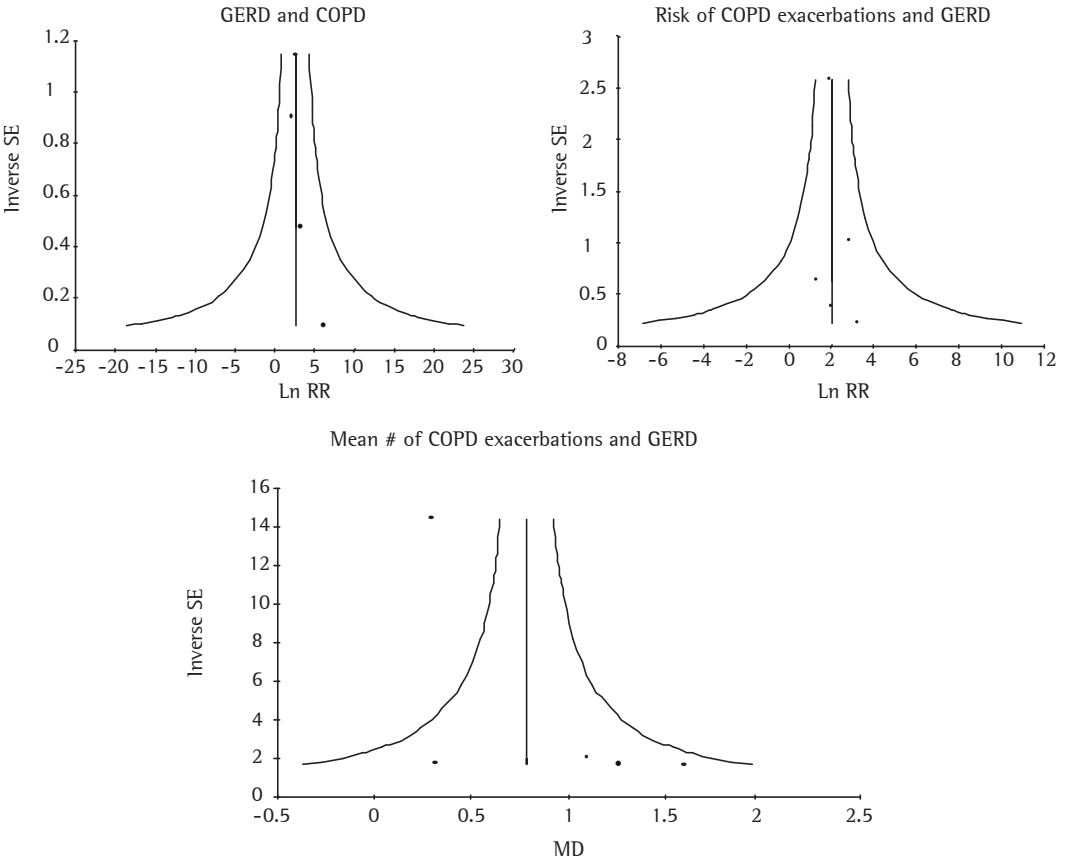

Figure 5 - Funnel plots. GERD: gastroesophageal reflux disease; Ln RR: linear relative risk; and MD: mean difference.

In conclusion, we found that COPD patients with GER symptoms were more likely to experience exacerbations than were those lacking these symptoms. Objectively evaluating the presence of GER in such patients might determine future strategies to reduce or control GER and, subsequently, decrease the number of COPD exacerbations.

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Effects of an outpatient education program in patients with uncontrolled asthma*

Efeitos de um programa educativo ambulatorial em pacientes com asma não controlada

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Abstract

Objective: To evaluate the effects of an outpatient education program in patients with uncontrolled asthma. **Methods:** This was an uncontrolled study evaluating an educational intervention and involving patients with uncontrolled asthma ≥ 14 years of age. The participants completed a questionnaire designed to assess the level of asthma control, the inhalation technique, and quality of life. All of the patients underwent pulmonary function testing, after which they participated in an education program consisting of one 45-min face-to-face session, followed by phone interviews at two, four, and eight weeks. The participants were reevaluated after three months. **Results:** Sixty-three patients completed the study. There was a significant improvement in the level of asthma control ($p < 0.001$). Of the 63 patients, 28 (44.4%) and 6 (9.5%) were classified as having partially controlled asthma and controlled asthma, respectively. The mean FEV_1 was 63.0 ± 20.0% and 68.5 ± 21.2% of the predicted value prior to and after the educational intervention, respectively ($p = 0.002$), and all of the quality of life scores improved ($p < 0.05$ for all). The same was true for the proportion of patients prior to and after the educational intervention using the proper inhalation technique when using metered dose inhalers (15.4% vs. 46.2%; $p = 0.02$) and dry powder inhalers (21.3% vs. 76.6%; $p < 0.001$). The logistic regression analysis revealed that an incorrect inhalation technique identified during the first evaluation was independently associated with a favorable response to the educational intervention. **Conclusions:** This study suggests that an outpatient education program for asthma patients improves the level of asthma control, lung function parameters, and quality of life. An incorrect inhalation technique identified during the first evaluation was predictive of a favorable response to the educational intervention.

Keywords: Asthma/prevention and control; Quality of life; Respiratory function tests; Ambulatory care; Health education.

Resumo

Objetivo: Avaliar os efeitos de um programa educativo ambulatorial em pacientes com asma não controlada. **Métodos:** Estudo não controlado, avaliando uma intervenção educacional e envolvendo pacientes com idade ≥ 14 anos com asma não controlada. Os participantes responderam a um questionário para avaliar o grau de controle da asma, a qualidade de vida e a técnica inalatória e foram submetidos a testes de função pulmonar. A seguir, participaram do programa educativo, que consistia de uma sessão inicial de 45 min e de entrevistas telefônicas em duas, quatro e oito semanas. Os participantes foram reavaliados após três meses. **Resultados:** Completaram o estudo 63 pacientes. Houve melhora significativa no grau de controle da asma ($p < 0,001$). Dos 63 pacientes, 28 (44,4%) e 6 (9,5%) passaram a apresentar asma parcialmente controlada e controlada, respectivamente. Antes e depois a intervenção educacional, a média de VEF_1 foi, respectivamente, 63,0 ± 20,0% do previsto e 68,5 ± 21,2% do previsto ($p = 0,002$), e todos os escores de qualidade de vida melhoraram ($p < 0,05$ para todos). O mesmo ocorreu com a proporção de pacientes com técnica inalatória adequada no uso de inalador pressurizado (15,4% vs. 46,2%; $p = 0,02$) e de dispositivo de pó (21,3% vs. 76,6%; $p < 0,001$). A análise de regressão logística identificou que a técnica inalatória incorreta na primeira avaliação estava independentemente associada com a resposta favorável à intervenção educativa. **Conclusões:** Este estudo sugere que um programa educativo ambulatorial resultou em uma melhora no grau de controle da asma, na função pulmonar e na qualidade de vida. A técnica inalatória incorreta na avaliação inicial foi preditora da resposta favorável à intervenção educativa.

Descritores: Asma/prevenção e controle; Qualidade de vida; Testes de função respiratória; Assistência ambulatorial; Educação em saúde.

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Introduction

Asthma is one of the most common chronic conditions, as well as being a global health problem.[1] In Brazil, it is estimated that there are approximately 20 million individuals with asthma.[2]

The goal of asthma management is to achieve and maintain disease control.[3] However, despite the implementation of guidelines for asthma management around the world and the availability of highly effective drugs for controlling symptoms and for treating the underlying inflammatory process, asthma remains a poorly controlled disease.[4] The lack of disease control might be due to the fact that patients are being prescribed inappropriate medications or that they are using the prescribed medications incorrectly. In addition, asthma severity and comorbidities, such as gastroesophageal reflux, obesity, and smoking, can affect the level of asthma control.[5]

In addition to prescription and provision of pharmacological treatment that is appropriate to the level of asthma severity, education and guidance on asthma self-management have recently become recognized as aspects that must also be addressed within their clinical context.[1] Various types of asthma education programs have been developed. Such programs differ in terms of approach, treatment setting, and outcomes of interest.[6-17] The need to adapt this knowledge about asthma education to clinical practice and to make it accessible at public outpatient clinics specializing in asthma motivated a study to evaluate the impact of an individualized educational intervention on disease management.

The objective of the present study was to evaluate the effects of an individualized outpatient education program in patients with uncontrolled asthma.

Methods

This was a prospective uncontrolled study using a two-phase (prior to and after an educational intervention) comparison of variables. All patients who met the inclusion criteria and agreed to participate were studied sequentially.

The study protocol was approved by the Research Ethics Committee of the *Hospital de Clínicas de Porto Alegre* (HCPA, Porto Alegre *Hospital de Clínicas*—Process no. 08553). Written informed consent was obtained from all patients or their legal guardians, in the case of those under 18 years of age.

The study population comprised patients treated at the Pulmonology Department outpatient clinics of the HCPA, which is located in the city of Porto Alegre, Brazil. We included patients aged 14 years or older who had been diagnosed with asthma in accordance with either of two sets of consensus criteria,[18,19] had been classified as having uncontrolled asthma in accordance with the Global Initiative for Asthma (GINA) criteria,[19] and had made at least two prior visits to one of the outpatient clinics mentioned above.

The level of asthma control was assessed by using the classification proposed by the 2007 GINA guidelines.[19] Asthma was considered controlled if all of the following characteristics were present: daytime symptoms twice a week or less and no asthma attacks in the last 3 months; no limitation of activities of daily living; no asthma-related nocturnal symptoms or awakenings; rescue medication required twice a week or less; and normal airflow (FEV_1 and PEF equal to or greater than 80% of predicted). Asthma was considered partially controlled if one or two of those characteristics were absent, and it was considered uncontrolled if more than two of those characteristics were absent or if the patient had been admitted to the ER or hospitalized for asthma in the last 12 months. An asthma attack was defined as an exacerbation requiring the use of systemic corticosteroids.

Patients who had been diagnosed with other chronic lung diseases were excluded, as were those who did not complete the steps recommended by the study and those who did not give written informed consent.

The volunteers were interviewed by means of a questionnaire that assessed the following variables: age; gender; race; marital status; level of education; family income; smoking status; comorbidities; form of medication acquisition; regularity of use of asthma medications; type of inhaler used; correctness of inhalation technique; and classification of asthma severity.

The first interview, as well as the initial evaluations and the evaluation at 3 months, was performed by the same rater.

The questionnaire included a checklist for evaluating the patients' handling of the device used for inhaling the corticosteroid, and patients were asked to demonstrate their inhalation technique,

using placebo. For metered dose inhalers, patients were evaluated on the correctness of the following steps: a) shaking the inhaler before using it; b) exhaling normally before using the inhaler; c) holding the inhaler at an appropriate distance (3-5 cm) from the lips if a spacer is not used or, if a spacer is used, placing the inhaler in the mouth and creating an adequate seal with the lips; d) inhaling slowly and deeply after squeezing the inhaler; and e) performing a breath-hold of at least 10 seconds (after inhalation). For dry powder inhalers, patients were evaluated on the correctness of the following steps: a) exhaling normally before using the inhaler; b) placing the inhaler in the mouth and creating an adequate seal with the lips; c) inhaling as forcefully and deeply as possible; and d) performing a breath-hold of at least 10 seconds (after inhalation). The patients' inhalation technique for each type of device was considered correct only if all the steps were properly performed.

Asthma severity was classified on the basis of the daily medication regimen in use, as proposed by the 2002 GINA guidelines.[20]

Pulmonary function was assessed, with the use of a computerized spirometer (Jaeger-v4.31; Jaeger, Würzburg, Germany), at the initial interview and 3 months later. We recorded FVC, FEV_1, and the FEV_1/FVC ratio. All parameters are expressed as absolute values or as a percentage of predicted values for age, gender, and height.[21]

We measured PEF using a portable peak flow monitor (Vitalograph; Boehringer Ingelheim, Ingelheim am Rhein, Germany). The results are expressed as absolute values or as a percentage of predicted values for age, gender, and height.[22]

Quality of life was assessed by using a specific questionnaire—the Asthma Quality of Life Questionnaire (AQLQ) [23-26]—which has been translated into Portuguese and validated for use in Brazil.[27] This questionnaire contains 32 questions, grouped into four domains: activity limitation; symptoms; emotional function; and environmental stimuli. The AQLQ can be administered by an interviewer, or it can be self-administered. The total score of the questionnaire is the arithmetic mean of all items, the minimum score being 1 and the maximum score being 7. Higher scores mean better asthma-related quality of life. The minimum significant change in score is 0.5, with a 1-point change being considered moderate and a 1.5-change being considered large. In the present study, the questionnaire was self-administered.

The educational intervention consisted of an initial multistep approach and of phone interviews at 2, 4, and 8 weeks.

The education step was started after an outpatient visit and involved one face-to-face session of approximately 45 min, delivered by the research team's physical therapist. The session followed a structured schedule that included verbal and written instruction and addressed the following points: what asthma is and what its symptoms are; environmental control and how to avoid asthma triggers; the importance of inhaled corticosteroids, as well as of combined inhaled corticosteroids and long-acting β_2 agonists, for preventive disease management; how to obtain asthma medications via the public health care system and how to overcome the limitations; inhalation technique assessment and correction of any errors found; the need for using a spacer when inhaled corticosteroids are delivered by a metered dose inhaler; and clarification and additional instruction as needed.

The education step was followed by 30-min phone interviews at 2, 4, and 8 weeks after inclusion in the study. In each interview, patients were assessed on their level of asthma control; the importance of the use of inhaled corticosteroids was reviewed and reinforced, as were the steps required for correct use; the use of a spacer with a metered dose inhaler was reviewed and stimulated; the level of environmental control was assessed; clarification was provided; and solutions were sought to potential problems.

The participants were reevaluated in a routine visit 3 months after the initial interview.

The primary outcome measure of the study was the proportion of patients who, after the educational intervention, were classified as having controlled asthma or partially controlled asthma. Secondary outcome measures were the quality of life scores and lung function parameters (PEF and FEV_1 values).

Effective use of inhaled corticosteroids and long-acting β_2 agonists was defined as self-reported adherence of five days a week or more.

Data were analyzed with the Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago, IL, USA). Quantitative data are expressed as mean and standard deviation or as median and interquartile range, whereas qualitative

data are expressed as absolute numbers and percentages. Quantitative data were compared by the t-test for paired samples or by the Wilcoxon matched-pair sign-rank test, whereas qualitative data were analyzed by the chi-square test or by McNemar's test.

The variables gender, race, age, age at asthma diagnosis, level of education (dichotomized into ≤ 9 years of schooling and < 9 years of schooling), family income (dichotomized into ≤ 3 times the national minimum wage and > 3 times the national minimum wage), marital status (dichotomized into married and single/widowed/separated), asthma severity (dichotomized into severe and mild/moderate), FEV_1, inhalation technique (performing all the steps correctly or performing any of the steps incorrectly), type of inhaler (metered dose inhaler or dry powder inhaler), and form of medication acquisition (fully on the patient or fully on public funds) were included individually in a binary logistic regression model (enter method) in order to identify characteristics predictive of a favorable response to the educational intervention. A favorable response was defined as a change in classification to that of controlled asthma or partially controlled asthma after the educational intervention. An unfavorable response was defined as no change in the classification of uncontrolled asthma after the educational intervention. Variables with significance at 0.1 or less, adjusted for gender and age, were included in the multivariate binary logistic regression model (enter method) for predictors of a favorable response.

All statistical tests were two-tailed. The level of significance was set at 5%.

The sample size was calculated by using PASS 2005: Power Analysis and Sample Size software (NCSS, Kaysville, UT, USA), considering the proportion of patients who, after the educational intervention, would be classified as having controlled asthma or partially controlled asthma. The proportion value for testing the alternative hypothesis was fixed at 0.25, whereas that for testing the null hypothesis was fixed at 0.05. Assuming an alpha value of 0.05 and a power of 80%, we estimated that it would be necessary to study at least 63 patients.

Results

Between March of 2009 and March of 2011, 79 patients with uncontrolled asthma were evaluated. Of those, 5 declined to participate in the study, 10 withdrew from the study after the first evaluation (did not report for reevaluation at 3 months), and 1 was excluded for having COPD. Therefore, 63 patients completed the study.

Table 1 shows the general characteristics of the patients. Of the 63 patients, 53 (84.1%) were female and 48 (76.2%) were White. The mean age of the individuals was 49.3 ± 14.1 years, and the median age at asthma diagnosis was 20.0 years.

Fifty-five patients (87.3%) presented with at least one comorbidity, whereas 31 patients (49.2%) were obese (body mass index ≥ 30 kg/m^2), 21 (33.3%) had cardiovascular disease, and 19 (30.2%) had gastroesophageal reflux.

Table 2 shows the level of asthma control and lung function results prior to and after the educational intervention. After the intervention, there was a significant improvement in the level of asthma control ($p < 0.001$). Of the 63 patients, 28 (44.4%) were classified as having partially controlled asthma, and 6 (9.5%) were classified as having controlled asthma, whereas 29 (46%) continued to be classified as having uncontrolled asthma. There was significant reduction in the proportion of patients who were treated in the emergency room for asthma exacerbation prior to and after the intervention (50.8% vs. 25.4%; $p = 0.007$). There was a significant improvement for the following variables: PEF, in % of predicted ($p = 0.019$); FVC, in L ($p = 0.031$); FVC, in % predicted ($p = 0.024$); FEV_1, in L ($p = 0.003$); FEV_1, in % of predicted ($p = 0.002$); and FEV_1/FVC ratio, in % of predicted ($p = 0.07$). However, the change in FEV_1 was less than 200 mL and than 12%.

Table 3 shows data on medication acquisition, asthma medication use, and inhalation technique prior to and after the educational intervention. There were no significant differences for the proportion of patients who obtained the medications with their own funds ($p = 1.00$), for the proportion of patients who obtained the medications via the health care clinic ($p = 0.549$), or for the proportion of patients who obtained the medications via the State Department of Health ($p = 1.00$). There was also no significant change in effective use of medications containing inhaled corticosteroids ($p = 0.18$) or of medications containing long-acting β_2 agonists ($p = 1.00$). The proportion of patients who performed all

the steps of the inhalation technique correctly increased significantly from 15.4% to 46.2% (p = 0.021) among those who used metered dose inhalers and from 21.3% to 76.6% (p < 0.001) among those who used dry powder inhalers. The proportion of patients who used a spacer with their metered dose inhaler increased significantly from 36% to 68% (p = 0.021).

Table 1 - General characteristics of the 63 patients with uncontrolled asthma included in the study.[a]

Variables	Values
Gender	
Male	10 (15.9)
Female	53 (84.1)
Race	
White	48 (76.2)
Non-White	15 (23.8)
Age, years[b]	49.3 ± 14.1
Age at diagnosis, years[c]	20.0 (34.0)
Level of education	
9 years of schooling	41 (65.1)
High school	16 (25.4)
College	6 (9.5)
Family income, number of times the national minimum wage	
≤ 3	58 (92.1)
4-10	4 (6.3)
> 10	1 (1.6)
Asthma severity	
Mild persistent	2 (3.2)
Moderate persistent	10 (15.9)
Severe persistent	51 (81.0)
Smoking status	
Never smoker	47 (74.6)
Current smoker	0 (0)
Former smoker	16 (25.4)

[a]Values expressed as n (%), except where otherwise indicated [b]Values expressed as mean ± SD. [c]Values expressed as median (interquartile range).

Table 4 shows quality of life assessment data prior to and after the educational intervention. The AQLQ total score and domain scores improved significantly (p < 0.001 for all).

In the binary logistic regression to identify predictors of a favorable response to the educational intervention, age, % predicted FEV_1, and inhalation technique reached a significance of p < 0.1. These variables were included in the multivariate binary logistic regression model, adjusted for gender and age. Table 5 shows the results of this analysis. An incorrect inhalation technique was independently associated with a favorable response to the educational intervention (p = 0.005).

Discussion

In the present study, we observed that an individualized outpatient education program for patients with uncontrolled asthma had a positive effect on the level of asthma control in a clinical follow-up of 3 months. Of the 63 patients with uncontrolled asthma studied, 28 (44.4%) were reclassified as having partially controlled asthma and 6 (9.5%) were reclassified as having controlled asthma. Secondarily, there was improvement in lung function parameters (although it did not reach the minimum clinically significant change) and in all AQLQ domains.[23,24] The proportion

Table 2 - Level of asthma control and pulmonary function results prior to and after the educational intervention.[a]

Variables	Pre-intervention	Post-intervention	p
Level of asthma control			
Controlled	0.0 (0.0)	6 (9.5)	< 0.001
Partially controlled	0.0 (0.0)	28 (44.4)	
Uncontrolled	63 (100.0)	29 (46.0)	
Emergency room visit for asthma	32 (50.8)	16 (25.4)	0.007
Pulmonary function[b]			
PEF, L/min	229.7 ± 102.1	248.4 ± 96.4	0.053
PEF, % of predicted	47.5 ± 19.8	52.5 ± 20.3	0.019
FVC, L	2.57 ± 0.90	2.70 ± 0.90	0.031
FVC, % of predicted	79.7 ± 19.0	83.7 ± 19.7	0.024
FEV_1, L	1.68 ± 0.70	1.83 ± 0.80	0.003
FEV_1, % of predicted	63.0 ± 20.0	68.5 ± 21.2	0.002
FEV_1/FVC, %	0.64 ± 0.12	0.66 ± 0.11	0.086
FEV_1/FVC, % of predicted	0.78 ± 0.14	0.81 ± 0.13	0.07

[a]Values expressed as n (%), except where otherwise indicated. [b]Values expressed as mean ± SD.

Table 3 - Form of medication acquisition, asthma medication use, and inhalation technique prior to and after the educational intervention.[a]

Variables	Pre-intervention	Post-intervention	p
Form of medication acquisition			
Fully on the patient	40 (63.5)	40 (63.5)	1.00
Fully on the Health care clinic	40 (63.5%)	37 (38.7)	0.549
Fully on the State Department of Health	5 (7.9)	5 (7.9)	1.00
Effective use of the medications			
Inhaled corticosteroids	55 (87.3)	60 (95.2)	0.180
Short-acting β_2 agonists	42 (66.7)	43 (68.3)	1.00
Type of inhaler, n (%)			
Metered dose inhaler	31 (49.2)	28 (44.4)	0.375
Dry powder inhaler	32 (50.8)	35 (55.6)	
Inhalation technique, n (%)			
Metered dose inhaler			
Correct	4 (15.4)	12 (46.2)	0.021
Incorrect	22 (84.6)	14 (53.8)	
Dry powder inhaler			
Correct	10 (21.3)	36 (76.6)	< 0.001
Incorrect	37 (78.7)	11 (23.4)	
Use of a spacer with a metered dose inhaler	9 (36)	17 (68)	0.021

[a]Values expressed as n (%).

Table 4 - Quality of life assessment by means of the Asthma Quality of Life Questionnaire prior to and after the educational intervention.

AQLQ	Pre-intervention	Post-intervention	p
Activity limitation	3.2 (1.6)	4.3 (2.3)	< 0.001
Symptoms	3.4 (1.8	5.0 (3.2)	< 0.001
Emotional function	2.8 (2.8)	4.0 (3.6)	< 0.001
Environmental stimuli	2.5 (2.5)	4.3 (3.8)	< 0.001
Total score	3.2 (1.5)	4.5 (2.6)	< 0.001

AQLQ: Asthma Quality of Life Questionnaire.

Table 5 - Multivariate binary logistic regression (enter method) for predictors of a favorable response to the educational intervention.[a]

Variable	β	p	OR	95% CI
Gender	–0.213	0.804	0.808	0.150-4.346
Age	0.029	0.201	1.029	0.985-1.076
FEV_1	–0.021	0.160	0.979	0.952-1.008
Inhalation technique	1.720	0.005	5.583	1.699-18.343
Constant	–0.975	0.561	0.377	-

[a]A favorable response was defined as a change in classification to that of controlled asthma or partially controlled asthma after the educational intervention.

of patients who performed all the steps of the inhalation technique correctly increased from 15.4% to 46.2% among those who used metered dose inhalers and from 21.3% to 76.6% among those who used dry powder inhalers. Among the patients who used dry powder inhalers, the educational intervention resulted in an increase in the proportion of those who used a spacer from 36% to 68%. An incorrect inhalation technique identified during the first evaluation was independently associated with a favorable response to the educational intervention.

One of the educational focuses of the present study was to highlight the importance of inhaled

corticosteroids, as well as of combined inhaled corticosteroids and long-acting β_2 agonists, for preventive disease management, with an emphasis on adherence. However, the proportion of patients who reported effective use (≥ five days a week) of inhaled corticosteroids and long-acting β_2 agonists did not increase. In contrast, a previous study[10] showed that a short-term educational intervention involving 174 asthma patients resulted in a significant increase in the use of inhaled corticosteroids. The difference is probably due to the fact that the present study included patients with greater disease severity, all of whom had uncontrolled asthma.

At the time of the study, not all medications for the maintenance treatment of asthma were available via the public health care system in the state of Rio Grande do Sul. Beclomethasone dipropionate and short-acting β_2 agonist bronchodilators for use in metered dose inhalers were available in primary health care facilities in most cities. However, long-acting β_2 agonists (formoterol and salmeterol), as well as the combination of inhaled corticosteroids and long-acting β_2 agonists, were available for free to only a minority of these patients. In the present study, the educational intervention included explanations of the administrative procedures involved in obtaining medications via the public health care system. Nevertheless, the intervention did not result in an increase in the proportion of patients who obtained the medications via the public health care system.

The efficacy of asthma treatment depends also on the patient's ability to perform the inhalation technique correctly. Other studies have also shown that education has a significant impact on the proportion of patients who use inhalers correctly.[6,11,15] The present study, by demonstrating that an incorrect inhalation technique is an independent predictor of response to the educational intervention, contributes an important finding.

In Brazil, other studies have addressed asthma educational interventions. One group of authors[28] evaluated the impact of a five-day educational camp program for children with asthma, reporting a positive impact on knowledge and improvement in asthma management skills. Another group of authors[10] evaluated the effects of a short-term individualized asthma education program on treatment adherence, inhalation techniques, and disease control, finding improvement in the use of medications for asthma control and a decrease in the number of emergency room visits. Another study[6] reported increased knowledge about the disease and clinical improvement in patients with moderate or severe persistent asthma after they had participated in an education program delivered during routine outpatient visits, over a 2-year period.

The major limitation of the present study is related to its uncontrolled design. The fact that this was not a randomized clinical trial, without parallel monitoring of a control group not receiving the intervention, prevents us from stating definitely that the impact observed on the factors studied is attributable exclusively to the educational intervention and not to other treatment components. Another aspect is that the medication for the treatment of asthma was not made widely available to all patients for free. Therefore, difficulties in obtaining the medication might have lessened the impact of the intervention.

In conclusion, the present study suggests that an individualized outpatient education program has positive effects on the level of asthma control, with improvement in lung function parameters and in quality of life scores. An incorrect inhalation technique identified during the first evaluation was predictive of a favorable response to the educational intervention.

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Does thromboprophylaxis prevent venous thromboembolism after major orthopedic surgery?*,**

A tromboprofilaxia evita o tromboembolismo venoso após cirurgia ortopédica de grande porte?

Evrim Eylem Akpinar, Derya Hoşgün, Burak Akan, Can Ateş, Meral Gülhan

Abstract

Objective: Pulmonary embolism (PE) is an important complication of major orthopedic surgery. The aim of this study was to evaluate the incidence of venous thromboembolism (VTE) and factors influencing the development of VTE in patients undergoing major orthopedic surgery in a university hospital. **Methods:** Patients who underwent major orthopedic surgery (hip arthroplasty, knee arthroplasty, or femur fracture repair) between February of 2006 and June of 2012 were retrospectively included in the study. The incidences of PE and deep vein thrombosis (DVT) were evaluated, as were the factors influencing their development, such as type of operation, age, and comorbidities. **Results:** We reviewed the medical records of 1,306 patients. The proportions of knee arthroplasty, hip arthroplasty, and femur fracture repair were 63.4%, 29.9%, and 6.7%, respectively. The cumulative incidence of PE and DVT in patients undergoing major orthopedic surgery was 1.99% and 2.22%, respectively. Most of the patients presented with PE and DVT (61.5% and 72.4%, respectively) within the first 72 h after surgery. Patients undergoing femur fracture repair, those aged ≥ 65 years, and bedridden patients were at a higher risk for developing VTE. **Conclusions:** Our results show that VTE was a significant complication of major orthopedic surgery, despite the use of thromboprophylaxis. Clinicians should be aware of VTE, especially during the perioperative period and in bedridden, elderly patients (≥ 65 years of age).

Keywords: Orthopedics; Pulmonary embolism; Venous thrombosis.

Resumo

Objetivo: A embolia pulmonar (EP) é uma complicação importante de cirurgia ortopédica de grande porte. Este estudo visou avaliar a incidência de tromboembolismo venoso (TEV) e os fatores que influenciam o desenvolvimento de TEV em pacientes submetidos a cirurgia ortopédica de grande porte em um hospital universitário. **Métodos:** Pacientes submetidos a cirurgia ortopédica de grande porte (artroplastia de quadril, artroplastia do joelho ou reparação de fratura de fêmur) entre fevereiro de 2006 e junho de 2012 foram incluídos retrospectivamente no estudo. As incidências de EP e de trombose venosa profunda (TVP) foram avaliadas, assim como os fatores que influenciaram sua ocorrência, tais como o tipo de cirurgia, idade e comorbidades. **Resultados:** Foram revisados os prontuários médicos de 1.306 pacientes. As proporções de artroplastia do joelho, artroplastia de quadril e reparação de fratura de fêmur foram, respectivamente, de 63,4%, 29,9% e 6,7%. A incidência cumulativa de EP e TVP nos pacientes submetidos a cirurgia ortopédica de grande porte foi, respectivamente, de 1,99% e 2,22%. A maioria dos pacientes apresentou EP e TVP (61,5% e 72,4 %, respectivamente) nas primeiras 72 h após a cirurgia. Pacientes submetidos à reparação de fratura de fêmur, aqueles com idade ≥ 65 anos, e pacientes acamados tinham um risco maior de desenvolver TVP. **Conclusões:** Nossos resultados demonstram que o TEV foi uma complicação importante de cirurgia ortopédica de grande porte, apesar da utilização de tromboprofilaxia. Os médicos clínicos devem estar alerta para a ocorrência de TEV, especialmente no período perioperatório e em pacientes idosos (com idade ≥ 65 anos) e acamados.

Descritores: Ortopedia; Embolia pulmonar; Trombose venosa.

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Introduction

Venous thromboembolism (VTE), specifically deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important cause of morbidity and mortality.[1] The risk of VTE is highest in patients undergoing major orthopedic surgery, particularly hip and knee arthroplasty. The American College of Chest Physicians (ACCP) guidelines recommend that each hospital implement strategies to identify the risk of VTE in medical and surgical patients in order to prevent morbidity and mortality due to this important clinical condition.[2]

Clinically significant bleeding occurs infrequently in patients who are taking an anticoagulant at a prophylactic dose.[3] However, the risk of bleeding might limit the adequate use of anticoagulants in patients undergoing major orthopedic surgery. Because perioperative VTE is asymptomatic in the majority of the cases (95%), this important clinical condition might be underestimated by surgeons, resulting in inadequate use of prophylactic anticoagulants.[4]

Not only is the use but also the duration of thromboprophylaxis important, especially for high-risk patients. In one meta-analysis, the incidence of symptomatic and fatal PE was found to be 3.2% and 0.1%, respectively, in patients who had undergone hip or knee arthroplasty within a 3-month period and who had received short-term (7-10 days) thromboprophylaxis.[5]

In the present study, we evaluated the incidence of VTE and the factors influencing the development of VTE in patients undergoing major orthopedic surgery in a university hospital.

Methods

Between February of 2006 and June of 2012, all of the patients who had been referred to the Department of Orthopedics and Traumatology of the Ufuk University Hospital, located in the city of Ankara, Turkey, and submitted to surgery were retrospectively studied. The medical records of 7,580 patients were selected. The patients who underwent major orthopedic surgery (hip arthroplasty, knee arthroplasty, or femur fracture repair) were included in the study. The department had a standard protocol for thromboprophylaxis (enoxaparin 40 mg/day s.c., and the use of graded compression stockings).This protocol was used during the period of the study.

The study was approved by the Research Ethics Committee of Ufuk University. The medical records of the patients were used in order to evaluate the incidence of DVT and PE within 45 postoperative days. Patients who underwent major orthopedic surgery in the hospital were routinely controlled on postoperative day 15, 30, and 45. Patients who had respiratory symptoms (pleuritic chest pain, dyspnea, hemoptysis, or cough), with or without signs and symptoms consistent with DVT (swelling, pain, tenderness, increase in the diameter of lower limbs, or local heat), were evaluated by a pulmonologist. The patients suspected of having VTE were submitted to chest CT angiography and Doppler ultrasound of the lower extremities by an expert radiologist. Chest CT angiography was performed with a 16-section multidetector CT scanner (LightSpeed 16; GE Healthcare, Milwaukee, WI, USA) within 24 h. PE was diagnosed when an intraluminal filling defect surrounded by intravascular contrast or total occlusion of the pulmonary arterial lumen was detected at any level of the pulmonary arteries. Doppler ultrasound of the deep veins of the lower extremities was performed with a standard method using a dedicated ultrasound unit (LOGIQ 7; GE Healthcare) with a 10L linear array transducer (bandwidth, 6-10 MHz) in order to investigate the presence/absence of intravenous thrombi.

Data on the type of surgical procedure, the type and duration of anesthesia, and other potential risk factors for VTE, including obesity, immobility (bed rest > 48 h), malignancy, previous history of VTE, COPD, congestive heart failure, trauma, thrombocytosis, and history of hormone replacement, were also recorded. In addition, the time of initiation and the duration of thromboprophylaxis were collected.

The data were analyzed using the Statistical Package for the Social Sciences for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistical analysis results were presented as absolute and relative frequencies. Differences between groups for categorical variables were analyzed using the chi-square test or Fisher's exact test, where appropriate. The three clinically important variables among those which were found significantly effective in the development of VTE in the univariate analysis were evaluated by multiple logistic regression analysis in order to define independent risk factors of outcome variables. Adjusted odds ratios and respective

95% CIs were calculated. The level of statistical significance was set at $p < 0.05$.

Results

The data of 1,306 patients were assessed. The mean age of the patients was 66.36 ± 18.00 years. Females and males accounted for 77.2% and 22.8%, respectively. General anesthesia was administered to 18.8% of the patients, whereas 81.2% of the patients were treated with combined spinal-epidural anesthesia. The proportions of knee arthroplasty, hip arthroplasty, and femur fracture repair were 64.0%, 29.6%, and 6.4%, respectively. Of the 1,306 patients, 29 (2.22%) and 26 (1.99%), respectively, were diagnosed with DVT and PE.

All of the patients wore compression stockings and received VTE prophylaxis. Enoxaparin (40 mg/day) was the anticoagulant used for all of the patients, who received VTE prophylaxis during 30 postoperative days. Data related to demographics, type of surgical procedure, anesthesia, and type of thromboprophylaxis are shown in Table 1.

Prophylaxis was started at the tenth postoperative hour. Major bleeding (gastrointestinal bleeding) was reported in 1 patient (0.07%) with a diagnosis of Crohn's disease. Nearly one-third of the patients (31.8%) presented with one or more than one risk factor for VTE other than the orthopedic surgery. Additional risk factors for VTE are included in Table 2.

The incidence of symptomatic DVT and PE in the patients studied was 2.22% and 1.99%, respectively. All of the patients with PE were also diagnosed with concomitant DVT. The incidences of PE following knee arthroplasty, hip arthroplasty, and femur fracture repair were 0.7%, 2.0% and 4.6%, respectively.

Of the patients who had PE and DVT, 61.5% and 72.4%, respectively, developed them within the first 72 postoperative hours. The time for the onset of PE and DVT in the patients is shown in Table 3. In this sample of patients, 15.4% of the patients with PE died, creating a mortality rate of 0.3%. Thrombolytic treatment was required in 15.4% of the patients with PE and was followed with standard heparin and warfarin treatment. Patients not receiving thrombolytic treatment were initially administered low-molecular-weight heparin (LMWH) and continued on warfarin therapy.

Table 1 - Demographic data, type of surgery, and type of anesthesia used in the patients included in the study (n = 1,306).[a]

Variable	Result
Age, years[b]	66.36 ± 18.00
Gender	
Male	298 (22.8)
Female	1,008 (77.2)
Type of surgery	
Knee arthroplasty	836 (64.0)
Hip arthroplasty	387 (29.6)
Femur fracture repair	83 (6.4)
Type of anesthesia	
General	246 (18.8)
Combined spinal-epidural	1,060 (81.2)

[a]Values expressed as n (%), except where otherwise indicated. [b]Value expressed as mean ± SD.

Table 2 - Distribution of potential risk factors other than major orthopedic surgery for pulmonary embolism.[a]

Additional risk factor	Study sample (n = 1,306)
Obesity	59 (4.5)
Immobility	197 (15.1)
Malignancy	10 (0.8)
Previous history of VTE	39 (3.0)
COPD	17 (1.3)
Congestive heart failure	60 (4.6)
Trauma	10 (0.8)
Hormone replacement	10 (0.8)
Thrombocytosis	8 (0.6)

VTE: venous thromboembolism. [a]Values expressed as n (%).

The majority of the patients (84.6%) who developed PE were aged ≥ 65 years ($p = 0.004$). No significant differences were found regarding the gender or the type of anesthesia administered in the group of patients who developed PE ($p > 0.05$).

The multiple logistic regression analysis revealed that the patients undergoing femur fracture repair were at a greater risk for the development of PE than those who underwent knee or hip arthroplasty (OR = 4.413; 95% CI: 1.185-16.44; $p = 0.027$). Patients aged ≥ 65 years also had higher rates of PE (OR = 4.856; 95% CI: 1.074-21.953; $p = 0.040$). Table 4 shows the independent factors influencing the risk of developing PE.

The incidence of PE was higher in bedridden patients than in those who were not ($p = 0.004$). However, the incidence of PE in obese

Table 3 - Time for the onset of pulmonary embolism and deep vein thrombosis in the study sample.

Onset of PE, postoperative days	Study sample (n = 1,306)	
	n	%
1	5	19.2
2	9	34.6
3	2	7.7
4	1	3.8
7	1	3.8
15	4	15.4
45	2	7.6
TOTAL	26	100.0
Onset of DVT, postoperative days		
1	6	20.68
2	10	34.48
3	5	17.24
4	1	3.44
7	1	3.44
15	4	13.79
45	2	6.89
TOTAL	29	100.0

PE: pulmonary embolism; and DVT: deep vein thrombosis.

Table 4 - Factors influencing the development of pulmonary embolism in patients undergoing major orthopedic surgery.

Factor	OR	95% CI	p
Type of surgery			
Knee arthroplasty	1.00		
Hip arthroplasty	2.904	0.977-8.635	0.055
Femur fracture repair	4.413	1.185-16.440	0.027
Age, years			
< 65	1.00		
≥ 65	4.856	1.074-21.953	0.040
Additional risk factor[a]	2.371	0.881-6.375	0.087

[a]Obesity and previous history of venous thromboembolism, COPD, congestive heart failure, trauma, hormone replacement, or thrombocytosis.

patients or in patients with a previous history of VTE, COPD, congestive heart failure, trauma, hormone replacement, or thrombocytosis was not significantly higher than in the other participants ($p > 0.05$ for all).

Discussion

The incidence of PE and DVT in the patients following major orthopedic surgery was 1.99% and 2.22%, respectively. Most of the patients developed PE or DVT within the first 72 postoperative hours. The patients undergoing femur fracture repair, those aged ≥ 65 years, and those who were bedridden were at a higher risk for developing VTE.

In approximately 50% of the patients undergoing major orthopedic surgery (knee or hip arthroplasty), DVT occurs in the proximal leg veins.[6] Because these patients are at a high risk for VTE, thromboprophylaxis is routinely recommended by current guidelines.[2]

In one review, the rates of patients receiving prophylaxis after hip arthroplasty, knee arthroplasty, and femur fracture repair were reported as 84%, 76%, and 45%, respectively.[7] All of the patients undergoing major orthopedic surgery in the hospital under study received VTE prophylaxis. Femur fracture, which is a long bone fracture, increases the risk for VTE. The surgery creates an additional risk for the development of VTE. It has been previously reported that VTE can develop following hip fracture surgery despite thromboprophylaxis.[8] The incidence of PE was highest in the patients submitted to femur fracture repair (4.6%) among the major orthopedic surgeries in our study population. This can be explained by the following factors: patients undergoing femur fracture repair are commonly older, and long bone fracture itself increases the risk for VTE due to prolonged immobility and increased endothelial injury.

It has been previously reported that the low incidence of symptomatic VTE perioperatively (5%) might mislead surgeons into considering PE as a rare complication of major orthopedic surgeries.[9,10] On the contrary, the present study demonstrated that approximately 60% of symptomatic PE occurred within the first 72 postoperative hours, despite the routine use of prophylaxis. It is well known that damage to vascular endothelium and venous stasis resulting in endothelial hypoxia can cause the activation of the coagulation cascade. The natural fibrinolytic activity of the body tries to overcome the formation of thrombosis.[11] The development of PE, more commonly within 3 days after surgery, might be due to the early intense effect of endothelial injury and hypoxia because of the surgical trauma and venous stasis.

Bleeding as a complication from medical prophylaxis is one of the factors that might lead to its inadequate use by the surgeons, especially following procedures such as a major orthopedic surgery. However, previous studies showed that

the risk of clinically significant bleeding did not increase with medical prophylaxis.[3] The incidence of major bleeding was very low in the present study (0.07%), supporting the former data. Only 1 patient experienced major bleeding in the present study, and that patient had a prior diagnosis of Crohn's disease, which might have caused the bleeding.

In one study, the incidence of PE in patients who did not receive prophylaxis was approximately 50%.[10] The use of prophylaxis decreased the incidence but did not completely resolve the problem. In one meta-analysis, it was reported that the incidence of PE within 3 months after the procedure was 3.2% in patients receiving short-term prophylaxis (7-10 days).[5] The incidence of PE was lower in the present study than in that meta-analysis. This difference between the results might be explained by the long-term prophylaxis (30 days) and the short duration of the follow-up of the patients (45 postoperative days) in our study, in contrast to the results in the studies included in that meta-analysis.

Previous studies showed that the duration of prophylaxis reduced the risk of symptomatic DVT.[12,13] However, despite the long-term use of thromboprophylaxis in our study population, the prevention of this important complication was not completely achieved. Enoxaparin was the anticoagulant therapy administered to the high-risk population for prophylaxis. The commonly used dose of the medication was 40 mg/day (4,000 IU) in all of the patients despite their weight. The recommended dose of LMWH for thromboprophylaxis is > 3,400 IU in accordance with the ACCP guidelines, although weight-based dose adjustments of LMWHs might provide more effective prophylaxis. ACCP recommends long-term thromboprophylaxis (30-35 days) after major orthopedic surgery.[2] When we retrospectively reviewed the LMWH dose in the protocol, we realized that the dose was consistent with the ACCP guidelines.

White et al. reported that the incidence of VTE after hip arthroplasty was higher than that of VTE after knee arthroplasty (2.8% vs. 2.1%).[14] Our study showed a more striking difference between the incidence of PE following hip and knee arthroplasty (2.0% vs. 0.7%). Similarly to previous data,[15,16] the highest incidence of PE in the present study (4.6%) occurred in the group undergoing femur fracture repair.

Shorr et al. found the incidence of PE after major orthopedic surgery in patients receiving enoxaparin to be 2.3%.[17] In the present study, the incidence of PE was found to be 1.99% in patients receiving enoxaparin for thromboprophylaxis. The shorter duration of prophylaxis in the study by Shorr et al. might explain the difference in the incidences of PE (3.9 days vs. 30 days). In another study,[18] the incidence of PE after major orthopedic surgery was 1.47%, which is similar to our result (1.99%).

Patients undergoing major orthopedic surgery are generally older. Additional risk factors other than surgery, such as malignancy and immobility, might increase with age. It is known that patients aged > 40 years are at a greater risk for VTE than younger patients and that prolonged immobility, together with other major risk factors, increases the risk for VTE.[10] Similarly to previous studies, the present study showed that patients aged ≥ 65 years were at a significantly higher risk for PE after major orthopedic surgery. Immobility was also found to be one factor increasing the risk for VTE.

Although a previous history of VTE and obesity are known risk factors for VTE,[10] these two conditions were not found to be independent risk factors for VTE in the present study. In our study, the previous history of VTE of patients might not have been adequately documented on the medical records.

For patients undergoing major orthopedic surgery, the latest ACCP guidelines (9th edition) recommend extended pharmacological prophylaxis (up to 35 days) with LMWH or other anticoagulant medications rather than short-term prophylaxis. The guidelines also recommend that thromboprophylaxis should be started at least within the first 12 postoperative hours.[5] The protocol of the hospital in the current study was consistent with the ACCP recommendations with regard to the method, duration, and time of initiation of thromboprophylaxis after major orthopedic surgery, and, as a result, only 1 patient developed PE after the continuation of the prophylactic treatment.

The present study had several limitations. First, because this was a retrospective study, the follow-up period of the patients after major orthopedic surgery was short (45 days), and only symptomatic VTE was evaluated. Second, the dose, the duration, and the type of medical

prophylaxis used were the same to all of the patients.

Prospective randomized studies in which patients are followed for a longer period of time are necessary in order to evaluate the incidence of VTE more precisely, as well as to determine the optimum dose of medications for thromboprophylaxis and duration of the treatment following major orthopedic surgery.

In conclusion, the present study showed that VTE was an important complication of major orthopedic surgery, despite the use of compression stockings and pharmacological thromboprophylaxis with enoxaparin. Clinicians should be aware of VTE, especially during the perioperative period and in patients aged ≥ 65 years.

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Inhaler use in adolescents and adults with self-reported physician-diagnosed asthma, bronchitis, or emphysema in the city of Pelotas, Brazil*

Uso de inaladores na população de adolescentes e adultos com diagnóstico médico autorreferido de asma, bronquite ou enfisema em Pelotas, RS

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Abstract

Objective: To evaluate the characteristics of users of inhalers and the prevalence of inhaler use among adolescents and adults with self-reported physician-diagnosed asthma, bronchitis, or emphysema. **Methods:** A population-based study conducted in the city of Pelotas, Brazil, involving 3,670 subjects ≥ 10 years of age, evaluated with a questionnaire. **Results:** Approximately 10% of the sample reported at least one of the respiratory diseases studied. Among those individuals, 59% reported respiratory symptoms in the last year, and, of those, only half reported using inhalers. The use of inhalers differed significantly by socioeconomic status (39% and 61% for the lowest and the highest, respectively, p = 0.01). The frequency of inhaler use did not differ by gender or age. Among the individuals reporting emphysema and inhaler use, the use of the bronchodilator-corticosteroid combination was more common than was that of a bronchodilator alone. Only among the individuals reporting physician-diagnosed asthma and current symptoms was the proportion of inhaler users higher than 50%. **Conclusions:** In our sample, inhalers were underutilized, and the type of medication used by the individuals who reported emphysema does not seem to be in accordance with the consensus recommendations.

Keywords: Metered dose inhalers; Asthma; Pulmonary disease, chronic obstructive; Bronchitis; Emphysema; Dry powder inhalers.

Resumo

Objetivo: Avaliar as características dos usuários de dispositivos inalatórios e a frequência de uso desses em adolescentes e adultos com diagnóstico médico autorreferido de asma, bronquite ou enfisema. **Métodos:** Estudo de base populacional realizado em Pelotas, RS, incluindo 3.670 indivíduos com idade ≥ 10 anos, avaliados com um questionário. **Resultados:** Aproximadamente 10% da amostra referiram pelo menos uma das doenças respiratórias investigadas. Entre esses, 59% apresentaram sintomas respiratórios no último ano, e, desses, apenas metade usou inaladores. O uso de inaladores diferiu significativamente de acordo com o nível socioeconômico (39% e 61% entre mais pobres e mais ricos, respectivamente; p = 0,01). Não houve diferença na frequência de uso de inaladores por sexo ou idade. Entre indivíduos com enfisema, o uso da combinação broncodilatador + corticoide inalatório foi mais frequente que o uso isolado de broncodilatador. Somente entre os indivíduos que referiram diagnóstico médico de asma e sintomas atuais, a proporção de uso de inaladores foi maior que 50%. **Conclusões:** Em nossa amostra, os inaladores foram subutilizados, e o tipo de medicamento usado por aqueles que referiram enfisema parece não estar de acordo com o preconizado em consensos sobre essa doença.

Descritores: Inaladores dosimetrados; Asma; Doença pulmonar obstrutiva crônica; Bronquite; Enfisema; Inaladores de pó seco.

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Introduction

Inadequate management of asthma and COPD is detrimental to the quality of life of patients and generates avoidable costs to the health care system.[1,2] Among the available drugs, those administered via inhaler devices constitute the treatment of choice for the control of asthma and COPD and are indicated for all such patients, except for those who have cognitive deficits or who do not adapt to inhaler devices and opt for a nebulizer.[1,2]

In Brazil, the number of hospitalizations for asthma in adults dropped in the last decade; however, asthma is still among the leading causes of hospitalization and, in 2011, was the fourth leading cause of hospitalization among patients of all ages.[1] Another leading cause of hospitalization is COPD, and the burden of the disease on the health care system is expected to increase in the coming years.[2,3] By 2020, COPD is expected to have become the fifth leading cause of disability-adjusted life years.[3]

Although the worsening of symptoms and the frequency of exacerbations do not always indicate disease progression, they can indicate poor treatment adherence or inability to use inhalers,[4] which is aggravated by the fact that many health professionals do not have enough knowledge to instruct patients on how to use inhaler devices correctly.[5] According to data from the *Projeto Latino-Americano de Investigação em Obstrução Pulmonar* (PLATINO, Latin-American Project for the Investigation of Pulmonary Obstruction), the proportion of patients receiving inhaled medication is smaller than expected, and the form of administration and frequency of use are not in accordance with the recommendations.[6] Regarding asthma, despite advances in asthma control, the proportion of patients seeking emergency room treatment because of poor adherence to inhaled corticosteroid (IC) therapy is high.[7,8]

Studies investigating inhaler use among asthma and COPD patients are needed in order to identify shortcomings and, indirectly, assess the quality of the health care provided to such patients. However, a recent review of the literature revealed no population-based studies conducted in Brazil and primarily focusing on inhaler use.

In this scenario, the objective of the present study was to describe inhaler use among individuals with self-reported physician-diagnosed asthma, bronchitis, emphysema, or any combination of the three in the city of Pelotas, Brazil.

Methods

This was a descriptive, cross-sectional, population-based study conducted in the city of Pelotas between February and June of 2012 as part of a large population health survey. The strategy used is designated "research consortium",[9] whereby several researchers combine their questionnaires into a single instrument, thus streamlining data collection and reducing costs. The target population consisted of individuals aged 10 years or older.

Sampling was conducted in two stages: in the first stage, 130 of the 495 census sectors in the urban area were systematically selected, the probability being proportional to the number of households; because the number of households in each census sector had last been determined in 2010 by the Brazilian Institute of Geography and Statistics, we mapped the households in each sector before starting the fieldwork; in the second stage, the number of selected households was defined by the growth of the sector in relation to the 2010 count, and an average of 13 households were selected in each sector, a total of 1,722 households having been selected.

All of the residents that were in the target age group were invited to participate, institutionalized or mentally disabled individuals being excluded. Standardized questionnaires addressing demographic, socioeconomic, behavioral, and health aspects were administered by trained interviewers.

The use of inhalers was evaluated only in those who reported having any of the following physician-diagnosed respiratory diseases: asthma/wheezy bronchitis, bronchitis, emphysema, or any combination of the three. The adolescents (i.e., those in the 10-19 year age bracket) were asked only about asthma/wheezy bronchitis.

Whenever an individual gave at least one affirmative answer, the individual was asked about symptoms and inhaler use. We determined the presence of symptoms in the previous year by asking the following question: "Since (month) of last year, have you had attacks or symptoms of this/these disease(s), such as wheezing, cough, or breathlessness? (yes/no)". The interviewers were instructed to replace the word "month" with the corresponding month in the 12-month

recollection period. For the same period, we asked about nebulizer use (yes/no) and inhaler use (yes/no), using the terms "pump, dry powder inhaler, or any other medication for inhalation/aspiration".

Those who had used an inhaler were asked to provide the package for collection of the name(s) of the drug(s). Those who did not have the package were shown a catalog of drugs so that they could indicate the drug or drugs that they had used. The drugs were categorized by type of inhaler, i.e., metered dose inhaler (MDI) or dry powder inhaler (DPI), and type of medication, i.e., bronchodilator (BD), IC, or a combination of both (BD + IC).

Those who reported not having used an inhaler were asked why they had not, the reasons being grouped into the following categories: belief that there was no need to use an inhaler; lack of financial resources to purchase an inhaler; lack of physician recommendation; difficulty using inhalers; and fear of side effects.

Of the demographic, socioeconomic, and behavioral variables collected, the following were used in the present study: gender; age; years of completed schooling; the *Indicador Econômico Nacional* (IEN, National Economic Indicator),[10] categorized into quintiles (in ascending order by socioeconomic status, from the lowest to the highest); and smoking status, i.e., never smoker, smoker (having smoked at least one cigarette per day for more than one month), and former smoker (having smoked no cigarettes for more than one month).

Data were collected through netbooks running the Pendragon Forms 6.1 software (Pendragon Software Corporation, Libertyville, IL, USA) with the questionnaire, and the interviews were synchronized weekly to the database. For quality control, 10% of the participants answered 14 of the questions again in a visit that took place within up to 15 days after the interview. The question regarding the diagnosis of asthma/wheezy bronchitis showed a kappa statistic of 0.65.

The findings were expressed as absolute and relative frequencies, with the respective 95% CIs. We used the chi-square test for heterogeneity for nominal categorical variables and the chi-square test for linear trend for ordinal categorical variables. Data analysis was performed with the STATA statistical software package, version 12.0 (Stata Corp., College Station, TX, USA).

The participants or their legal guardians gave written informed consent, and the study project was approved by the Research Ethics Committee of the Federal University of Pelotas School of Medicine, located in the city of Pelotas, Brazil, on December 1, 2011 (Protocol no. 77/11).

Results

Of the 4,168 eligible individuals, 3,670 were included in the study sample (12.1% having been lost to follow-up or having declined to participate). Of those, 402 (11%) reported having been diagnosed with at least one of the respiratory diseases under study. The overall prevalence of asthma was 7.5% (95% CI, 6.6-8.3), the overall prevalence of bronchitis was 6.1% (95% CI, 5.2-6.9), and the overall prevalence of emphysema was 1.6% (95% CI, 1.2-2.1; Table 1). The characteristics of the study sample and the prevalence of each disease (according to the demographic characteristics, socioeconomic characteristics, and smoking status) are shown in Table 1.

Of the 402 individuals who reported having a respiratory disease, 146 (36.2%; 95% CI, 31.4-40.9) had used an inhaler device in the previous year, and 237 (59%) reported having had symptoms in the same period. Of the 237 symptomatic individuals, 120 (50.6%; 95% CI, 44.2-57.0) reported having used an inhaler. Of those who remained asymptomatic, 25 (15.2%; 95% CI, 9.7-20.8) reported having used an inhaler.

Figure 1 shows the distribution of inhaler users by IEN quintile among the individuals who reported having had respiratory symptoms in the previous year. Although the 95% CIs overlapped, a higher IEN translated to a higher frequency of inhaler use, a linear trend being observed ($p = 0.010$). Similar results were obtained with the use of other socioeconomic indicators, such as the Brazilian Association of Survey Firms classification[11] (data not shown). The frequency of inhaler use did not differ by gender or age in the sample as a whole or in the symptomatic individuals.

The proportion of individuals who had not used any type of inhaler was higher than 50% among those who reported having bronchitis or emphysema. Among those who had used an inhaler in the previous year, MDIs were the most widely used by patients with asthma or bronchitis, whereas there was no difference between MDI

Table 1 - Description of the sample and prevalence of self-reported physician-diagnosed respiratory disease, Pelotas, Brazil, 2012.

Variable	Sample	Respiratory disease		
		Asthma	Bronchitis	Emphysema
	n (%)	(n = 274)	(n = 178)	(n = 47)
Gender		p = 0.063	p = 0.110	p = 0.838
Male	1,562 (42.6)	6.5 (5.3-7.8)	5.2 (4.0-6.5)	1.7 (0.9-2.4)
Female	2,108 (57.4)	8.2 (7.0-9.3)	6.7 (5.5-7.8)	1.6 (1.0-2.2)
Age		p < 0.001**	p = 0.957**	p < 0.001**
10-19[a]	743 (20.3)	13.3 (10.8-15.8)	-	-
20-29	612 (16.7)	6.7 (4.7-8.7)	6.2 (4.3-8.1)	-
30-39	540 (14.7)	7.0 (4.9-9.2)	5.7 (3.8-7.7)	0.4 (0.0-0.9)
40-49	595 (16.2)	5.4 (3.6-7.2)	5.9 (4.0-7.8)	0.8 (0.1-1.6)
50-59	514 (14.0)	5.8 (3.8-7.9)	6.8 (4.6-9.0)	2.3 (1.0-3.6)
60 or older	666 (18.2)	5.1 (3.4-6.8)	5.9 (4.1-7.6)	4.2 (2.7-5.7)
Schooling[b], years		p = 0.031**	p = 0.061**	p < 0.001**
Up to 4	651 (17.8)	9.2 (7.0-11.4)	8.6 (6.2-11.0)	4.2 (2.5-5.9)
5-9	1,313 (35.8)	7.3 (5.9-8.7)	5.2 (3.7-6.7)	1.5 (0.7-2.3)
10-14	1,217 (33.2)	7.6 (6.2-9.1)	6.1 (4.7-7.6)	1.1 (0.4-1.7)
15 or more	486 (13.3)	5.1 (3.2-7.1)	5.0 (3.0-6.9)	0.2 (0.0-0.6)
IEN[c], quintiles		p = 0.094**	p = 0.477**	p = 0.010**
1st (the poorest)	735 (20.2)	8.0 (6.1-10.0)	7.0 (4.9-9.0)	2.4 (1.1-3.6)
2nd	723 (19.9)	7.9 (6.0-9.9)	6.5 (4.5-8.6)	2.2 (1.0-3.4)
3rd	732 (20.1)	7.7 (5.7-9.6)	4.6 (2.9-6.3)	1.4 (0.4-2.3)
4th	720 (19.8)	8.6 (6.6-10.7)	6.2 (4.3-8.2)	1.4 (0.4-2.3)
5th (the richest)	727 (20.0)	5.1 (3.5-6.7)	6.0 (4.1-8.0)	0.7 (0.0-1.4)
Smoking status		p = 0.726	p = 0.001	p = 0.001
Never smoker	2,397 (65.3)	7.7 (6.7-8.8)	5.1 (4.1-6.2)	0.9 (0.4-1.3)
Former smoker	634 (17.3)	6.9 (5.0-8.9)	5.5 (3.7-7.2)	2.2 (1.1-3.4)
Smoker	639 (17.4)	7.0 (5.1-9.0)	9.4 (7.1-11.7)	3.0 (1.6-4.3)
Total	3,670 (100)	7.5 (6.6-8.3)	6.1 (5.2-6.9)	1.6 (1.2-2.1)

IEN: *Indicador Econômico Nacional* (National Economic Indicator). [a]Patients in this age bracket were asked only about asthma or wheezy bronchitis. [b]3 observations ignored. [c]33 observations ignored. *Chi-square test for heterogeneity, except where otherwise indicated. **Chi-square test for linear trend.

use and DPI use among those with emphysema (Figure 2).

Regarding the drug regimen used by the symptomatic individuals, Figure 3 shows the distribution of BD use and BD + IC use. Only among those reporting emphysema was the proportion of BD + IC users higher than was that of BD-only users. Two of the respondents did not know the type of inhaler that they had used.

Of the 117 individuals who reported that they had had symptoms and had not used any type of inhaler, 38% reported nebulizer use. The most common reasons for not using an inhaler were "belief that there was no need to use an inhaler" (60.7%) and "lack of physician recommendation" (23.9%), followed by "fear of side effects", "lack of financial resources to purchase an inhaler", and "difficulty using inhalers".

Discussion

Inhaler devices are of great importance in the treatment of respiratory diseases, having advantages such as direct deposition of the drug in the target organ and rapid effect in reducing symptoms.[12] The objective of the present study was to describe inhaler use among individuals who gave affirmative answers to questions regarding asthma, bronchitis, and emphysema. It is of note that this cannot be considered the real prevalence of inhaler use in the population, because inhalers can be indicated for other conditions or used as self-medication. Another limitation of the present study is the use of self-reported diagnosis,

which can lead to information bias. However, unlike other studies conducted in Brazil and investigating inhaler use—most of which evaluated samples of individuals selected from among those being treated at primary health care clinics or hospitals—our study evaluated a sample that was representative of the general population.

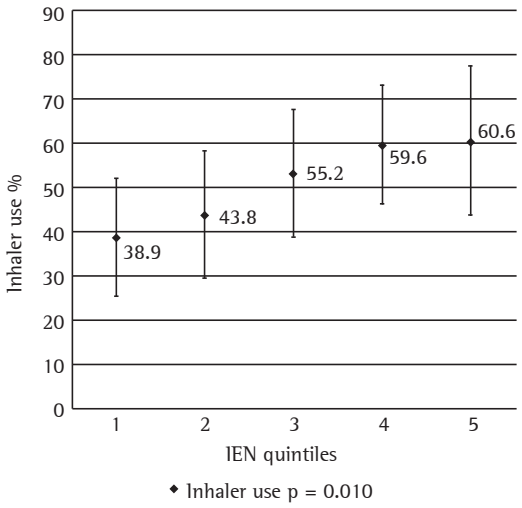

Figure 1 - Prevalence of inhaler use in those who reported symptoms in the previous year (n = 234), by *Indicador Econômico Nacional* (IEN, National Economic Indicator) quintile, Pelotas, Brazil, 2012. p = 0.01, as assessed by the chi-square test for linear trend.

The prevalence of self-reported physician-diagnosed asthma was investigated in adults (20 years of age or older) in studies conducted in the city of Pelotas in 2000[13] and 2010.[14] However, the criteria used in those studies in order to define the outcome differ from those used in the present study, and it is therefore difficult to compare the studies in terms of the reported prevalence. The prevalence of self-reported asthma in the previous year has been reported to be 4.7%[13] and 5.2%.[14] In the present study, by combining the questions regarding the diagnosis of asthma (no specific recollection period) and symptoms in the previous year, we found that 4.5% of those who were 20 years of age or older reported this condition. In addition, when analyzing that age group, we found significant differences between the genders in terms of the prevalence of asthma; this finding is consistent with those of previous studies,[13,14] the prevalence of asthma being higher among females (7.1% vs. 4.3%; p = 0.002).

In individuals in the 10-19 year age bracket, the prevalence of asthma found in the present study was similar to that found in a study conducted in the city of Santa Maria, Brazil, i.e., 14.9% for self-reported physician-diagnosed asthma ever; however, that study investigated individuals in the 13-14 year age bracket.[15] Both proportions are superior to the 7.4% prevalence of self-reported

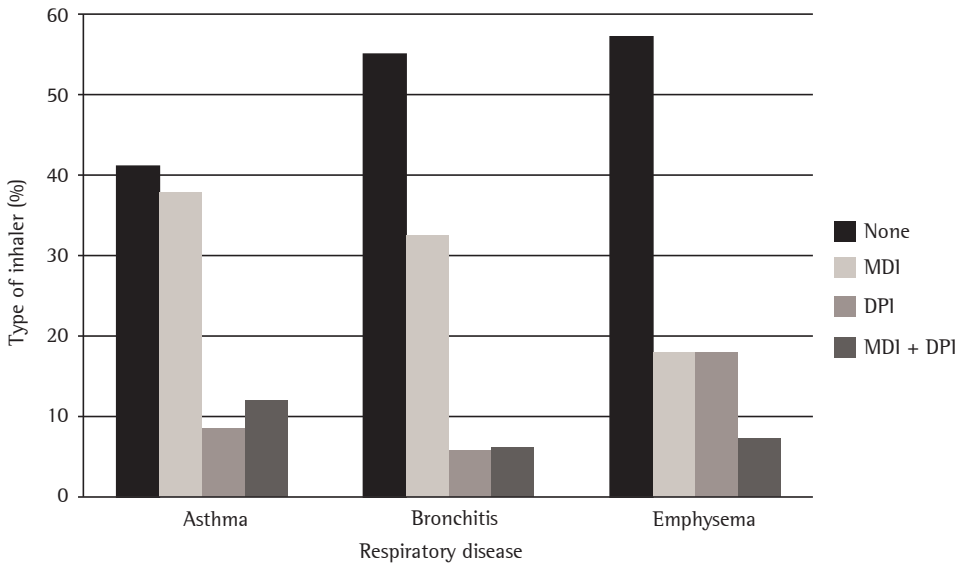

Figure 2 - Type of inhaler used in the previous year by those who reported symptoms in the previous year (n = 235), by self-reported diagnosis, Pelotas, Brazil, 2012. None: no inhaler use in the previous year; MDI: metered dose inhaler; and DPI: dry powder inhaler.

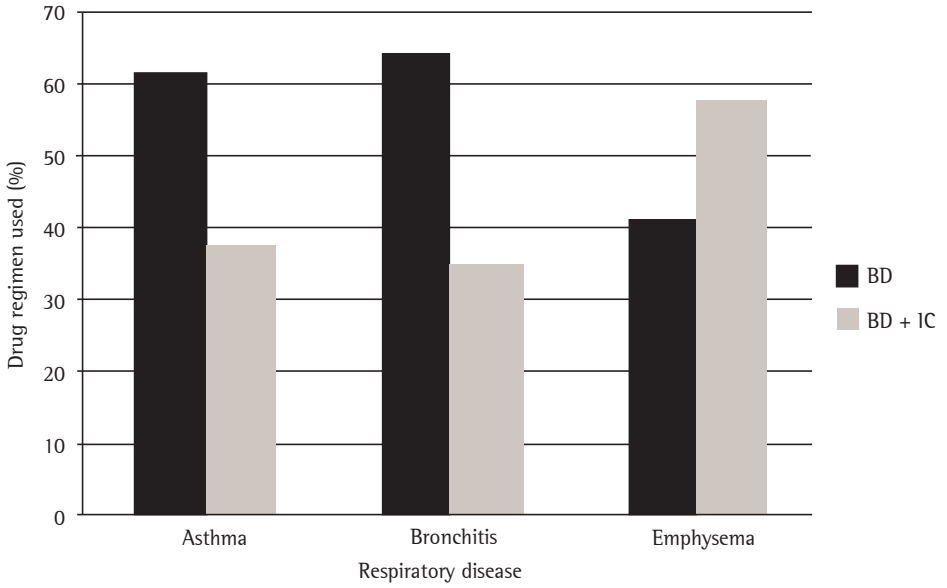

Figure 3 - Drug regimen used by those who reported symptoms in the previous year (n = 118), by self-reported diagnosis, Pelotas, Brazil, 2012. BD: bronchodilator; and IC: inhaled corticosteroid.

asthma found in individuals in the 10-19 year age bracket in southern Brazil in 2008.[16]

The questions regarding bronchitis and emphysema were asked only to adults (20 years of age or older) because COPD affects individuals over 40 years of age.[2] Because the term "bronchitis" is used by asthma and COPD patients alike, we believe that the prevalence found in the present study refers to both conditions. It is likely that the smokers or former smokers over 40 years of age reporting bronchitis have COPD. The proportion of individuals with self-reported bronchitis was highest among current smokers.

Regarding emphysema, data from the PLATINO[17] showed that the prevalence of self-reported physician-diagnosed emphysema in the city of São Paulo, Brazil, in 2003 was 1.2%. We found a higher prevalence in individuals 20 years of age or older (i.e., 1.6%) and in those 40 years of age or older (i.e., 2.5%), the latter age group being the target of the PLATINO.

We chose the terms "bronchitis" and "emphysema" because the population is more familiar with those terms than it is with the term "COPD". In the PLATINO,[17] the prevalence of self-reported physician-diagnosed COPD was 0.8%, whereas, in a study conducted in the city of São Paulo in the 2008-2009 period,[18] the prevalence of COPD was 4.2%, suggesting greater familiarity with the term.

Half of those who were expected to have used an inhaler (i.e., those with a self-reported diagnosis of respiratory disease and symptoms in the previous year) had. However, 38% of those who reported no inhaler use reported nebulizer use; that is, 12% of the symptomatic individuals had not used any type of inhalation treatment. It is of note that nebulizer use has disadvantages in comparison with inhaler use, including the lack of standardization of the devices regarding the emission of aerosol particles, causing uncertainty regarding the inhaled dose[19]; nebulizer use is indicated only for those who do not adapt to the inhalation of a controlled dose, such as debilitated patients or those with cognitive deficits, who fail to use the medication, even with a spacer.[1]

Each type of inhaler device has its own particularities, and the choice of inhaler to be prescribed depends on factors such as personal preferences, cost-benefit ratio, and patient cognition.[1,4,19] Of the two types of inhalers, MDIs are the most readily available in the public health care system, being the most widely used in the present study.

The main reason for not having used an inhaler was the belief that there was no need to use it. This finding might reflect treatment nonadherence in those patients. In a study[20] evaluating the treatment of eight chronic diseases, only 16% of all asthma patients were considered to have

adhered to treatment, that proportion being the lowest proportion of treatment adherence among the diseases investigated; COPD ranked third, 38% of all COPD patients having adhered to treatment.

The lack of adherence to inhaler use has been attributed to factors such as difficulty using inhalers, little satisfaction with the benefits of inhaler use, fear of adverse effects, prolonged duration of use, periods of symptom remission, and drug costs.[21,22]

A significant number of individuals reported lack of physician recommendation as the reason for not using inhalers; this reflects a situation that is common in Brazil and other countries; that is, the medication is not prescribed as recommended in consensus guidelines.[1,2]

In a study conducted in the city of Porto Alegre, Brazil,[23] the medical records of patients treated in a pulmonology department were analyzed. Approximately 68% of the patients had received treatment that was not in accordance with the recommendations in current guidelines, and 71% of those patients had uncontrolled asthma that was not being treated with corticosteroids. In the USA, the medical records of asthma patients were investigated, and it was found that less than 40% of the patients had been prescribed short-acting β_2 agonists and that less than 10% of the patients who used BDs daily had been prescribed ICs[24]; regarding COPD, 72% of the patients with the disease had been prescribed at least one BD, and 64% of the patients with frequent exacerbations had been prescribed ICs.[25]

The individuals who, despite having reported symptoms, believed that there was no need to use an inhaler, those who reported that they feared side effects, and those who reported having difficulty using inhalers are a reflection of the need for educational activities emphasizing the importance of inhaler use.

Our analysis of the drug regimens used by the individuals in our study sample showed that the proportion of combination therapy (BD + IC) users was highest among the individuals who reported having emphysema. The use of ICs in COPD patients is controversial. A recent systematic review highlighted that ICs should be used only in those with frequent exacerbations.[26] According to the Global Initiative for Chronic Obstructive Lung Disease guidelines, ICs should be reserved for those belonging to high-risk groups.[2] In our study, we did not evaluate the frequency or type of symptoms that can lead to an estimation of the severity of COPD; however, data from a previous population-based study showed that those for whom ICs are indicated account for only approximately 1% of all COPD patients.[6]

It is of note that inhalers are underused among socioeconomically disadvantaged populations, despite the fact that those populations have been reported as being the most affected by chronic respiratory diseases.

When the present study was conducted, the public health care system was going through a transition phase regarding inhalers provided free of charge. At the beginning of data collection, inhalers were restricted to two types of medication delivered via MDIs, and asthma patients with more severe disease had access to other inhalers.[7] In addition, the Brazilian Popular Pharmacy program[27] offered discounts of up to 90% on some of those drugs. As of June of 2012, certain types of inhalers had come to be provided free of charge under the program,[28] and, more recently, after the end of our data collection, new drugs began to be provided free of charge in the public health care system, with the objective of improving the treatment of patients diagnosed with COPD.[29] Such changes can soon translate to changes in the inhaler use scenario, expanding the possibilities at the time of prescription and improving treatment adherence.

In the evaluation of the association between low socioeconomic status and lower use of inhalers, mediators other than low income should be taken into account. The underuse of inhalers can also be due to other factors, such as the type of facility used, access to specialist consultations, and the quality of the information provided. Although no such data were collected in the present study, the abovementioned factors can influence inhaler use and therefore should be examined in future studies. Therefore, multiple factors can be addressed in the development of measures to benefit this population and reduce the numbers of emergency room visits and hospitalizations due to preventable causes.[30]

We conclude that inhaler use among individuals with self-reported physician-diagnosed asthma, bronchitis, emphysema, or any combination of the three is far from ideal, especially among those of lower socioeconomic status. A significant proportion of symptomatic individuals reported

nebulizer use only; however, this type of drug administration should not be the first choice for most individuals.[1] The type of inhaled medication recommended for individuals with emphysema also deserves attention because it does not seem to be in accordance with the recommendations.[2,26] Finally, the implementation of new policies for the free distribution of these drugs will meet the needs identified in the present study, because although few individuals reported lack of financial resources to purchase an inhaler as the reason for not using an inhaler, inhaler use is lowest among those of lowest socioeconomic status.

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Evaluation of atopy in patients with COPD*

Avaliação de atopia em portadores de DPOC

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Abstract

Objective: To determine the prevalence of atopy and to evaluate clinical, laboratory, and radiological profiles in patients with COPD. **Methods:** This was a cross-sectional study involving outpatients with stable COPD (defined by the clinical history and a post-bronchodilator $FEV_1/FVC < 70\%$ of the predicted value). The patients completed a questionnaire regarding clinical characteristics and atopy, after which they underwent nasal lavage cytology, skin prick testing, chest X-rays, arterial blood gas analyses, and determination of total serum IgE. **Results:** Of the 149 subjects studied, 53 (35.6%), 49 (32.8%), and 88 (59.1%) presented with nasal eosinophilia, a positive skin prick test result, and symptoms of allergic rhinitis, respectively. Correspondence analysis confirmed these findings, showing two distinct patterns of disease expression: atopy in patients with COPD that was less severe; and no evidence of atopy in those with COPD that was more severe (reduced FEV_1 and hyperinflation). There was a statistically significant association between nasal eosinophilia and a positive bronchodilator response. **Conclusions:** Using simple and reproducible methods, we were able to show that there is a high frequency of atopy in patients with COPD. Monitoring inflammation in the upper airways can be a useful tool for evaluating respiratory diseases in the elderly and in those with concomitant asthma and COPD, a clinical entity not yet fully understood.

Keywords: Pulmonary disease, chronic obstructive; Allergy and immunology; Nasal lavage fluid; Asthma; Rhinitis, allergic, perennial.

Resumo

Objetivo: Determinar a prevalência de atopia e avaliar o perfil clínico, laboratorial e radiológico de pacientes com DPOC. **Métodos:** Estudo de corte transversal com pacientes ambulatoriais portadores de DPOC estável (definida pela história clínica e relação $VEF_1/CVF < 70\%$ do previsto após broncodilatador). Os pacientes responderam um questionário clínico e de atopia e foram submetidos a citologia de lavado nasal, teste cutâneo de alergia, radiografia de tórax, hemogasometria arterial e dosagem de IgE total. **Resultados:** Dos 149 indivíduos avaliados, 53 (35,6%), 49 (32,8%) e 88 (59,1%), respectivamente, apresentavam eosinofilia no lavado nasal, teste cutâneo positivo e sintomas de rinite alérgica. A análise de correspondência confirmou esses achados, evidenciando dois perfis distintos de doença: a presença de atopia em pacientes com estágios mais leves de DPOC, e a ausência de características de atopia em pacientes com aspectos de doença mais grave (VEF_1 reduzido e hiperinsuflação). Houve uma associação estatisticamente significante entre eosinofilia no lavado nasal e prova farmacodinâmica positiva. **Conclusões:** Este estudo identificou uma alta frequência de atopia em pacientes com DPOC, utilizando ferramentas simples e reprodutíveis. A monitorização inflamatória de vias aéreas parece ser uma ferramenta útil para avaliar as doenças respiratórias em idosos, assim como em pacientes com sobreposição de asma e DPOC, entidade clínica ainda pouco compreendida.

Descritores: Doença pulmonar obstrutiva crônica; Alergia e imunologia; Líquido da lavagem nasal; Asma; Rinite alérgica perene.

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Introduction

A progressive inflammatory disease of the lower airways, COPD is characterized by airflow limitation that is not fully reversible.[1,2] The symptoms result from an abnormal inflammatory response of the lungs to the inhalation of noxious particles or gases and are mainly caused by smoking. It is estimated that 10% of the world population over 40 years of age have COPD, with a major impact on the quality of life of patients and on health care systems.[1,2] Despite being preventable and treatable, COPD is the fifth leading cause of death worldwide (2.7 million deaths/year)[3,4] and will become the third one by 2020, according to World Health Organization estimates.[1]

A heterogeneous and multifactorial disease, COPD results from genetic and environmental factors.[1,4] The classical phenotypes are emphysema and chronic bronchitis, which is often associated with bronchial hyperreactivity (BHR). Inflammation of the bronchial wall is characterized by the presence of neutrophils and macrophages and by increased concentrations of IL-8 and Th1 cytokines, as well as by a proteinase/antiproteinase imbalance, and this could explain the poorer response to inhaled corticosteroids (ICs) seen in COPD.[5-7]

The association of COPD with asthma and allergic rhinitis (AR), which are diseases characterized by atopy, with Th2 inflammatory response, eosinophilia, and increased IL-4 levels, has been discussed. This association is more common in the elderly with late-onset asthma and risk factors for COPD (a post-bronchodilator FEV_1 < 70% of the predicted value, hyperinflation, and smoking).[7] Patients with this profile can present with a positive skin prick test (SPT) result, increased serum IgE levels, bronchial remodeling, and eosinophilic inflammation, similarly to those with asthma.[8-11] Common to allergic respiratory diseases, BHR has been described as a risk factor for the development of COPD, even without reported asthma.[12,13]

The association of COPD and atopy, despite current evidence, has been discussed since 1960, with the advent of the "Dutch hypothesis", and has been corroborated by recent studies demonstrating the importance of sputum eosinophilia in patients with COPD and the potential benefits of the use of ICs in such patients. The existence of a subgroup of patients with COPD who have a greater bronchodilator response (a positive bronchodilator response), according to the Dutch hypothesis, is due to the fact that asthma, chronic bronchitis, and emphysema have the same genetic basis, are modulated by the environment, and have varying phenotypic expressions (chronic non-specific lung disease).[14] This hypothesis is supported by the occurrence of COPD in only 10-15% of smokers, supposedly more genetically predisposed to developing COPD.[4]

The relationship between asthma and COPD appears to be bidirectional and complex. Asthma patients who smoke are known to have more frequent exacerbations, a poorer response to ICs, and early functional impairment, and sometimes it is difficult to distinguish between COPD and severe asthma, the inflammation of which can mimic the neutrophilic inflammation of COPD.[15] Paradoxically, a high frequency of eosinophilic bronchitis has been described in patients with stable COPD.[9] There is evidence of a subgroup of COPD patients who have a greater response to high doses of ICs, a positive bronchodilator response, frequent exacerbations, and an FEV_1 < 50% of the predicted value. However, it is necessary to establish the profile of these patients more accurately, reducing the side effects and costs related to the use of high doses of ICs in nonresponding patients.[16]

Inflammatory response markers that are useful as indicators for therapy with ICs in patients with COPD have yet to be established; however, studies have revealed that sputum examination by nasal lavage cytology (NLC) can measure the degree of inflammation in asthma, in COPD, and in other lung diseases both qualitatively and quantitatively, with the advantage of being a simple, inexpensive, and reproducible test.[17,18] There is evidence of eosinophilic bronchitis in up to 17% of patients with COPD, although the authors of that study did not conclude whether it was associated with a greater response to ICs.[9] There is an association between eosinophilia on NLC and asthma severity in adults,[19] but it is unclear whether this relationship occurs in COPD. This seems important since recent studies have described the overlap between COPD and asthma (overlap syndrome),[9,11,20] although this association has yet to be further investigated, as well as requiring a clinical and laboratory approach, in order to establish the profile of COPD patients with evidence of atopy.

The Dutch hypothesis suggests that atopy and BHR, which are important markers of asthma, can be involved in the pathogenesis of COPD, although there is no clear evidence regarding the frequency of atopy (including asthma), AR, eczema, or increased IgE levels in patients with COPD, because most studies have involved small samples and limited evaluation of atopy, usually using only SPTs and not evaluating clinical parameters. In addition, the profile of disease severity in these COPD patients with evidence of atopy is unknown. The objective of the present study was to determine the prevalence of atopy in patients with COPD, as well as to establish their clinical, laboratory, and radiological profiles.

Methods

This was a cross-sectional study aimed at estimating the frequency of atopy in outpatients with COPD who were followed in the Department of Pulmonology of the Federal University of Bahia Professor Edgard Santos University Hospital, located in the city of Salvador, Brazil. Patients who were admitted to the outpatient clinic with a diagnosis of stable COPD (any stage) between November of 2008 and March of 2011 and who gave written informed consent were consecutively included in the study. The diagnosis of COPD was defined by clinical history (dyspnea, chronic cough, sputum, pulmonary exposure to noxious particles or gases) and by spirometry (a post-bronchodilator $FEV_1/FVC < 70\%$ of the predicted value).[1] We excluded patients who had respiratory tract infection in the previous month, who used nasal or systemic corticosteroids in that period, or who used antihistamines in the previous week. We also excluded patients with chest X-ray findings of parenchymal lesions not consistent with COPD. The study was approved by the local research ethics committee.

The patients underwent thorough history taking and a complete physical examination, with an emphasis on the clinical parameters of COPD and atopy and on the history of comorbidities. We used the quality of life questionnaire known as Airway Questionnaire *20* (AQ20), which has been validated for use in Brazil.[21] A case definition of AR was established by the presence of nasal symptoms triggered by aeroallergens (at least two of the following: rhinorrhea; sneezing fits; congestion, or nasal itching).[22] The patients underwent SPTs, spirometry, determination of serum IgE, arterial blood gas analyses, chest X-rays, and stool examination for parasites. All tests were required during a single visit and were performed at the aforementioned hospital by trained staff within two months after the initial evaluation of each patient.

All SPTs were performed with material from the US Food and Drug Administration, using antigens from *Aspergillus fumigatus, Blomia tropicalis, Dermatophagoides pteronyssinus*, cat and dog dander, house dust, and histamine. A positive test result was defined as the presence of papules > 3 mm in diameter to at least one antigen. For NLC, eosinophilia was defined as an eosinophil count ≥ 5%, whereas neutrophilia was defined as a neutrophil count ≥ 5%. Infectious vasomotor rhinitis was defined as a cell count > 1,000,000 cells. In addition, the presence of bacteria and fungi was assessed.

The parameters measured by spirometry included FEV_1, the FEV_1/FVC ratio, and response to a short-acting bronchodilator (albuterol challenge), expressed as the difference between pre- and post-bronchodilator FEV_1 divided by the predicted value for FEV_1. A positive challenge response was defined as a ratio ≥ 7%. Arterial blood samples were collected for blood gas analysis, with the patients breathing spontaneously on room air. Serum IgE levels were measured by ELISA. Posteroanterior and lateral chest X-rays were requested for evaluation of hyperinflation, defined as an increased anteroposterior chest diameter, increased retrosternal air space, a reduced/compressed cardiac silhouette, the presence of bullae, vascular attenuation, and flattening of the hemidiaphragms.[23] Three stool samples were requested from each patient for stool examination for parasites, including testing for *Strongyloides stercoralis* by the Baermann method, in order to rule out parasitic eosinophilia.

The patients were divided into two groups: atopic group (those with a positive SPT result and/or AR symptoms accompanied by eosinophilia on NLC) and non-atopic group (the remaining patients, who did not meet any of the previous criteria).

We used the Statistical Package for the Social Sciences, version 11.0 (SPSS Inc., Chicago, IL, USA). Proportions were compared with the chi-square test or Fisher's exact test. The Mann-Whitney test for independent samples was used to compare the distribution of quantitative variables between

the two groups studied. Multivariate logistic regression analysis was performed to obtain adjusted ORs (the Z approximation), and 95% CIs were calculated. For all analyses, the level of significance was set at 5%.

Multiple correspondence analysis (classification technique) was performed to obtain the final model, which was configured on a Cartesian grid with four quadrants, each representing a profile of patients. Each point in the model represents one category of variables, and a closer proximity between points in the same quadrant translates into a higher affinity between the corresponding variables in the sample.

Results

We evaluated 149 patients. The general characteristics of the sample are presented in Table 1. Eight patients were receiving supplemental oxygen via nasal cannula, at a flow of 1-2 L/min, at the time of arterial blood gas analysis and were therefore excluded from it.

Table 1 - Demographic, clinical, radiological, spirometric, and laboratory characteristics of the study sample (n = 149).[a]

Variable	Result
Male gender	104 (70.0)
Age, years[b]	70.3 ± 8.5
COPD stage	
I	1 (0.7)
II	37 (24.8)
III	100 (67.1)
IV	11 (7.4)
MRC dyspnea scale	
1	8 (5.4)
2	23 (15.4)
3	42 (28.2)
4	34 (22.8)
5	42 (28.2)
Hyperinflation	130 (87.2)
Positive skin prick test result	49 (32.9)
Childhood asthma	6 (4.0)
Heart disease	30 (20.1)
Diabetes mellitus	26 (17.5)
Helminthiasis	12 (8.1)
FEV_1, L/min[b]	1.25 ± 0.6 (0.36-3.56)
FEV_1, % of predicted[b]	50.6 ± 20.7 (16.0-110.0)
SaO_2, %[b]	93.5 ± 3.7 (74.0-99.0)
PaO_2, mmHg[b]	76.8 ± 10.9 (46.0-100.0)
$PaCO_2$, mmHg[b]	42.3 ± 6.2 (28.0-63.0)
Total serum IgE, [b]	523.6 ± 728.2 (1.5-4392.0)

MRC: Medical Research Council. [a]Values expressed as n (%), except where otherwise indicated. [b]Values expressed as mean ± SD or as mean ± SD (range).

Regarding the division of patients into groups, 62 (41.6%) showed evidence of atopy, whereas 87 (58.4%) did not have a positive SPT result or AR symptoms accompanied by eosinophilia on NLC. Among the patients in the atopic group, 49 (79.0%) had a positive SPT result, 38 (61.3%) had AR symptoms with eosinophilia on NLC, and 25 (40.3%) presented with both parameters. The differences between the groups studied are shown in Table 2.

When eosinophilia on NLC and the other study variables were compared, some of the associations found were statistically significant, as shown in Table 3.

Table 4 presents the result of the logistic model with multiple variables, showing adjusted OR values. There were risk relationships between several independent variables and eosinophilia on NLC (dependent variable of the model). Eosinophilia on NLC was found to be positively associated with a positive SPT result and vasomotor rhinitis, the association being statistically significant. The variables Medical Research Council (MRC) dyspnea scale score and smoking history correlated negatively with eosinophilia, but these associations did not achieve statistical significance. Gender and hyperinflation showed a weak association with the dependent variable of the model (OR values close to 1).

Figure 1 shows the multiple correspondence analysis results. The characteristics are found to be distributed into two distinct profiles of patients—one group of patients with variables indicating less severe COPD and with evidence of atopy, such as eosinophilia on NLC, a positive SPT result, and AR symptoms (left lower quadrant of the graph), and one group without evidence of atopy but with indicators of more severe COPD (i.e., MRC scale scores ≥ 4, reduced FEV_1, hyperinflation, hypercapnia, longer hospital stays, and a long smoking history) and with a higher proportion of female patients (upper right quadrant).

Discussion

The results of the present study show a high frequency of patients with evidence of atopy, considering SPT results and AR symptoms accompanied by nasal eosinophilia: 41.6% of the patients studied, a value that is higher than that reported in a previous study, which found

Table 2 - Clinical, laboratory, and radiological characteristics of the COPD patients studied, by group (atopic vs. non-atopic).[a]

Variable	Group		p
	Atopic	Non-atopic	
	(n = 62)	(n = 87)	
Age, years	65.7 ± 8.5	69.7 ± 8.4	< 0.01
Male gender[b]	48 (77.4)	56 (64.4)	0.09
Height, m	1.63 ± 0.1	1.62 ± 0.1	0.25
Weight, kg	67.5 ± 14.5	61.6 ± 13.2	0.01
FEV_1, L/min	1.4 ± 0.6	1.2 ± 0.6	0.03
FEV_1, % of predicted	52.8 ± 21.7	49.6 ± 20.1	0.48
COPD stage[b]			0.65
I and II	17 (27.4)	21 (24.1)	
III and IV	45 (72.6)	66 (75.9)	
Exacerbations/year	4.7 ± 3.5	5.8 ± 4.9	0.17
Hospital admissions/year	1.5 ± 1.6	1.8 ± 1.5	0.17
Length of hospital stay, days	10.7 ± 14.0	17.5 ± 26.7	0.20
AQ20 questionnaire, %	57.1 ± 24.8	60.3 ± 24.2	0.44
Smoking history, pack-years	44.1 ± 18.1	47.3 ± 18.6	0.24
Positive bronchodilator response[b]	26 (42.6)	22 (25.3)	0.03
Hyperinflation[b]	51 (82.3)	79 (90.8)	0.12
SaO_2, %	93.7 ± 3.8	93.4 ± 3.6	0.59
PaO_2, mmHg	78.7 ± 10.0	75.5 ± 11.4	0.19
$PaCO_2$, mmHg	41.7 ± 6.3	42.8 ± 6.2	0.53
Asthma[b]	4 (6.5)	2 (2.3)	0.20
Nasal lavage fluid characteristics[b]			
Eosinophilia	47 (75.8)	6 (6.9)	< 0.001
Neutrophilia	22 (35.5)	28 (32.2)	0.67
Bacteria	18 (29.0)	22 (25.3)	0.61
Vasomotor rhinitis	16 (25.8)	22 (25.3)	0.94
Fungi	7 (11.3)	4 (4.6)	0.12

AQ20: Airway Questionnaire 20. [a]Values expressed as mean ± SD, except where otherwise indicated. [b]Values expressed as n (%).

Table 3 - Variables showing statistically significant differences (p < 0.05) between the patients with and without eosinophilia on nasal lavage fluid cytology.[a]

Variable	Eosinophilia on NLC		p
	Yes	No	
	(n = 53)	(n = 96)	
FEV_1, L/min	1.5 ± 0.5	1.1 ± 0.6	< 0.01
FEV_1, % of predicted	55.3 ± 22.2	48.0 ± 19.5	0.04
Positive bronchodilator response[b]	24 (45.3)	24 (25.3)	0.01
Symptoms of allergic rhinitis[b]	38 (71.7)	50 (52.1)	0.02
Bacteria on NLC[b]	20 (37.7)	20 (20.8)	0.03
Vasomotor rhinitis on NLC[b]	19 (35.8)	4 (19.8)	0.03
Fungi on NLC[b]	7 (13.2)	4 (4.2)	0.04

NLC: nasal lavage cytology. [a]Values expressed as mean ± SD, except where otherwise indicated. [b]Values expressed as n (%).

17% of cases of atopy among patients with COPD.[9] Although studies have estimated that the worldwide prevalence of AR in adults is 10%,[22] in specific subgroups of patients, such as patients with COPD, the rate has yet to be determined. In the present study, 88 patients (59.1% of the sample) had AR symptoms triggered by allergens, a frequency that is much higher than the world average.[22] However, the fact that the diagnosis of AR is determined on the basis of information

Table 4 - Logistic model with multiple independent variables in relation to the presence of eosinophilia on nasal lavage fluid cytology.

Independent variable	OR (95% CI)
Positive skin prick test result	11.2 (4.72-28.72)
Male gender	1.1 (0.43-2.98)
Hyperinflation	1.2 (0.33-4.77)
Vasomotor rhinitis	4.1 (1.59-11.39)
Symptoms of allergic rhinitis	2.4 (0.97-6.17)
MRC scale score > 3	0.5 (0.18-1.45)
Smoking history ≥ 20 pack-year	0.6 (0.14-2.23)
Length of hospital stay > 1 day	0.6 (0.26-1.57)

MRC: Medical Research Council. Area under the curve = 158; pseudo R^2 = 49.9%.

provided by the patient, although this is the recommendation in major consensus guidelines for rhinitis,[22] represents a limitation of the study. In addition, one cannot state that it is in fact rhinitis of allergic etiology. Therefore, we sought to associate this finding from history taking with the laboratory finding of eosinophilia on NLC in order to increase the specificity of the criterion for defining the disease (AR).

One group of authors concluded that only half of the cases of rhinitis have an allergic etiology, the remaining cases being classified as nonallergic rhinitis, without systemic manifestations of atopy

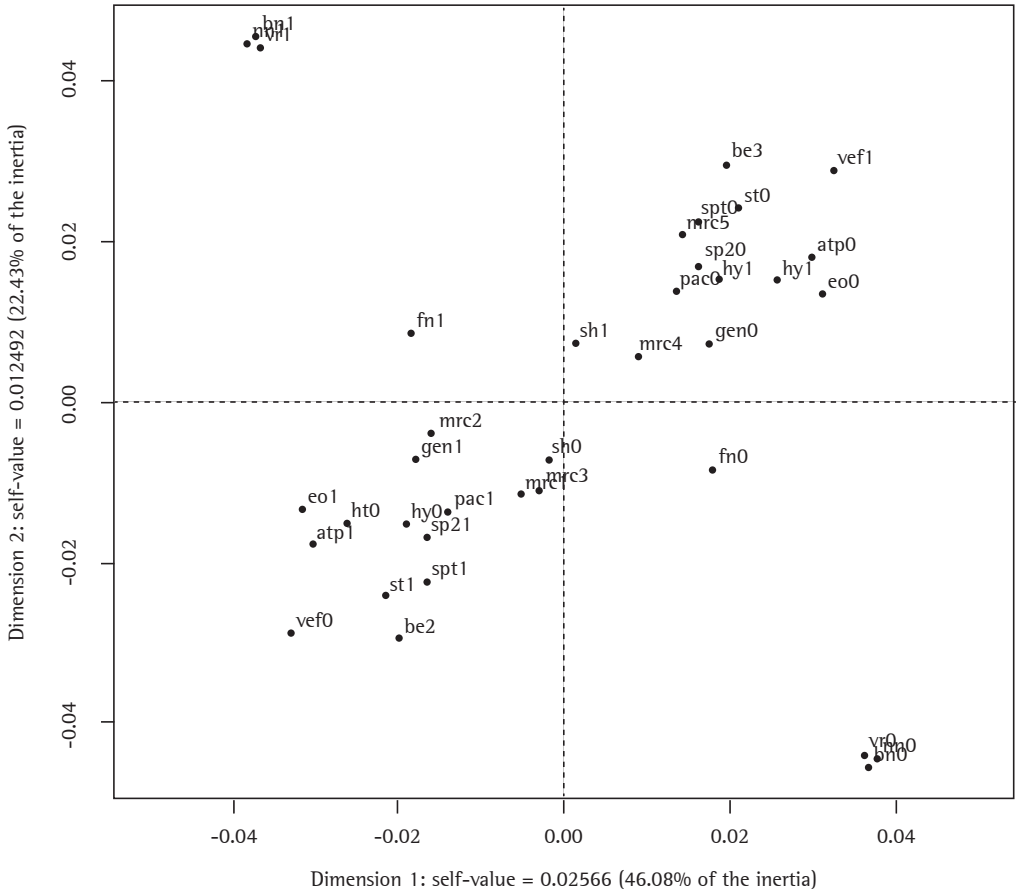

Figure 1 - Correspondence analysis of multiple variables. gen0: female gender; gen1: male gender; fev0: $FEV_1 \geq 1$ L/min; fev1: $FEV_1 < 1$ L/min; pac0: $PaCO_2 > 46$ mmHg; pac1: $PaCO_2 \leq 46$ mmHg; sp20: $SpO_2 > 90\%$; sp21: $SpO_2 \leq 90\%$; mrc1: Medical Research Council (MRC) dyspnea scale = 1; mrc2: MRC dyspnea scale = 2; mrc3: MRC dyspnea scale = 3; mrc4: MRC dyspnea scale = 4; mrc5: MRC dyspnea scale = 5; hy0: no hyperinflation; hy1: hyperinflation; sh0: smoking history < 20 pack-years; sh1: smoking history ≥ 20 pack-years; spt0: negative skin prick test (SPT) result; spt1: positive SPT result; rs0: no allergic rhinitis (AR) symptoms ; rs1: AR symptoms; eo0: no eosinophilia on nasal lavage cytology (NLC); eo1: eosinophilia on NLC; atp0: eosinophilia on NLC and no symptoms of AR; atp1: eosinophilia on NLC and/or symptoms of AR; vr0: no vasomotor rhinitis on NLC; vr1: vasomotor rhinitis on NLC; fn0: no fungi on NLC; fn1: fungi on NLC; ht0: length of hospital stay < 1 day; ht1: length of hospital stay > 1 day; be2: blood eosinophilia; be3: blood eosinophilia.

(as determined by SPTs or testing for serum IgE specific to environmental allergens).[24] In contrast, other authors have described an entity designated local AR, which seems to account for 25% of the total number of patients with rhinitis in allergy clinics and 40% of patients previously diagnosed with nonallergic rhinitis.[25] Local AR is characterized by an inflammatory response limited to the nasal mucosa, with local production of specific IgE, in the absence of systemic atopy. However, locally, there is inflammation, involving eosinophil degranulation, positive responses to nasal challenge with allergens, and a local Th2 immune response. This entity has been found to be associated with ocular symptoms, childhood onset of symptoms (in approximately 40% of cases), and bronchial asthma.[25] Therefore, these data support the fact that, in our study, subjects with allergen-induced nasal symptoms and eosinophilia on NLC, even without a positive SPT result or increased specific IgE levels, were included in the group of patients with evidence of atopy and those with symptoms but no nasal eosinophilia were removed from this group. The resulting number of patients was still much larger than the populations statistics (38 patients had symptoms accompanied by nasal eosinophilia, and this is equivalent to 25.5% of our sample). These data underscore the association between COPD and atopy, which has been described since 1960.[14]

Atopy, a condition that has an increasing prevalence worldwide and remains little studies in many countries, is associated with worsening of quality of life. In Brazil, data have been collected for the International Study of Asthma and Allergies in Childhood, a population survey assessing the prevalence of allergy in children and adolescents. Disease prevalence was found to be 25.7% in Brazilian schoolchildren and 29.6% in Brazilian adolescents, on the basis of the clinical criterion (symptoms) of disease status.[22,26] However, the clinical impact of AR and atopy on patients with COPD, especially in terms of quality of life, has yet to be clearly defined. In the present study, there was no significant difference in quality of life, as assessed by the AQ20 questionnaire, between subjects with and without atopy.

Bivariate analysis comparing the groups revealed that atopic patients showed evidence of more severe COPD (less reduction in absolute FEV_1) and greater reversibility of airflow obstruction, as measured by bronchodilator response ($p = 0.03$). Although they were not statistically significant, differences were found in the frequency of exacerbations, length of hospital stay, hyperinflation, and PaO_2, suggesting less disease severity among atopic individuals, which is in contrast to previous findings.[16] It is possible that these observed trends could have reached statistical significance if the sample size (and, consequently, the power of the study) were larger.

The difference found between absolute FEV_1 values (L/min), which were significantly higher in the atopic group, and the absence of this difference when percentage values were compared can be explained, at least in part, by the fact that this group comprised patients who were younger (a 4-year difference, on average, in relation to non-atopic patients) and heavier (approximately a 6-kg difference, on average). These data could affect the absolute values of this spirometric parameter but not its relationship with the predicted values.

In order to evaluate the influence of upper airway inflammation on the clinical, spirometric, and laboratory characteristics of COPD, we analyzed the variable eosinophilia on NLC and its relationship with the other study variables. Eosinophilia was found to be significantly associated both with higher absolute and higher percentage FEV_1 values. These results suggest that this inflammatory marker is more strongly associated with less severe COPD (less impaired pulmonary function) than is the SPT.

In addition, there was a higher frequency of AR symptoms and other NLC findings in patients with nasal eosinophilia, which indicates agreement between symptoms and laboratory findings in nasal lavage fluid. The fact that patients with nasal eosinophilia had greater bronchodilator response can be explained by the type of airway inflammation and its association with reversibility of airflow obstruction.[16] This finding is consistent with those of previous studies.[27]

Logistic regression analysis confirmed the inverse relationship between atopy and severity of COPD in the study sample—there was an inverse relationship of eosinophilia on NLC with higher MRC scale scores, smoking history, and length of hospital stay. In contrast, a positive SPT result and vasomotor rhinitis correlated positively with nasal eosinophilia, which shows the agreement between these two atopy parameters studied (of

which one is local and one is systemic) and, at the same time, the relationship between two NLC findings suggestive of upper airway inflammation. Correspondence analysis confirmed the results of the previous analyses by graphically defining the profile of patients with evidence of atopy and less severe COPD and of those with no evidence of atopy and more severe COPD.

Unpublished data from a multicenter study involving Latin American cities have shown that 13.2% of patients with COPD have a combined pattern of asthma and COPD (overlap). This finding can contribute to the development of strategies for the therapeutic management of COPD.[12,13,28] However, only 4% of the patients studied reported a concomitant diagnosis. This can suggest a local characteristic of the patients in the present study, although the sample was similar to that described in the literature in terms of gender, age, severity, pulmonary function, hyperinflation, and smoking history.[1]

Many authors have evaluated markers to identify patients with COPD and atopy (atopic phenotype of COPD), who seem to show a better response to ICs.[12,16] One group of authors suggested that a definition of COPD on the basis of phenotypic characteristics, instead of the current definition, which is based on severity, be used to define treatment strategies.[28] In addition, there have been reports of side effects of ICs in elderly patients, who are often taking several medications, as well as of the high costs of large-scale use of this treatment approach.[16] Major consensus guidelines for COPD recommend the use of ICs in patients with an FEV_1 < 50% of predicted or with frequent exacerbations of COPD.[1,2]

Preliminary analyses at our facility revealed that more than 80% of patients used ICs (data not shown). The use of these drugs was not based on bronchodilator response or on evidence of atopy but rather on pulmonary function deterioration (FRV_1 < 50% of predicted) and on the occurrence of frequent exacerbations. There seems to be no difference between the study groups in terms of the use of ICs; therefore, it is unlikely that these drugs could have affected, to some extent, the results obtained. The use of ICs by nearly all patients puts them on a similar footing for evaluation. In addition, the systemic effects associated with ICs are small, compared with those of systemic corticosteroids (excluded from the study), and the influence of these effects on NLC have not been described. Furthermore, the influence of the use of ICs on the study population would be that it would underestimate the finding of an increased prevalence of evidence of atopy, and not the other way around.

The presence of fungi on NLC in 11 patients (7.4%) who were not taking concomitant ICs is relevant because these are uncommon agents, the progression of which has yet to be fully elucidated.[29] There is evidence of fungal sinusitis increases due to previous antibiotic therapy, use of ICs and systemic corticosteroids, and immunosuppression, these microorganisms being associated with greater severity and the need for surgical treatment.[29] With the exception of the use of ICs, none of these risk factors were found in the study population. This underscores the importance of monitoring the upper airways in COPD, even in immunocompetent subjects who are not taking risky medications.

In the present study, we chose NLC over induced sputum cytology, which is associated with complications, especially in the presence of impaired pulmonary function. The NLC technique, which is inexpensive and easy to perform,[17] was used by one group of authors who described the association between asthma severity and the degree of upper airway inflammation.[19] Inhaled nitric oxide, which is a marker of airway eosinophilia, was not used because of its cost and its lower reproducibility.[30] The fact that total IgE varied widely in the present study, although the mean total IgE was much higher than normal, and that it has low specificity in diagnosing atopy explained the exclusion of this variable from the study analyses. Determination of specific IgE was not used because of its high cost.

Compared with previous studies evaluating atopy and COPD, the present study differs in sample size and in that it used several variables to establish evidence of atopy, previously determined only on the basis of positive SPT results and increased serum IgE levels.[29] Our results, together with those of future studies, may inform individualized treatment with the use of ICs in the subgroup of COPD patients with evidence of atopy.

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Screening for F508del as a first step in the molecular diagnosis of cystic fibrosis*,**

Pesquisa da mutação F508del como primeiro passo no diagnóstico molecular de fibrose cística

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Abstract

Objective: To determine the relevance of screening for the F508del mutation of the cystic fibrosis transmembrane conductance regulator gene as a first step in the genetic diagnosis of cystic fibrosis (CF) by associating the genotype with various clinical variables. **Methods:** We evaluated 180 CF patients regarding the F508del mutation. The clinical data were obtained from the medical records of the patients and from interviews with their parents or legal guardians. **Results:** Of the 180 patients studied, 65 (36.1%) did not carry the F508del mutation (group 0 [G0]), 67 (37.2%) were F508del heterozygous (G1), and 48 (26.7%) were F508del homozygous (G2). All three groups showed associations with the clinical variables. Homozygosis was associated with younger patients, younger age at CF diagnosis, and younger age at the first isolation of *Pseudomonas aeruginosa* (PA), as well as with higher prevalence of pancreatic insufficiency (PI) and non-mucoid PA (NMPA) colonization. In comparison with G1+G2 patients, G0 patients were older; first experienced clinical symptoms, digestive disease, and pulmonary disease at an older age; were older at CF diagnosis and at first PA isolation; and had a lower prevalence of PI and meconium ileus, as well as of colonization by NMPA, mucoid PA, and *Burkholderia cepacia*. In G1 patients, values were intermediate for age at CF diagnosis; age at first PA isolation, first pulmonary symptoms, and first clinical manifestations; MPA colonization; and OR for PI. **Conclusions:** The identification of F508del in 63.9% of the patients studied showed that this can be a useful tool as a first step in the genetic diagnosis of CF. The F508del genotype was associated with clinical severity of the disease, especially with the variables related to CF onset.

Keywords: Cystic Fibrosis; Cystic Fibrosis Transmembrane Conductance Regulator; Genotype; Mutation.

Resumo

Objetivo: Verificar a importância da detecção da mutação F508del no gene *cystic fibrosis transmembrane conductance regulator* como primeiro passo no diagnóstico genético de fibrose cística (FC), associando-se o genótipo com várias variáveis clínicas. **Métodos:** Foram avaliados 180 pacientes com FC quanto à mutação F508del. As variáveis clínicas foram obtidas dos prontuários médicos dos pacientes e de entrevistas com seus pais ou responsáveis. **Resultados:** Dos 180 pacientes estudados, 65 (36,1%) não apresentavam a mutação F508del (grupo 0 [G0]), 67 (37,2%) eram heterozigotos (grupo 1 [G1]), e 48 (26,7%) eram homozigotos (grupo 2 [G2]). Todos os três grupos mostraram associações com as variáveis clínicas. A homozigose associou-se a pacientes mais jovens, menor idade ao diagnóstico e menor idade no primeiro isolamento de *Pseudomonas aeruginosa* (PA), bem como maior prevalência de insuficiência pancreática (IP) e colonização por PA não mucoide (PANM). Na comparação com os pacientes G1+G2, os pacientes G0 eram mais velhos, com início de sintomas clínicos, doença digestiva e doença pulmonar mais tardio, diagnóstico tardio, PA isolada tardiamente, e menor prevalência de IP, íleo meconial e colonização por PANM, PA mucoide e *Burkholderia cepacia*. Nos pacientes G1, os valores foram intermediários para idade ao diagnóstico, idade no primeiro isolamento de PA, idade no início de doença pulmonar e de manifestações clínicas, colonização por PAM e OR para IP. **Conclusões:** A identificação de F508del em 63,9% dos pacientes estudados mostrou que ela pode ser uma ferramenta útil como primeiro passo no diagnóstico genético de FC. O genótipo F508del foi associado à gravidade clínica da doença, particularmente às variáveis relacionadas com o início da doença.

Descritores: Fibrose cística; Regulador de Condutância Transmembrana em Fibrose Cística; Genótipo; Mutação.

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Introduction

Cystic fibrosis (CF) is the most common lethal genetic disease in childhood in Caucasian populations.[1] The disease is caused by mutations in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene, which encodes the protein of the same name.[2-4] Nearly 2,000 disease-causing mutations have been observed in the *CFTR* gene. [5] These mutations are classified in six classes according to the absence of changes or qualitative and quantitative changes in the CFTR protein.[6]

The most common *CFTR* mutation is a three-nucleotide deletion that causes the absence of amino acid 508 of the normally 1,480-amino acid protein. This mutation, which lacks a single phenylalanine codon, is commonly referred to as F508del (c.1521_1523delCTT for the DNA mutation and F508del for the mutant protein). Worldwide, the main mutation of *CFTR* gene is F508del, with a prevalence ranging from 30-80%. In Caucasian populations, the F508del mutation is found in approximately 70-88% of the alleles in CF patients.[5,7] The remaining 12-30% of the alleles comprise the other 2,000 different mutations, each of which, individually, have a very low frequency (few mutations have a worldwide frequency above 0.1%, but some can reach high prevalences in selected populations).[5,8,9]

The variability in CF severity is associated principally with genetic factors, such as modifier genes and *CFTR* mutation classes, as well as with environmental factors.[9-15] The F508del mutation is a class II mutation (causing misprocessed/misfolded CFTR proteins), and it is associated with higher clinical severity of CF.[9]

Nowadays, it is not possible to identify the full spectrum of *CFTR* mutations in most countries. Together with the newborn screening program that uses immunoreactive trypsinogen testing, the Brazilian public health system has currently been providing assistance for screening of *CFTR* gene mutations. However, because of the costs, only one mutation is screened. Therefore, studies on the screening for the F508del mutation are necessary and important because that is the only test that can be currently performed in most of the countries. In this context, the objective of the present study was to verify the importance of the screening for the F508del mutation as a first step in the genetic diagnosis of CF by associating the F508del genotype with 28 clinical variables.

Methods

This was a cross-sectional study conducted at a university center for CF between 2010 and 2011. The diagnosis of CF was confirmed by two determinations of sweat sodium and chloride (concentrations > 60 mEq/L) in all patients. We selected 215 patients for the study. Among those, 35 patients were excluded because of the lack of clinical data or of a written informed consent.

We used the phenol/chloroform method for DNA extraction, and, in all genetic analyses, DNA concentration was 50 ng/mL, determined with a spectrophotometer (NanoVue™; GE Healthcare Biosciences, Pittsburgh, PA, USA).

The determination of the F508del mutation was performed by polymerase chain reaction (PCR), using a pair of primers—sense (5'-GGC ACC ATT AAA GAA AAT ATC-3') and antisense (5'-TGG CAT GCT TTG ATG ACG C-3')—resulting in a 74-bp fragment (F508del homozygosis), a 77-bp fragment (absence of F508del), or the presence of both fragments (F508del heterozygosis). The procedure for thermal cycling consisted of initial denaturation at 94°C for 5 min, subsequent denaturation at 94°C for 1 min, annealing at 53.5°C for 1 min, and extension at 72°C for 1 min, repeated for 35 cycles, and followed by a final extension at 72°C for 10 min. The PCR contained 25 µL of a solution with 50 ng of DNA, 1 µM of each primer, 200 µM of dNTP, 1.0 mM of $MgCl_2$, 50 mM of KCl, 10 mM of Tris-HCl (pH, 8.4 at 25°C), and 1.5 U of Taq DNA polymerase. After the addition of 5 µL of glycerol-based loading buffer, 10 µL of the reaction product was applied on acrylamide gel.[16]

The determination of *CFTR* mutations was performed in the laboratory of molecular genetics of the institution using the RFLP method (G542X, R1162X, R553X, G551D, and N1303K). Some mutations were obtained by sequencing or multiplex ligation-dependent probe amplification: S4X, 2183A>G, 1717-G>A, and I618T. For both methods, we used the MegaBace1000 DNA sequencer (GE Healthcare Biosciences).[16]

Clinical data, anthropometric variables, pulmonary function results, and sputum or oropharyngeal swab culture results were collected.

The following clinical variables were investigated: clinical scores (Shwachman-Kulczycki, Kanga, and Bhalla scores)[17]; body mass index (BMI) —for the patients older than

19 years, we used the formula BMI = weight/(height)^2; for the remaining patients, we used WHO Anthro, version 3.0.1 and WHO Anthro Plus, version 1.0.2, respectively, for children under 5 years of age and for those aged 5-19 years; age (dichotomized between ≤ 154 months and > 154 months); age at diagnosis (dichotomized between ≤ 24 months and > 24 months); first digestive symptoms (dichotomized between ≤ 3 months and > 3 months); first pulmonary symptoms (dichotomized between ≤ 6 months and > 6 months); age at the first isolation of *Pseudomonas aeruginosa* (dichotomized between ≤ 30 months and > 30 months); airway colonization (mucoid *P. aeruginosa* [MPA], nonmucoid *P. aeruginosa* [NMPA], *Achromobacter xylosoxidans, Burkholderia cepacia*, and *Staphylococcus aureus*); transcutaneous SaO_2; spirometry results; and comorbidities—nasal polyps, osteoporosis, meconium ileus (MI), diabetes mellitus, and pancreatic insufficiency (PI).

All of the scores were determined by two pediatric pulmonologists, and, in case of disagreement, a third specialist was invited to review the scores in order to determine the final results.

All of the patients aged ≥ 7 years were submitted to spirometry with a CPFS/D spirometer (MedGraphics, Saint Paul, MN, USA). Data were recorded using Breeze PF, version 3.8B for Windows 95/98/NT (Medical Graphics Corp., Saint Paul, MN, USA), and the following variables were included: FVC, % of predicted; FEV_1, % of predicted; FEV_1/FVC ratio, % of predicted; and $FEF_{25-75\%}$.

The present study was approved by the Research Ethics Committee of the State University at Campinas School of Medical Sciences (Protocol no. 528/2008).

For the purposes of the statistical analysis, the variables that showed non-normal distribution (age at diagnosis, age at the first pulmonary and digestive symptoms; and age at the first isolation of *P. aeruginosa*) were categorized into two groups, using as the cutoff point the median value of each variable. The data categorized by the median were divided into two cohorts with similar sample sizes.

For the clinical evaluation of the scores, SaO_2, and spirometry tests, the analyses were performed without adjusting the data.

Bacteria isolated from the airways of the patients were used as markers according to the presence or absence of specific bacteria in three consecutive cultures within the last year.

Comorbidities were compared in terms of their presence or absence.

The statistical analyses were performed with the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA).

In order to avoid spurious data due to the problem of multiple testing,[18] the level of significance α was adjusted using the Bonferroni correction for three groups: G0, without the F508del mutation (patients with no F508del on the two alleles or those whose *CFTR* mutation could not be determined); G1, heterozygous F508del mutation (patients with the F508del mutation on one of the alleles, with or without another *CFTR* mutation identified); and G2, homozygous F508del mutation (patients with F508del on both alleles).

The statistical power of the sample was calculated with the freeware G*Power, version 3.0.5,[19] which showed a statistical power above 80% for the analysis performed and $\alpha = 0.05$, using a population of 159 CF patients.

The data were compared with one-way ANOVA, the Kruskal-Wallis test, the Mann-Whitney U test, and Pearson's chi-square test. For the comparisons between genotypes and variables with numerical distribution, the Kruskal-Wallis test was used for F508del genotypes, and the Mann-Whitney test was used for the F508del groups. For categorical variables, we used Pearson's chi-square test and ORs.

Results

The numerical and categorical data of the clinical variables in 180 CF patients are described in Table 1. The distribution of the patients among the groups (G0, G1, and G2) was, respectively, 65 (36.1%), 67 (37.2%), and 48 (26.7%). The population was found not to be in Hardy-Weinberg equilibrium regarding the F508del mutation ($p < 0.001$). The distribution of the patients according to *CFTR* mutation genotype is shown in Table 2.

Regarding numerical variables, SaO_2 and the Shwachman-Kulczycki scores were significantly higher in G1 and in G2 than in G0 ($p = 0.034$ and $p = 0.046$, respectively; Table 3).

Regarding the clinical categorical variables, G2 patients were associated with younger age in general ($p \leq 0.001$), younger age at CF diagnosis ($p < 0.001$), younger age at the first isolation of

Table 1 - Characteristics of the patients included in the study (n = 180).[a]

Variable	Result
Males	50.00
Age, years	17.72 ± 15.75 (0.60-24.00)
Caucasoid	91.70
Underweight and extremely underweight	22.47
Identification of one F508del allele	37.20
Identification of two F508del alleles	26.70
Age at first clinical manifestations, years	2.90 ± 8.88 (0.00-13.00)
Age at diagnosis, years	7.62 ± 13.63 (0.00-14.23)
Age at first digestive symptoms, years	3.39 ± 9.11 (0.00-12.45)
Age at pulmonary symptoms, years	2.90 ± 9.89 (0.00-13.00)
SaO_2, %	94.92 ± 4.26 (66.00-99.00)
Bhalla score	8.74 ± 5.72 (0.00-25.00)
Kanga score	18.85 ± 5.84 (10.00-40.00)
Shwachman-Kulczycki score	65.85 ± 16.77 (20.00-95.00)
FVC, % of predicted	79.29 ± 23.55 (19.00-135.00)
$FEV_{1,}$ % of predicted	71.29 ± 27.47 (17.00-132.00)
FEV_1/FVC, % of predicted	83.46 ± 15.95 (37.00-137.00)
$FEF_{25-75\%}$	59.05 ± 35.55 (7.00-150.00)
Nasal polyps	18.64
Diabetes mellitus	18.64
Osteoporosis	16.38
Pancreatic insufficiency	79.90
Meconium ileus	15.08
Age at first isolation of *Pseudomonas aeruginosa*, years	8.55 ± 14.45 (2.00-15.00)
Colonization[b]	
P. aeruginosa	56.42
Mucoid *P. aeruginosa*	42.46
Burkholderia cepacia	13.97
Achromobacter xylosoxidans	10.05
Staphylococcus aureus	78.77

[a]Values expressed as % or as mean ± SD (range). [b]Positive colonization based on three consecutive positive respiratory cultures in the past year.

P. aeruginosa (p = 0.009), and higher prevalence of PI (p = 0.001) and NMPA (p = 0.025; Table 4). In comparison with G1+G2 patients, G0 patients were older (p < 0.001), had first clinical symptoms at an older age (p < 0.001), had digestive disease at an older age (p = 0.023), had pulmonary disease at an older age (p = 0.006), were older at CF diagnosis (p < 0.001), had a lower prevalence of PI (p < 0.001), had a lower prevalence of MI (p = 0.047), were older at the first isolation of *P. aeruginosa* (p = 0.001), and had a lower prevalence of colonization by NMPA (p = 0.025), MPA (p = 0.068), and *B. cepacia* (p = 0.001; Table 4). Intermediate values were found in G1 patients: age at CF diagnosis (p < 0.001), age at the first isolation of *P. aeruginosa* (p = 0.001), age at first pulmonary symptoms (p = 0.006), age at first clinical manifestations (p < 0.001), MPA colonization (p = 0.068), and OR for PI (p < 0.001).

Table 5 shows the association of the major variables with the F508del genotype.

Discussion

The use of molecular genetics in the clinical practice has been improving, and it is considered important in various aspects related to patient care. The molecular technique is essential to the diagnosis of CF, especially in cases in which there is uncertainty, i.e., when the patient presents with CF symptoms not confirmed by sweat tests, when the onset of CF symptoms occurs in adult life, in cases of atypical CF, and when CF is caused by *CFTR* mutations belonging to classes IV, V, or VI. In CF patients with clinical variability, the genetic

Table 2 - *Cystic fibrosis transmembrane conductance regulator* genotype according to F508del mutation group.

		Patient		
F508del mutation group	*CFTR* mutation genotype	n	%	% per group
G0	-/-	43	23.9	36.1
	G542X/-	5	2.8	
	G542X/R1162X	1	0.6	
	G542X/I618T	1	0.6	
	G542X/2183A>G	1	0.6	
	G542X/2183AA→G	1	0.6	
	G542X/P205S	1	0.6	
	G542X/R334W	1	0.6	
	I507V/-	1	0.6	
	R334W/R1066C	1	0.6	
	R334W/R334W	1	0.6	
	3120+1G>A/3120+1G>A	1	0.6	
	3120+1G>A/-	1	0.6	
	TG11-5T/-	1	0.6	
	622-2A>G/711+1G>T	1	0.6	
	R1162X/R1162X	1	0.6	
	R1162X/-	1	0.6	
	D110H/V232H	1	0.6	
G1	F508del/-	40	22.2	37.2
	F508del/G542X	13	7.2	
	F508del/R1162X	5	2.8	
	F508del/N1303K	4	2.2	
	F508del/R553X	2	1.1	
	F508del/S4X	1	0.6	
	F508del/1717-1G>A	1	0.6	
	F508del/exon 6B-16 duplication	1	0.6	
	F508del/2184insA	1	0.6	
G2	F508del/F508del	48	26.7	26.7

G0: absent F508del; G1: heterozygous F508del patients; and G2: homozygous F508del patients.

Table 3 - Significantly different numerical variables in the groups studied.*

Variable	Genotype group	Median	Mean	SD	p
Shwachman-Kulczycki score	G0	95	93.38	5.935	0.046
	G1+G2	96	95.50	2.869	
SaO_2	G0	60	61.40	17.844	0.034
	G1+G2	65	67.91	15.893	

G0: absent F508del; G1: heterozygous F508del patients; and G2: homozygous F508del patients. *Mann-Whitney U test.

analysis might allow a better understanding of the disease and promote targeted therapies and better outpatient care.

Molecular tests are not available in our public health care system; however, centers linked to universities screen the major *CFTR* mutations. Among the *CFTR* mutations, screening for F508del is routinely performed in our research center in all of the patients with two sodium and chloride tests in sweat with values above 60 mEq/L. The screening for F508del is not expensive and allows the definitive diagnosis in 26.7% of the patients in our center, 37.2% of whom being identified as heterozygous. Our study showed that the identification of the F508del mutation is important in a country with great ethnic diversity, because 63.9% of our patients had at least one F508del allele. Therefore, the implementation of screening for F508del in the public health care system is necessary and should be implemented in all developing countries. The

Table 4 - Significantly different categorical variables in the groups studied.*

Group	Variable	Categorization		p	OR	95% CI	Variable	Categorization		p	OR	95% CI
	Age	≤ 154 mo	> 154 mo				Age at first clinical manifestations	≤ 3 mo	> 3 mo			
G0		18	46	< 0.001	0.238	0.121-0.457		19	37	< 0.001	0.239	0.119-0.47
G1		36	31		1.202	0.654-2.217		48	18		2.974	1.539-5.884
G2		37	11		4.754	2.263-10.53		30	18		1.366	0.689-2.749
	Age at diagnosis	≤ 24 mo	> 24 mo				Age at digestive disease	≤ 3 mo	>3 mo			
G0		15	44	< 0.001	0.157	0.007-0.315		13	27	0.023	0.362	0.165-0.77
G1		41	23		1.95	1.034-3.725		37	25		1.852	0.958-3.615
G2		36	12		3.563	1.715-7.74		26	22		1.227	0.615-2.464
	Age at pulmonary disease	≤ 6 mo	> 6 mo				PI	Presence	Absence			
G0		20	32	0.006	0.385	0.179-0.704		35	29	< 0.001	0.08	0.03-0.192
G1		44	21		2.258	1.181-4.391		62	5		4.71	1.817-14.35
G2		28	20		1.158	0.586-2.312		46	2		7.007	2.136-51.37
	MI	Presence	Absence				Age at first PA isolate	≤ 3 mo	> 3 mo			
G0		5	60	0.047	0.335	0.108-0.892		9	26	0.001	0.229	0.093-0.535
G1		13	54		1.569	0.683-3.576		30	25		1.263	0.627-2.552
G2		10	38		1.662	0.682-3.906		28	13		2.794	1.29-6.248
	MPA	Presence	Absence				NMPA	Presence	Absence			
G0		21	44	0.068	0.553	0.2731-0.984		28	37	0.025	0.438	0.233-0.814
G1		35	32		1.914	1.034-3.56		41	26		1.39	0.752-2.593
G2		20	28		0.97	0.491-1.898		32	16		1.82	0.916-3.702
	BC	Presence	Absence									
G0		4	61	0.101	0.313	0.088-0.91						
G1		12	55		1.83	0.757-4.426						
G2		8	40		1.447	0.548-3.618						

mo: months; G0: absent F508del; G1: heterozygous F508del patients; G2: homozygous F508del patients; MI: meconium ileus; PA: *Pseudomonas aeruginosa*; MPA: mucoid PA colonization; BC. *Burkholderia cepacia* colonization; PI: pancreatic insufficiency; PA: *P. aeruginosa*; and NMPA: non-mucoid PA colonization. *Chi-square test.

Table 5 - Variables significantly associated with the *cystic fibrosis transmembrane conductance regulator* genotype according to F508del mutation groups.*

Clinical variable	Genotype	G2 vs. G0+G1	G0 vs. G1+G2
	p	p	p
Sex	0.473	0.400	1
Ethnicity	0.353	0.549	0.407
Age	< 0.001	< 0.001	< 0.001
Age at first clinical manifestations	< 0.001	0.394	< 0.001
Age at diagnosis	< 0.001	0.001	0.01
Onset of digestive symptoms	0.022	0.602	< 0.001
Onset of pulmonary symptoms	0.006	0.731	0.004
BMI	0.227	0.22	0.186
Bhalla score	0.163	0.283	0.06
Kanga score	0.509	0.466	0.264
Shwachman-Kulczycki score	0.098	0.889	0.046
SaO_2	0.068	0.076	0.034
FVC, % of predicted	0.514	0.368	0.29
FEV_1, % of predicted	0.321	0.054	0.383
FEV_1/FVC, % of predicted	0.49	0.232	0.596
$FEF_{25-75\%}$	0.29	0.27	0.132
Nasal polyposis	0.521	0.516	0.842
Diabetes mellitus	0.948	1	0.842
Osteoporosis	0.236	0.255	0.139
Pancreatic insufficiency	< 0.001	0.001	< 0.001
Meconium ileus	0.047	0.238	0.016
First isolation of *Pseudomonas aeruginosa*	0.001	0.009	0.001
Colonization			
P. aeruginosa	0.025	0.092	0.012
Mucoid *P. aeruginosa*	0.068	1	0.059
Burkholderia cepacia	0.332	0.46	0.04
Achromobacter xylosoxidans	0.101	0.261	0.301
Staphylococcus aureus	0.758	1	0.572

G0: absent F508del; G1: heterozygous F508del patients; and G2: homozygous F508del patients; and BMI: body mass index. *Kruskal-Wallis one-way ANOVA (numerical data) and Pearson's chi-square test (categorical data).

identification of the F508del mutation allows improved genetic counseling.

In the state of São Paulo, newborn screening for CF has become possible by the determination of immunoreactive trypsinogen since 2010. Neonatal screening and sweat chloride/sodium determinations are free for all patients. Our clinic receives approximately US$ 30/patient from the government for the screening for *CFTR* mutations. This amount allows us to perform only the screening for the F508del mutation. The identification of additional mutations is performed by funded research projects. The main objective of the present study was to assess the importance of identifying the F508del mutation in our patients, due to the current amendment for public neonatal screening in Brazil, which provides subsidies to molecular analysis in order to identify positive cases in neonatal patients, as well as studies on new drugs for CF.

In our study, we analyzed 28 clinical variables that were associated with the F508del mutation. Associations with the F508del mutation were found mainly in the variables related to the onset of the disease. No patient was diagnosed by neonatal screening in our study. Therefore, the association between the F508del genotype and the variables related to the onset of the disease, such as age at first clinical symptoms and age at diagnosis, should be related to the clinical severity and not to the diagnosis, treatment, and follow-up of the patients.

With the inclusion of a neonatal screening program for CF in the state of São Paulo in 2010,

screening for F508del has become important as a means of predicting the clinical manifestations of CF, enabling a better monitoring of the patients in our health care clinic.

The patients in G0 presented with a lower risk for early clinical manifestations of CF and a protective factor for some of the variables studied (age, age at CF diagnosis, first clinical symptoms, digestive and pulmonary diseases, MI, and age at the first isolation of *P. aeruginosa*). In addition, there was a protective factor against MPA, NMPA, and *B. cepacia* colonization, which is an important risk factor for pulmonary disease. Corroborating the literature, PI was less common in G0 than in G1/G2 in our study.

The patients in G2 were younger, were diagnosed with CF at a younger age, were younger at the first isolation of *P. aeruginosa*, and were more commonly diagnosed with PI.

Some of the variables studied were significantly different in G1 than in G0 and G2 (age at first clinical manifestation, age at the onset of pulmonary disease, and MPA colonization). In addition, PI and age at CF diagnosis showed intermediate results.

In the analysis for gene clusters regarding variables with numerical data, patients in G1 and G2 presented with significantly higher Shwachman-Kulczycki scores and SaO_2. Higher values for these variables are associated with less severe disease; however, those patients were younger, and this is associated with the variation in the Shwachman-Kulczycki score and SaO_2.

When measuring the risk factors for long-term survival in a group of older CF patients (> 40 years of age), one group of authors reported that the residual activity of CFTR was not a factor associated with increased life expectancy but with other factors, such as BMI.[20] The greater importance of the F508del mutation and its identification is associated with the onset of the illness. In the present study, markers of initial severity of the pathophysiology were more evidently associated with the F508del genotype than were other clinical variables.[20] Thus, we believe that the genotype has a greater importance in the onset of disease and that the environment progressively becomes a higher risk factor with increasing age. In addition, we believe that survival selection is related to the class of mutation in the *CFTR* gene.

Another fact which underscores the importance of screening for F508del is that this mutation has been the most commonly studied, and the use of new drugs has been focused on patients with this mutation, which could favor their treatment. The study of correctors of F508del-CFTR depends on the use of pharmacological chaperones that stabilize the protein in its native state, of target cells using proteostasis regulators in order to enhance the folding efficiency of the protein, or of both at the same time. Although stabilizing and folding correctors of F508del-CFTR have been developed, we need to know the entire mechanism of action of these drugs before using them in our clinical practice. Current efforts to identify correctors, based largely on phenotype screens, have not been successful in identifying highly efficient molecules.[21,22] Although there are numerous defects in the CFTR protein, some of them might be liable to correction. New treatments are aimed at correcting defective CFTR proteins.[22]

Despite the advances in the scientific knowledge on CF, not much is known about the management of the disease, and many controversies are still present.[23] Much remains to be learned about the mechanism that involves the expression of the CFTR protein associated with the F508del mutation,[24] because F508del acts in multiple steps in the biogenesis of CFTR.[25]

Currently, the study of the genetic variation in CF using molecular technology allows new therapeutic possibilities and provides knowledge about the unknown factors of the severity of the disease.[9] As the prevalence of F508del is higher than that of other *CFTR* mutations with clinical importance described, this is the main factor to be analyzed as a first step in the molecular diagnosis of CF. Mutation analysis in a predominantly Caucasian population might provide improvements in diagnosis, genetic counseling, use of new drugs that are still under study, less expensive molecular analysis, monitoring and targeting outpatients, and promoting molecular diagnosis in individuals with a positive neonatal screening test for CF even with the low subsidy provided. There should be an understanding and an association between the outpatient clinic and the research laboratory in order to promote better patient monitoring.[8]

We currently have priority areas for the study of CF: to explore the pathogenic mechanisms of

early pulmonary disease; to improve newborn screening; to develop a spectrum of early lung disease biomarkers that reflect the pathophysiology, the clinical course, and the response to treatment; to explore the role of genetics/genomics in the pathogenesis of the disease; to define the microbiological events in early lung disease; and to elucidate the changes in remodeling, inflammation, and repair mechanisms in the pulmonary disease.[26] Much has yet to be done in this context, and the determination of a point mutation might bring benefits as important as those brought by the identification of other *CFTR* mutations.

In our study, a univariate analysis was performed. A multivariate logistic regression model could have been used; however, a larger sample of CF patients would be necessary in order to adjust for age and other factors simultaneously. For instance, a 40-year-old patient is significantly more likely to be colonized than a 5-year-old patient. In our study, we directly analyzed the influence of the F508del genotype on CF patients.

A huge ethnic diversity is present in Brazil, and, therefore, it might be disadvantageous for some subjects to be tested for F508del only. However, and not surprisingly, our findings were similar to those in the literature, and the screening for only one CF mutation was able to demonstrate the genetic diagnosis in one third of the patients. Another third of the patients presented with at least one allele with this mutation. The screening for F508del is important, particularly in developing countries and in countries with limited resources.

In conclusion, the identification of F508del and its association with the clinical severity of the disease allowed a better understanding of its influence on the clinical manifestations in CF patients. The association with variables related to the onset of the disease highlights the importance of using the screening for this mutation at the time of diagnosis and after positive neonatal screening for CF. In the future, the use of new drugs designed to one particular genotype will be associated with molecular analysis. Due to its high prevalence in the CF population, F508del should be analyzed primarily, mainly in developing countries. The genetic counseling of parents and patients is better carried out with the knowledge of the mutation associated with disease. Outpatient care can be better performed, especially considering the importance of F508del in association with CF severity variables, such as the isolation of bacteria that cause chronic pulmonary infection. In summary, the identification of F508del promotes genetic counseling, management, monitoring, diagnosis, and the use of new drugs. We believe that genetic laboratories worldwide should only initially consider the screening for F508del in patients with two altered sweat sodium/chloride tests.

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Importance of slow vital capacity in the detection of airway obstruction*

Importância da capacidade vital lenta na detecção de obstrução das vias aéreas

Ana Raquel Gonçalves de Barros, Margarida Batista Pires, Nuno Miguel Ferreira Raposo

Abstract

Objective: To investigate the presence of airway obstruction by determining the FEV_1/FVC and FEV_1/slow vital capacity (SVC) ratios. **Methods:** This was a quantitative, retrospective cross-sectional study. The sample comprised 1,084 individuals who underwent spirometry and plethysmography in a central hospital in Lisbon, Portugal. The study sample was stratified into six groups, by pulmonary function. **Results:** The analysis of the FEV_1/FVC ratio revealed the presence of airway obstruction in 476 individuals (43.9%), compared with 566 individuals (52.2%) for the analysis of the FEV_1/SVC ratio. In the airway obstruction, airway obstruction plus lung hyperinflation, and mixed pattern groups, the difference between SVC and FVC (SVC – FVC) was statistically superior to that in the normal pulmonary function, reduced FEF, and restrictive lung disease groups. The SVC – FVC parameter showed a significant negative correlation with FEV_1 (in % of the predicted value) only in the airway obstruction plus lung hyperinflation group. **Conclusions:** The FEV_1/SVC ratio detected the presence of airway obstruction in more individuals than did the FEV_1/FVC ratio; that is, the FEV_1/SVC ratio is more reliable than is the FEV_1/FVC ratio in the detection of obstructive pulmonary disease.

Keywords: Airway Obstruction; Spirometry; Plethysmography.

Resumo

Objetivo: Investigar a ocorrência de obstrução das vias aéreas por meio da relação VEF_1/CVF e da relação VEF_1/capacidade vital lenta (CVL). **Métodos:** Estudo do tipo quantitativo, retrospectivo e transversal. A amostra foi constituída por 1.084 indivíduos que realizaram espirometria e pletismografia num hospital central da região de Lisboa, Portugal. A amostra foi estratificada em seis grupos funcionais respiratórios. **Resultados:** A análise da relação VEF_1/CVF revelou a presença de obstrução das vias aéreas em 476 indivíduos (43,9%), enquanto a relação VEF_1/CVL detectou a presença dessa em 566 indivíduos (52,2%). A diferença entre a CVL e a CVF (CVL – CVF) nos grupos relativos à obstrução brônquica, à obstrução brônquica com hiperinsuflação pulmonar e à alteração ventilatória mista foi estatisticamente superior àquela encontrada nos grupos sem alteração ventilatória, com diminuição dos FEFs e com restrição pulmonar. O parâmetro CVL – CVF apresentou correlação negativa significativa com VEF_1 em % do previsto apenas no grupo com obstrução brônquica com hiperinsuflação pulmonar. **Conclusões**: A relação VEF_1/CVL detectou a presença de obstrução das vias aéreas em um número maior de indivíduos que a relação VEF_1/CVF, ou seja, a relação VEF_1/CVL é mais confiável na detecção de alterações ventilatórias obstrutivas.

Descritores: Obstrução das vias respiratórias; Espirometria; Pletismografia.

* Study carried out at the Portuguese Red Cross School of Health and at the Northern Lisbon Hospital Center Pulido Valente Hospital, Lisbon, Portugal.

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Introduction

In 2005, vital capacity (VC) was described by the American Thoracic Society/European Respiratory Society (ATS/ERS)[1] as the volume of air mobilized between a maximal inspiratory maneuver and a maximal expiratory maneuver. An FVC maneuver or a slow vital capacity (SVC) maneuver can be used in order to determine VC.

When an FVC maneuver is performed, there is higher dynamic compression and airway collapse, reducing the ability to mobilize the volume of air during exhalation and therefore causing air trapping. Consequently, FVC values can be lower than SVC values; because SVC is measured through an unforced maneuver, there is less intrathoracic pressure, and, consequently, a larger volume of air can be mobilized.[2]

The factors influencing airway caliber can affect VC, principally FVC. In addition to those, other key factors should be analyzed. The determinants of TLC and RV also affect VC. Chest wall retraction, lung retraction, and the pressure resulting from respiratory muscle strength determine TLC and RV.[3,4]

In healthy individuals, the difference between SVC and FVC (SVC – FVC) is practically zero; however, in the presence of airway obstruction, these differences can become apparent and are mostly related to the presence of lung hyperinflation.[4]

According to the ATS/ERS,[1] the ratio between FEV_1 and maximal vital capacity, as measured by spirometry, can be used in order to determine the presence of airway obstruction. When pulmonary function tests are performed, analysis of the FEV_1/FVC ratio is sometimes used in order to determine the presence of airway obstruction because additional respiratory maneuvers are required in order to assess TLC. This is why this parameter is often not measured and is therefore given less weight.

The primary objective of the present study was to investigate the presence of airway obstruction by determining the FEV_1/FVC and FEV_1/SVC ratios. A secondary objective was to determine whether the SVC – FVC parameter correlated with lung disease severity, as determined by percent predicted FEV_1 (FEV_1%).

Methods

This was a quantitative, retrospective cross-sectional study. A non-probabilistic convenience sampling procedure was used.

Data collection was performed with the use of a database belonging to the institution where the study was conducted. The database contained information on the anthropometric and pulmonary function characteristics of the individuals in the study sample.

The study sample consisted of 1,084 individuals who underwent spirometry and plethysmography on the same day (between January of 2005 and December of 2011) in a central hospital in Lisbon, Portugal.

We included individuals who were 18 years of age or older and who had undergone spirometry and plethysmography for the first time in the facility where the study was conducted. We excluded individuals who had undergone bronchodilator therapy on the day of the test and those in whom pulmonary function testing did not include determination of TLC or meet the quality criteria.

The database used in the present study contained data regarding 1,321 patients; however, 237 patients were excluded from the analysis, the final study sample therefore consisting of 1,084 patients. Of the 237 individuals who were excluded, 41 had received bronchodilator therapy on the day of the test, 103 had not undergone determination of TLC, and 93 had undergone pulmonary function tests that did not meet the quality criteria.

For the present study, we considered only the pulmonary function tests that were performed in the first visit to the laboratory; that is, subsequent follow-up visits were not studied, in order to avoid repetition of results in the same individual.

In addition to spirometry, all of the individuals underwent plethysmography, because TLC is typically measured by plethysmography in the laboratory where the study was conducted. Furthermore, the lung volume data were essential for the characterization of the patients.

In the present study, spirometry and plethysmography were performed in accordance with the ATS/ERS guidelines, having met the quality criteria thereof.[5,6]

The pulmonary function test results were interpreted in accordance with the criteria proposed by the ATS/ERS.[1] The reference equations used in the present study have been described elsewhere.[7]

On the basis of the results of the pulmonary function tests, the study sample was divided

into six groups. The normal pulmonary function group comprised 176 individuals; the reduced FEF group (i.e., the group of individuals with decreased FEFs at different levels of VC) comprised 225 individuals; the airway obstruction group comprised 316 individuals; the airway obstruction plus lung hyperinflation group comprised 215 individuals; the restrictive lung disease group comprised 117 individuals; and the mixed pattern group (i.e., the group of individuals with mixed obstructive and restrictive lung disease) comprised 35 individuals.

In the present study, we used a Vmax Series Autobox 6200 plethysmograph (Sensormedics, Yorba Linda, CA, USA).

For the statistical characterization of the study sample, we calculated descriptive statistics. For quantitative variables, we used measures of central tendency (sample mean), dispersion (standard deviation), and association (Spearman's correlation coefficient). For qualitative variables, we analyzed the distribution of frequencies.

In order to test the normality of data distribution, we used the Kolmogorov-Smirnov test. Because the study variables showed a non-normal distribution, we used nonparametric statistical methods.

In order to determine whether the SVC – FVC parameter varied according to the type of respiratory pattern, we used the Kruskal-Wallis test. In order to identify the group (or groups) showing those differences, we used multiple comparisons of the means for independent samples.

For all statistical tests, the level of significance was set at 0.05.

Results

The analysis of the FEV_1/FVC ratio revealed the presence of airway obstruction in 476 individuals (43.9%), compared with 566 individuals (52.2%) for the analysis of the FEV_1/SVC ratio.

Table 1 shows the anthropometric characteristics of the individuals in the study sample, divided into six groups by pulmonary function. Females predominated in the normal pulmonary function and reduced FEF groups (62% and 68%, respectively), whereas, in the airway obstruction, airway obstruction plus lung hyperinflation, restrictive lung disease, and mixed pattern groups, males predominated (54.7%, 66.5%, 58.1% and 68.6% respectively).

Table 2 shows the pulmonary function parameters (spirometry and plethysmography) for the six groups of individuals. The differences between SVC and FVC were greater in the presence of an obstructive component, i.e., in the airway obstruction group (140.9 ± 9.20 mL), in the airway obstruction plus lung hyperinflation group (127.4 ± 9.83 mL), and in the mixed pattern group (134.3 ± 21.1 mL).

In order to determine whether the SVC – FVC parameter varied according to the type of respiratory pattern, we used the Kruskal-Wallis test, which revealed the existence of statistical differences ($p < 0.001$) in at least one of the pulmonary function groups ($p < 0.001$). In order to identify the groups showing those differences, we used multiple comparisons of the means for independent samples. The results are shown in Table 3.

Table 1 - Anthropometric characteristics of the patients under study.[a]

Variables	Groups					
	Normal pulmonary function	Reduced FEF	Airway obstruction	Airway obstruction with lung hyperinflation	Restrictive lung disease	Mixed obstructive and restrictive lung disease
	(n = 176)	(n = 225)	(n = 316)	(n = 215)	(n = 117)	(n = 35)
Gender						
Male	67 (38.0)	72 (32.0)	173 (54.7)	143 (66.5)	68 (58.1)	24 (68.6)
Female	109 (62.0)	153 (68.0)	143 (45.3)	72 (33.5)	49 (41.9)	11 (31.4)
Age, years	54.3 ± 14.5	57.9 ± 11.3	61.8 ± 13.1	61.2 ± 12.3	60.1 ± 12.6	64.1 ± 12.3
Height, m	1.61 ± 0.09	1.60 ± 0.09	1.63 ± 0.09	1.64 ± 0.09	1.62 ± 0.10	1.65 ± 0.08
Weight, kg	72.6 ± 15.7	74.8 ± 15.8	75.7 ± 15.4	71.1 ± 15.8	74.7 ± 15.6	76.2 ± 16.2
BMI, kg/m^2	28 ± 5	29 ± 6	28 ± 5	26 ± 6	28 ± 6	28 ± 5

BMI: body mass index. [a]Values expressed as n (%) or as mean ± SD.

In the airway obstruction, airway obstruction plus lung hyperinflation, and mixed pattern groups, the SVC – FVC parameter was statistically superior to that in the normal pulmonary function, reduced FEF, and restrictive lung disease groups ($p < 0.05$; Table 3). In terms of the SVC – FVC parameter, there were no significant differences among the airway obstruction, airway obstruction plus lung hyperinflation, and mixed pattern groups ($p \geq 0.05$ for all) or among the normal pulmonary function, reduced FEF, and restrictive lung disease groups ($p \geq 0.05$ for all; Table 3).

Table 4 shows Spearman's correlation coefficients for the correlations between the

Table 2 - Pulmonary function characteristics of the patients under study.[a]

Variables	Groups					
	Normal pulmonary function	Reduced FEF	Airway obstruction	Airway obstruction with lung hyperinflation	Restrictive lung disease	Mixed obstructive and restrictive lung disease
	(n = 176)	(n = 225)	(n = 316)	(n = 215)	(n = 117)	(n = 35)
FEV_1, L	2.78 ± 0.05	2.30 ± 0.04	1.90 ± 0.04	1.33 ± 0.04	1.90 ± 0.05	1.17 ± 0.07
FEV_1, %	109.5 ± 1.03	95.9 ± 0.74	74.8 ± 0.99	51.0 ± 1.17	75.8 ± 1.61	45.8 ± 2.65
FVC, L	3.43 ± 0.07	3.07 ± 0.05	3.04 ± 0.06	2.68 ± 0.05	2.38 ± 0.07	1.92 ± 1.16
FVC, %	111.3 ± 1.16	105.4 ± 0.91	96.4 ± 1.06	82.3 ± 1.28	76.3 ± 1.45	59.5 ± 3.31
SVC, L	3.51 ± 0.07	3.14 ± 0.06	3.18 ± 0.05	2.81 ± 0.06	2.45 ± 0.07	2.06 ± 0.12
SVC, %	110.0 ± 1.18	103.6 ± 0.87	97.4 ± 1.00	82.5 ± 1.30	75.9 ± 1.46	61.5 ± 3.20
SVC – FVC, mL	79.3 ± 7.61	74.5 ± 14.3	140.9 ± 9.20	127.4 ± 9.83	78.0 ± 9.41	134.3 ± 21.1
FEV_1/FVC, %	81.5 ± 0.29	75.3 ± 0.24	62.6 ± 0.48	49.4 ± 0.73	80.2 ± 0.57	61.3 ± 1.30
FEV_1/SVC, %	79.7 ± 0.34	73.8 ± 0.28	59.4 ± 0.47	47.2 ± 0.73	77.5 ± 0.63	57.0 ± 1.25
RV, L	1.64 ± 0.42	1.83 ± 0.43	2.35 ± 0.59	3.86 ± 0.95	1.39 ± 0.43	1.88 ± 0.50
RV, %	87.8 ± 18.9	96.6 ± 20.7	111.8 ± 20.0	180.3 ± 36.3	67.4 ± 17.8	86.3 ± 29.0
TLC, L	5.16 ± 1.05	4.97 ± 1.01	5.53 ± 1.19	6.67 ± 1.22	3.84 ± 0.93	3.94 ± 0.91
TLC, %	98.7 ± 11.5	97.6 ± 11.2	99.8 ± 10.7	117.0 ± 14.6	70.0 ± 9.16	68.7 ± 16.3
RV/TLC	32.4 ± 7.76	37.4 ± 7.47	43.1 ± 9.36	57.9 ± 9.08	36.9 ± 9.71	48.5 ± 9.75
FRC, L	2.51 ± 0.62	2.59 ± 0.63	3.18 ± 0.75	4.64 ± 1.07	2.04 ± 0.54	2.48 ± 0.59
FRC, %	87.7 ± 16.9	91.6 ± 17.2	104.2 ± 16.4	148.0 ± 25.0	67.1 ± 12.2	78.5 ± 19.6

SVC: slow vital capacity; and FRC: functional residual capacity. [a]Values expressed as mean ± SD.

Table 3 - Comparison of the means of the differences between slow vital capacity and FVC among the pulmonary function groups under study.

Groups	Groups					
	Normal pulmonary function	Reduced FEF	Airway obstruction	Airway obstruction with lung hyperinflation	Restrictive lung disease	Mixed obstructive and restrictive lung disease
	p	P	p	p	p	p
Normal pulmonary function	N/A	0.103	< 0.001	< 0.001	0.922	0.002
Reduced FEF	0.103	N/A	< 0.001	< 0.001	0.181	< 0.001
Airway obstruction	< 0.001	< 0.001	N/A	0.647	< 0.001	0.336
Airway obstruction with lung hyperinflation	< 0.001	< 0.001	0.647	N/A	0.001	0.245
Restrictive lung disease	0.922	0.181	< 0.001	0.001	N/A	0.002
Mixed obstructive and restrictive lung disease	0.002	< 0.001	0.336	0.245	0.002	N/A

Kruskal-Wallis test for independent samples for multiple comparisons of the means.

Table 4 - Spearman's correlation coefficients for the correlations of the difference between slow vital capacity and FVC with FEV_1 (in % of the predicted value).

Groups											
Normal pulmonary function		Reduced FEF		Airway obstruction		Airway obstruction with lung hyperinflation		Restrictive lung disease		Mixed obstructive and restrictive lung disease	
r	p	r	p	r	p	r	p	r	p	r	p
0.027	0.719	−0.719	0.292	−0.049	0.384	−0.156	0.022	−0.025	0.790	0.089	0.615

SVC – FVC parameter and FEV_1%, the latter being the parameter characterizing lung disease severity. The SVC – FVC parameter was found to correlate significantly with lung disease severity ($p < 0.05$) only in the airway obstruction plus lung hyperinflation group.

Discussion

In the present study, the FEV_1/SVC ratio detected the presence of airway obstruction in more individuals than did the FEV_1/FVC ratio. The former ratio detected the presence of airway obstruction in 52.2% of the sample as a whole, compared with 43.9% for the latter ratio. This means that there was a discrepancy of 8.4% between the two ratios.

Studies by Chhabra[8] and Rasheed et al.[9] also examined the use of the FEV_1/FVC ratio or the FEV_1/SVC ratio as a criterion for the presence of airway obstruction. The study by Chhabra[8] showed that the differences among the FEV_1/FVC, VEF_1/expiratory VC, and FEV_1/inspiratory VC ratios in healthy individuals and in those with mild obstruction were not significant; however, those differences were statistically significant in individuals with at least moderate obstruction.

The study by Rasheed et al.[9] examined two groups of individuals, grouped by underlying disease process (asthma or COPD), and showed a discrepancy between the FEV_1/SVC and FEV_1/FVC ratios in 17% of the sample as a whole; in the asthma and COPD groups, this discrepancy was observed in 22% and 13% of the patients, respectively.

In the present study, we performed a sub-analysis based on the respiratory pattern. The analysis showed that the differences between SVC and FVC (SVC – FVC) were greater in the presence of airway obstruction, a finding that is consistent with those of Chan and Irvin,[2] who reported that, in the presence of airflow limitation, the differences between the two variables are greater.

These results might be due to the fact that FVC maneuvers are forced maneuvers and can cause small airway collapse, therefore leading to an underestimation of this variable.

The greatest discrepancy in volumes between SVC and FVC occurred in the airway obstruction, airway obstruction plus lung hyperinflation, and mixed pattern groups. This might explain why the FEV_1/FVC ratios were higher than the FEV_1/SVC ratios in the present study. This is due to the fact that the denominator of the former ratio is lower than is that of the latter ratio, which therefore has greater airway obstruction detection capability.

In one study,[10] SVC – FVC was reported to be greater in individuals with asthma than in healthy individuals, being also greater in the presence of airway obstruction and increasing with the degree of respiratory disease severity. These findings are consistent with those in the study by Kawakami et al.,[11] in which SVC values were higher than FVC values in individuals with COPD.

In the airway obstruction, airway obstruction plus lung hyperinflation, and mixed pattern groups, the SVC – FVC parameter was found to be statistically superior to that in the normal pulmonary function, reduced FEF, and restrictive lung disease groups. This was due to the presence of an obstructive component in the first three groups. Therefore, it appears that the presence of obstruction is responsible for the differences found in the present study.

According to the ATS/ERS,[1] the degree of lung disease severity is characterized by FEV_1%, which is habitually used in order to determine disease severity in patients with obstructive lung disease, restrictive lung disease, or mixed

obstructive and restrictive lung disease. Therefore, in order to determine whether the differences between SVC and FVC were correlated with the severity of lung disease, we analyzed the correlation between the SVC – FVC parameter and FEV_1%.

The SVC – FVC parameter showed a significant negative correlation with FEV_1% only in the airway obstruction plus lung hyperinflation group. The results obtained suggest that the severity of lung disease cannot be explained by the differences observed, given that only one of the groups showed significant results.

The present study showed that the differences between SVC and FVC have statistical significance, the volumes obtained by unforced maneuvers being greater than those obtained by forced maneuvers. The differences between the two parameters were greater in the presence of an obstructive component, and our correlation analysis revealed that the differences increased as the degree of severity increased in the airway obstruction plus lung hyperinflation group.

The present study showed that the FEV_1/SVC ratio detected the presence of airway obstruction in more individuals than did the FEV_1/FVC ratio, given that the VC volume obtained by an SVC maneuver is greater than is that obtained by an FVC maneuver.

The present study allowed us to conclude that the use of the FEV_1/SVC ratio in the detection of airway obstruction does not underestimate the results of VC, therefore increasing the sensitivity of pulmonary function tests in the diagnosis of airway obstruction and avoiding interpretation errors that can prevent the initiation of appropriate therapeutic measures.

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Influenza A (H1N1) pneumonia: HRCT findings*

Pneumonia por vírus influenza A (H1N1): aspectos na TCAR

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Abstract

Objective: To describe aspects found on HRCT scans of the chest in patients infected with the influenza A (H1N1) virus. **Methods:** We retrospectively analyzed the HRCT scans of 71 patients (38 females and 33 males) with H1N1 infection, confirmed through laboratory tests, between July and September of 2009. The HRCT scans were interpreted by two thoracic radiologists independently, and in case of disagreement, the decisions were made by consensus. **Results:** The most common HRCT findings were ground-glass opacities (85%), consolidation (64%), or a combination of ground-glass opacities and consolidation (58%). Other findings were airspace nodules (25%), bronchial wall thickening (25%), interlobular septal thickening (21%), crazy-paving pattern (15%), perilobular pattern (3%), and air trapping (3%). The findings were frequently bilateral (89%), with a random distribution (68%). Pleural effusion, when observed, was typically minimal. No lymphadenopathy was identified. **Conclusions:** The most common findings were ground-glass opacities and consolidations, or a combination of both. Involvement was commonly bilateral with no axial or craniocaudal predominance in the distribution. Although the major tomographic findings in H1N1 infection are nonspecific, it is important to recognize such findings in order to include infection with the H1N1 virus in the differential diagnosis of respiratory symptoms.

Keywords: Pneumonia, viral; Tomography, X-ray computed; Influenza A virus, H1N1 subtype.

Resumo

Objetivo: Descrever os aspectos encontrados em TCAR do tórax de pacientes infectados pelo vírus influenza A (H1N1). **Métodos:** Foram analisadas retrospectivamente as TCAR de 71 pacientes (38 femininos e 33 masculinos) com diagnóstico confirmado de influenza A (H1N1) através da identificação laboratorial do vírus, estudados no período entre julho e setembro de 2009. A interpretação das TCAR foi realizada por dois radiologistas torácicos de forma independente, e, em caso de discordância, as decisões foram tomadas por consenso. **Resultados:** Os achados de TCAR mais comuns foram opacidades em vidro fosco (85%), consolidação (64%) ou a combinação de opacidades em vidro fosco e consolidação (58%). Outros achados foram nódulos do espaço aéreo (25%), espessamento das paredes brônquicas (25%), espessamento de septos interlobulares (21%), padrão de pavimentação em mosaico (15%), espessamento perilobular (3%) e aprisionamento aéreo (3%). As alterações foram frequentemente bilaterais (89%), com distribuição não específica (68%). Derrame pleural, quando observado, foi, em geral, de pequena monta. Não foram observadas linfonodomegalias. **Conclusões:** As alterações predominantes foram opacidades em vidro fosco, consolidações ou a combinação de ambas. O acometimento foi frequentemente bilateral e não houve predomínio quanto à distribuição (axial ou craniocaudal). Apesar de inespecíficos, é importante reconhecer os principais aspectos tomográficos da infecção por influenza A (H1N1) a fim de incluir essa possibilidade no diagnóstico diferencial de sintomas respiratórios.

Descritores: Pneumonia viral; Tomografia computadorizada por raios X; Vírus da influenza A subtipo H1N1.

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Introduction

In April of 2009, there began an epidemic of acute febrile respiratory illness caused by a new virus: the influenza A (H1N1) virus. The first cases occurred in Mexico, and the infection rapidly spread worldwide.[1] By August of 2010, 214 countries had been hit by the infection and more than 18,000 deaths had been confirmed.[1,2]

Although the number of cases of H1N1 infection has decreased significantly since the 2009 pandemic, various studies have reported that the virus is still circulating together with other seasonal viruses, with different prevalences. In Brazil, by October of 2012, approximately 20,000 patients had been hospitalized for severe acute respiratory syndrome. Of those, approximately 2,600 cases were caused by the influenza A (H1N1) post-pandemic virus.[3]

The most common clinical findings in the presentation of H1N1 infection are fever, cough, dyspnea, myalgia, and headache. Gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, have also been reported.[4-6] In most cases, the symptoms are mild and run a self-limiting course; however, a small proportion of individuals develop a severe course, which can result in respiratory failure and death.[4,7-10]

The most common laboratory test findings include increased serum lactate dehydrogenase levels (which can exceed 1,000 IU/L), bearing in mind that elevated lactate dehydrogenase levels are significantly associated with disease severity and ICU admission[6,11]; increased C-reactive protein levels; increased serum creatine kinase levels; lymphopenia; and thrombocytopenia. Elevated transaminase and D-dimer levels can occur in some patients.[4,7,12]

Chest X-ray provides adequate information for defining the approach in most of the affected patients.[13] However, HRCT often becomes an important tool for determining the extent of pulmonary involvement, as well as being useful in the evaluation of complications and in the clarification of suspected mixed infections or failure to respond to therapy.[4] Although the diagnosis of viral infection is based on the clinical profile and on identification of the virus, the recognition of some imaging features of the disease can become useful, especially in patients with *forme fruste* or atypical clinical manifestations. Therefore, the understanding of the imaging features of the disease becomes important in clinical practice.

The objective of the present study was to evaluate, by means of a retrospective analysis of HRCT scans of patients with confirmed H1N1 infection, the most common tomographic findings and the characteristics of their distribution in the lung parenchyma.

Methods

The study was approved by the Research Ethics Committee of the Clementino Fraga Filho University Hospital. This was a retrospective observational cross-sectional study in which we analyzed the HRCT scans of 71 patients from several hospitals in different states in Brazil between July and September of 2009.

The study population included patients presenting with flu-like symptoms and diagnosed with H1N1 infection, regardless of age or gender. The inclusion criterion was the diagnostic confirmation of H1N1 infection through laboratory testing (viral culture or real-time PCR) of aspiration material or of nasopharyngeal or oropharyngeal swab specimens. Another inclusion criterion was the required availability of complete chest HRCT scans of each study patient, performed during the acute phase of the disease. Patients with other pulmonary infections, confirmed through laboratory tests, were excluded, as were those with tomographic findings suggestive of pulmonary involvement resulting from chronic lung diseases. All HRCT scans were obtained 2-10 days after the onset of symptoms.

As multiple institutions were involved, imaging examination was performed with different tomography scanners, using the high-resolution technique, in accordance with the following protocol: patient in the supine position; 1- to 2-mm slice thickness in increments of up to 10 mm, from the lung apices through the hemidiaphragm, at the end of a deep inhalation; and a high spatial resolution reconstruction algorithm. Parenchymal and mediastinal window settings (width = 1,400-1,600 HU; level = −600 to −800 HU; and width = 350-450 HU; level = 15-25 HU, respectively) were used.

The following tomographic characteristics were analyzed: pattern of the findings (airspace consolidations, ground-glass opacities, airspace nodules, interlobular septal thickening, crazy-paving pattern, air trapping—when identified in

the inspiratory phase—and peribronchovascular interstitial thickening); and distribution of the lesions (central, peripheral, or random; unilateral or bilateral; upper, middle, or lower lung zone predominant, or any combination of the three). In addition, the presence of pleural effusion and lymphadenopathy was evaluated. The HRCT scans were independently interpreted by two experienced thoracic radiologists, and in case of disagreement, the decisions were made by consensus.

Consolidation was defined as increased attenuation of the lung parenchyma, resulting in the obscuration of the vascular outlines and adjacent airway walls; ground-glass opacity was defined as slightly increased attenuation of the lung parenchyma that is unrelated to the obscuration of the vessels and adjacent airway walls; interlobular septal thickening was defined as thin linear opacities, which correspond to the thickened peripheral connective septa; a crazy-paving pattern was defined as interlobular septal thickening superimposed on ground-glass opacities; airspace nodules were defined as ill-defined nodules smaller than 1 cm and tending to confluence; peribronchovascular thickening was defined as an increase in connective tissue around the bronchi, pulmonary arteries, and lymphatic vessels; a perilobular pattern was defined as thick and irregular polygonal opacities in the periphery of the secondary pulmonary lobule; and air trapping was defined as decreased attenuation of the lung parenchyma, revealed by a lower-than-usual density.[14,15] The bronchial walls were considered thickened if the bronchial lumen internal diameter was equal to or greater than 80% of its external diameter.[16]

The distribution of the lesions in the lung parenchyma was evaluated along the axial and craniocaudal axes. The craniocaudal distribution of the lesions was classified as upper, middle, or lower lung zone predominant, or any combination of the three. The axial distribution of the findings was classified as central or peripheral. In addition, the predominance of the findings in one lung or the lack of predominance along the two axes was recorded.

Results

Of the 71 patients, 38 (53.53%) and 33 (46.47%) were female and male, respectively. The mean age of the patients was 41.3 years (range, 16-92 years).

Pulmonary abnormalities were identified on the HRCT scans of all patients. The most common tomographic findings, in decreasing order, were as follows: ground-glass opacities, in 60 patients (85%); consolidations, in 46 (64%; Figures 1 and 2); airspace nodules, in 18 (25%; Figure 3); bronchial wall thickening, in 18 (25%); interlobular septal thickening, with or without ground-glass opacities, in 15 (21%); crazy-paving pattern, in 11 (15%); perilobular pattern, in 2 (3%); and air trapping, 2 (3%; Figure 4 and Table 1).

The most common findings were ground-glass opacities and consolidations. A combination of ground-glass opacities and consolidations in the same patient was observed in 41 cases (58%). Only 6 patients had no ground-glass opacities, consolidations, or a combination of both.

Of the patients who had ground-glass opacities, 11 (15%) also had interlobular septal thickening, characterizing a crazy-paving pattern. Septal thickening, without ground-glass opacities, was a mild secondary finding in 4 patients (6%). Airspace nodules were found in 18 cases (25%), and bronchial wall thickening was found in 18 (25%). Bronchial wall thickening was observed in all 6 patients who had no ground-glass opacities, consolidations, or a combination of both.

Air trapping was an uncommon finding, being observed in 2 patients. Peribronchovascular interstitial thickening was observed in 8 cases (11%), and, in all of these cases, there were ground-glass opacities and consolidations. A perilobular pattern was found in only 2 patients (3%). Minimal pleural effusion was observed in 19 patients (27%), being bilateral in 10 (52%).

Parenchymal involvement was bilateral in 63 cases (89%) and unilateral in 8 (11%). In 55 patients (77%), the lesions were evenly distributed between the two lungs; in 9 patients (13%), the lesions predominantly affected the right lung; and, in 7 patients (10%), the lesions predominantly affected the left lung. In 7 of the 8 cases (87%) in which the involvement was unilateral, only one lobe was affected. An analysis of the craniocaudal distribution of the lesions by lung zone revealed the following: no preferential distribution, in 35 patients (49%); lower third predominance, in 26 (37%); middle third predominance, in 4 (6%); lower and middle third predominance, in 5 (7%); and upper third

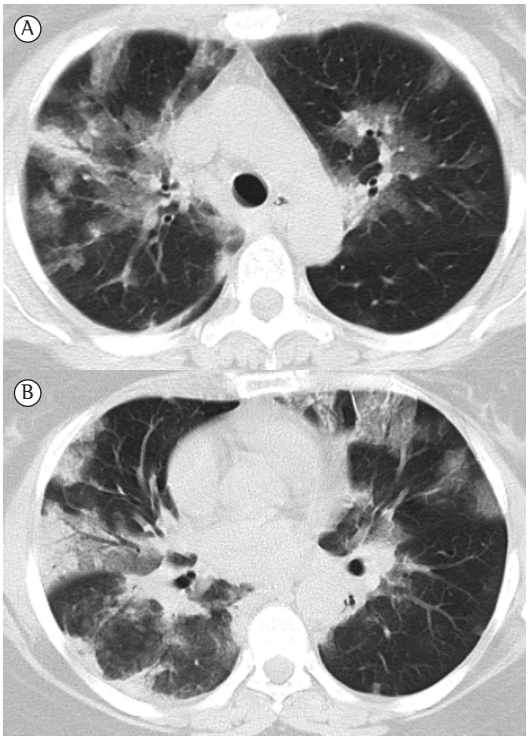

Figure 1 - HRCT scans. In A, areas of consolidation and ground-glass opacities in the upper lobes of both lungs. In B, areas of consolidation and ground-glass opacities in the lower lobes, with peripheral distribution of the lesions.

predominance, in only 1 (1.5%). An analysis of the axial distribution of the lesions revealed the following: no specific distribution, in 48 patients (68%); peripheral lung zone predominance, in 21 (29%); and central lung zone predominance, in 2 (3%). In 14 of the 21 patients (67%) with peripheral distribution, there were also lesions in the peribronchovascular interstitial space.

Discussion

In the present study, we retrospectively evaluated the HRCT scans of 71 patients with confirmed H1N1 infection. The most common tomographic findings were ground-glass opacities, consolidations, and a combination of ground-glass opacities and consolidations in the same patient. These data are similar to literature data showing that these tomographic findings predominate in patients with H1N1 infection.[4,17-21]

A crazy-paving pattern, in which ground-glass opacities are associated with septal thickening, has been reported in few cases in the literature.[22,23] In our study, 15% of the patients showed

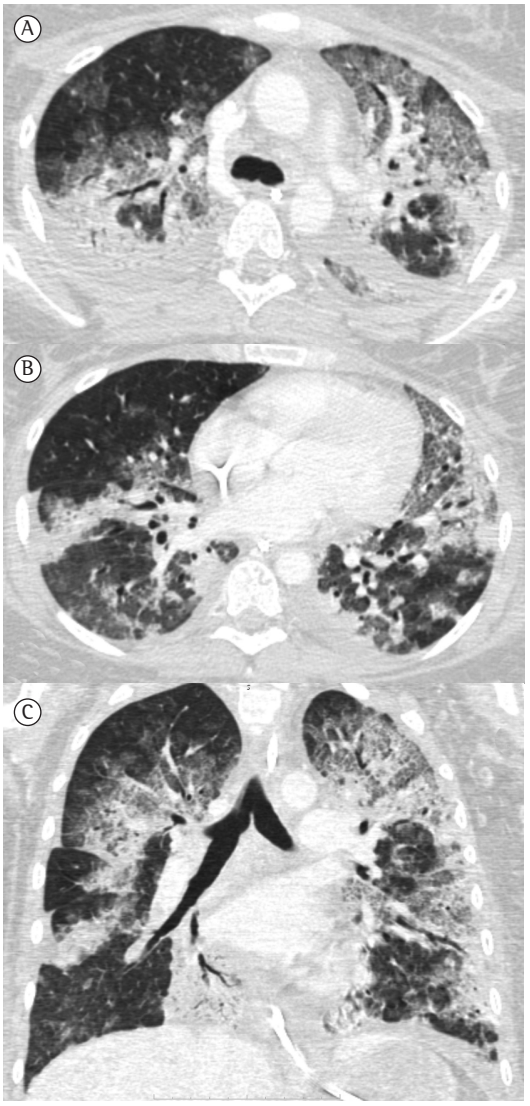

Figure 2 - Axial HRCT slices at the levels of the upper lobes (A) and lower lobes (B), as well as reformatted coronal image (C), showing extensive areas of consolidation with air bronchograms in both lungs.

this pattern. Septal thickening without ground-glass opacities was a mild secondary finding, being observed in only 4 patients (6%).

Airspace nodules were present in 25% of the cases, and this was the dominant finding in only 1. This finding has not commonly been reported in the literature, and few studies have described the presence of airspace nodules in patients with H1N1 infection.[21,24] This can be attributed to an alternative interpretation, by some authors, of airspace nodules being focal areas of consolidation, or it can even be attributed to the fact that airspace nodules can be obscured by

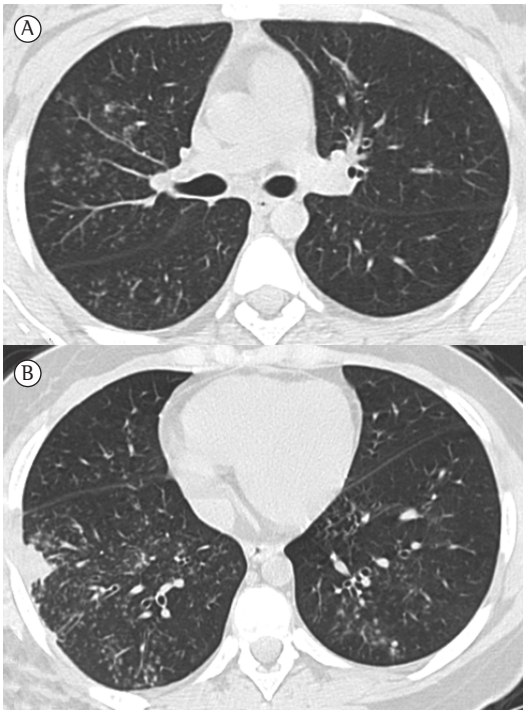

Figure 3 - Axial HRCT slices at the levels of the upper lobes (A) and lower lobes (B) revealing multiple small centrilobular nodules, some of which have a tree-in-bud pattern, distributed principally in the middle lobe and lower lobes. Note also bronchial wall thickening predominantly in the right lower lobe, as well as a small area of peripheral consolidation.

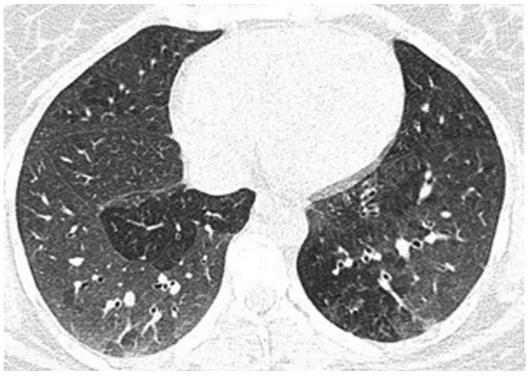

Figure 4 - Axial HRCT slice at the level of the lower lobes, obtained during the expiratory phase, showing bilateral areas of mosaic attenuation, as well as a well-defined area of air trapping in the lower lobe of the left lung.

other findings when there is extensive involvement by the disease.

Bronchial wall thickening was observed in one fourth of the patients in our sample. In the literature, these findings have been described in few studies and in varying frequencies.[21,24] One group of authors[24] found bronchial wall thickening in all of their patients. Other authors[25] suggested that these changes occur early in the disease course, a period when patients have not yet sought medical care, and is therefore poorly reported. Tanaka et al.[25] related the high frequency of these findings in their study (68%) to the fact that their patients had quick access to medical treatment. Likewise, the immunocompromised patients in another study[24] are probably patients who received prompt medical attention, given their comorbidities. In contrast, other authors[20] reported air trapping in a female patient in a late phase, three months after the onset of the disease.

Table 1 - Frequency distribution of the tomographic findings in the 71 patients in the sample.

Finding	Frequency	
	n	%
Ground-glass opacities	60	85
Consolidations	46	64
Airspace nodules	18	25
Bronchial wall thickening	18	25
Interlobular septal thickening	15	21
Crazy-paving pattern	11	15
Perilobular pattern	2	3
Air trapping	2	3

In our sample, a mosaic attenuation pattern was observed in 3% of the cases and was interpreted as being air trapping because it was associated with bronchial wall thickening. As occurred in our sample, air trapping related to H1N1 infection has rarely been described in the literature.[21,24] However, it should be emphasized that, in those studies, the expiratory phase, which increases sensitivity in the characterization of this pattern, was not performed. Li et al.[21] found a mosaic attenuation pattern due to air trapping in 13% of their patients and related it to the use of mechanical ventilation.

A perilobular pattern is a finding that is commonly associated with organizing pneumonia.[15] This finding was seen in 2 of our patients (3%), and it had not been described in H1N1 infection. Because patients affected by the pandemic virus can develop organizing pneumonia during the convalescence phase of the disease,[18,19,26] a perilobular pattern is an expected finding in these cases.

In the literature, the most common distribution of HRCT findings is bilateral multifocal involvement predominantly in the lower lobes.[4,20,21,24] However, in some studies, the distribution is diffuse, with no zonal predominance.[27] In our sample, the HRCT scans showed bilateral involvement in the vast majority of the cases (89%), and both lungs were similarly affected in 77% of them. The craniocaudal distribution of the lesions was random, with no zonal predominance in approximately half of the cases and with lower third predominance in 37%. The axial distribution of the findings showed no zonal predominance in most cases (68%), but, in approximately one third of the cases, it showed peripheral lung zone predominance. A central distribution was rarely observed. In the literature, data regarding the axial distribution of HRCT findings are varied, there being reports of central or peripheral predominance.[4,20,24] Regarding the craniocaudal distribution, the literature reports lower lung zone predominance.

Pleural effusion, either unilateral or bilateral and typically minimal, has been described in some cases.[4,17,21] In our sample, pleural effusion was observed in 27% of the cases, being bilateral in 52% and typically minimal. No mediastinal lymphadenopathy was identified in any of the patients studied.

Our study had some limitations. First, the study was retrospective, which made it impossible to establish a proper correlation between clinical and radiological findings. Second, there were some differences in relation to the technical parameters in tomography image acquisition, since we evaluated HRCT scans performed at various institutions.

In conclusion, the most common tomographic findings were ground-glass opacities and airspace consolidations, or a combination of both. The findings were predominantly bilateral, with no axial or craniocaudal predominance in the distribution in most cases. When zonal predominance was present, it was more common in the lower thirds and peripheral regions of the lungs. Pleural effusion, when observed, was typically minimal. No lymphadenopathy was identified. Although the major tomographic findings in H1N1 infection are nonspecific, it is important to recognize such findings in order to include infection with the H1N1 virus in the differential diagnosis of respiratory symptoms

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Extubation failure influences clinical and functional outcomes in patients with traumatic brain injury*

A falência da extubação influencia desfechos clínicos e funcionais em pacientes com traumatismo cranioencefálico

Helena França Correia dos Reis, Mônica Lajana Oliveira Almeida, Mário Ferreira da Silva, Mário de Seixas Rocha

Abstract

Objective: To evaluate the association between extubation failure and outcomes (clinical and functional) in patients with traumatic brain injury (TBI). **Methods:** A prospective cohort study involving 311 consecutive patients with TBI. The patients were divided into two groups according to extubation outcome: extubation success; and extubation failure (defined as reintubation within 48 h after extubation). A multivariate model was developed in order to determine whether extubation failure was an independent predictor of in-hospital mortality. **Results:** The mean age was 35.7 ± 13.8 years. Males accounted for 92.3%. The incidence of extubation failure was 13.8%. In-hospital mortality was 4.5% and 20.9% in successfully extubated patients and in those with extubation failure, respectively (p = 0.001). Tracheostomy was more common in the extubation failure group (55.8% vs. 1.9%; p < 0.001). The median length of hospital stay was significantly greater in the extubation failure group than in the extubation success group (44 days vs. 27 days; p = 0.002). Functional status at discharge was worse among the patients in the extubation failure group. The multivariate analysis showed that extubation failure was an independent predictor of in-hospital mortality (OR = 4.96; 95% CI, 1.86-13.22). **Conclusions:** In patients with TBI, extubation failure appears to lengthen hospital stays; to increase the frequency of tracheostomy and of pulmonary complications; to worsen functional outcomes; and to increase mortality.

Keywords: Brain injuries; Ventilator weaning; Intensive care units; Glasgow outcome scale.

Resumo

Objetivo: Avaliar a associação entre falência da extubação e desfechos clínicos e funcionais em pacientes com traumatismo cranioencefálico (TCE). **Métodos:** Coorte prospectiva com 311 pacientes consecutivos com TCE. Os pacientes foram divididos em dois grupos de acordo com o resultado da extubação: sucesso ou falência (necessidade de reintubação dentro de 48 h após extubação). Um modelo multivariado foi desenvolvido para verificar se a falência de extubação era um preditor independente de mortalidade hospitalar. **Resultados:** A média de idade foi de 35,7 ± 13,8 anos, e 92,3% dos pacientes eram do sexo masculino. A incidência de falência da extubação foi de 13,8%. A mortalidade hospitalar foi, respectivamente, de 20,9% e 4,5% nos pacientes com falência e com sucesso da extubação (p = 0,001). A realização de traqueostomia foi mais frequente no grupo falência da extubação (55,8% vs. 1,9%; p < 0,001). A mediana de tempo de permanência hospitalar foi significantemente maior nos pacientes com falência do que naqueles com sucesso da extubação (44 dias vs. 27 dias; p = 0,002). Os pacientes com falência da extubação apresentaram piores desfechos funcionais na alta hospitalar. A análise multivariada mostrou que a falência da extubação foi um preditor independente para a mortalidade hospitalar (OR = 4,96; IC95%, 1,86-13,22). **Conclusões:** A falência da extubação esteve associada a maior permanência hospitalar, maior frequência de traqueostomia e de complicações pulmonares, piores desfechos funcionais e maior mortalidade em pacientes com TCE.

Descritores: Traumatismos encefálicos; Desmame do respirador; Unidades de terapia intensiva; Escala de resultado de Glasgow.

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Introduction

Patients with traumatic brain injury (TBI) commonly need mechanical ventilation (MV) in order to maintain ventilation, optimize oxygenation, and protect the airway; however, the use of MV is associated with adverse effects.[1,2]

The first phase of withdrawal of MV is designated discontinuation of ventilatory support, and studies have been conducted with the objective of determining the best timing for initiation of withdrawal. When ventilatory support can be withdrawn, the decision to extubate has to be made.[3-5]

Although most patients are successfully removed from MV, a proportion of patients experience extubation failure; that is, there is a need for reintubation within 24-72 h after extubation. The extubation failure rate ranges from 5% to 20% depending on the population studied. Extubation failure has been associated with prolonged ICU and hospital stays, as well as with higher rates of tracheostomy and mortality.[6-10]

This scenario seems to be more complicated in patients with neurological involvement, higher extubation failure rates having been observed in this population.[11] Despite reports of worse outcomes in patients with extubation failure, the impact of extubation failure on the evolution of patients with TBI remains unknown and is possibly underestimated. In addition, the association between functional outcomes and extubation failure has yet to be explored. Therefore, we conducted a prospective study in a trauma referral center with the objective of determining whether extubation failure had any influence on the length of hospital stay, the length of ICU stay, in-hospital mortality, and ICU mortality, as well as on functional outcomes at hospital discharge and at ICU discharge, in patients with TBI.

Methods

This was a prospective cohort study conducted between November of 2008 and December of 2010 and involving patients with TBI admitted to the ICU of the Bahia State General Hospital, located in the city of Salvador, Brazil. The present study was approved by the Research Ethics Committee of the Bahia Foundation for Science Development, and patients were included in the study after their legal guardians had given written informed consent.

We included adult patients (≥ 18 years of age) who had been diagnosed with TBI, who had been on MV via an endotracheal tube for at least 48 h, and who passed the spontaneous breathing trial (SBT). We excluded patients with spinal trauma, those who subsequently died, those who underwent tracheostomy before the first extubation, and those who had unscheduled extubation.

The patients who met the inclusion criteria were observed daily until death or discharge from the ICU. For each patient included in the study, only the first extubation attempt was analyzed. Extubation outcome was classified as extubation success or extubation failure. Extubation failure was defined as reintubation within 48 h after extubation.[12]

All of the decisions regarding weaning, extubation, reintubation, tracheostomy, and use of noninvasive ventilation (NIV) were made by the teams of attending physicians, without the involvement of the researchers. In accordance with standard practices, the patients were considered eligible for an SBT when they showed reversal or control of the event that led to their being placed on MV, adequate gas exchange, and hemodynamic stability. The patients were extubated if they tolerated 30-120 min of spontaneous breathing on pressure support ventilation of 7 cmH_2O or unassisted through a T-tube.

For all of the patients who were reintubated, we collected the following data: date of reintubation; time of reintubation; and reason for reintubation. The time to reintubation was measured in hours, and the reasons for reintubation were dichotomized into airway problems (upper airway obstruction, aspiration/excess pulmonary secretions, and bronchospasm) and nonairway problems (excessive respiratory distress, reduced level of consciousness, and others).

The level of consciousness was assessed by the Glasgow Coma Scale (GCS) score. Because all of the patients had undergone orotracheal intubation and were on MV, those who gave a verbal response received a score of 1.

We analyzed the following clinical outcomes: death in the ICU; in-hospital death; need for tracheostomy; length of ICU stay and length of hospital stay; pulmonary complications in the ICU; and functional outcomes at ICU discharge and at hospital discharge.

Pulmonary complications during the ICU stay were defined as follows: pneumonia, defined as new or progressive pulmonary infiltrate on chest X-rays, accompanied by at least two of the following signs: purulent tracheal secretions, body temperature > 38.3°C, and 25% increase in baseline leukocyte count; atelectasis on chest X-rays, accompanied by acute respiratory symptoms; tracheobronchitis, defined as increased tracheobronchial secretion volume, changes in tracheobronchial secretion color, or purulent tracheobronchial secretion, accompanied by normal chest X-ray findings; and bronchospasm, defined as wheezing with acute respiratory symptoms requiring bronchodilator use.

The Glasgow Outcome Scale (GOS) has been widely used for evaluating outcomes in patients with TBI because the GOS addresses physical, social, and cognitive sequelae. We used the extended GOS in order to determine the functional outcome after TBI. The extended GOS consists of eight categories, the scores ranging from 1 to 8 points: total recovery (8 points); good recovery (7 points); upper moderate disability (6 points); lower moderate disability (5 points); upper severe disability (4 points); lower severe disability (3 points); persistent vegetative state (2 points); and death (1 point).[13] The patients were graded on the extended GOS at ICU discharge and at hospital discharge.

The extended GOS variable was dichotomized into independent (total recovery, good recovery, upper moderate disability, and lower moderate disability) and dependent (upper severe disability, lower severe disability, persistent vegetative state, and death).[14]

The patients who failed extubation were compared with those who were successfully extubated in terms of the length of ICU stay, the length of hospital stay, tracheostomy, ICU mortality, in-hospital mortality, pulmonary complications, and functional outcome.

Categorical variables were expressed as absolute and relative frequencies. Continuous variables were expressed as mean and standard deviation or as median and interquartile range (IR), when appropriate. In order to compare categorical variables, we used the chi-square test or Fisher's exact test, when appropriate. In order to establish the statistical significance of the difference between the means of the groups, we used the Student's t-test or the Mann-Whitney test, when appropriate.

A multiple logistic regression model was used in order to assess the ability of each independent variable to predict the expected outcome (in-hospital mortality). After the univariate analysis, the independent variables were included in the logistic model if they had a value of $p < 0.10$ and remained in the model if they remained significant ($p < 0.05$). For inclusion and exclusion of variables, a manual procedure was used.

The level of significance was set at $p < 0.05$. Statistical analysis of the results was performed with the Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, we included 311 consecutive patients with TBI extubated for the first time. The mean age of the patients was 35.7 ± 13.8 years. Of the 311 patients, 287 (92.3%) were male, and the mean GCS score was 9.7 ± 4.4 at admission. The most common type of accident was motorcycle accident, in 33.8%, followed by various causes, in 23.5%, automobile/automobile-pedestrian accident, in 18.0%, assault, in 16.4%, gunshot wound, in 5.8%, and stab wound, in 2.6%. Of the 311 patients, 232 (74.6%) underwent surgical treatment and 79 (25.4%) underwent conservative treatment. The median duration of MV was 7 h (IR, 5-10 h).

Extubation failure occurred in 43 patients (13.8%). The reasons for reintubation were respiratory failure, in 18 patients (41.9%); upper airway obstruction, in 11 (25.6%); reduced level of consciousness, in 7 (16.3%); excess pulmonary secretions/inability to protect the airways, in 4 (9.3%); bronchospasm, in 1 (2.3%); and other reasons, in 2 (4.7%). The median time to reintubation was 6.0 h (IR, 2.0-25.5 h). Most of the patients (27 cases, 62.8%) had extubation failure within up to 12 h after extubation; 4 (9.3%) had extubation failure within 12-23 h after extubation; 4 (9.3%) had extubation failure within 24-35 h after extubation; and 8 (18.6%) had extubation failure within 36-48 h after extubation. Of the 311 extubated patients, 18 (5.8%) received NIV after extubation. The need for NIV after extubation was more common in the patients who failed extubation than in those who were successfully extubated (11.6% vs. 4.9%, $p = 0.086$).

The patients who failed extubation had longer ICU and hospital stays. In addition, ICU mortality was significantly higher in the patients who failed extubation than in those who were successfully extubated. The need for tracheostomy was significantly more common in the extubation failure group than in the extubation success group (Table 1).

The results of the univariate analysis of in-hospital mortality are shown in Table 2. After adjustment for other variables, extubation failure was independently associated with in-hospital mortality (Table 3).

Regarding the evolution of the 43 patients with extubation failure, 23 underwent extubation again; of those, 6 (27.3%) failed extubation again. A tracheostomy was performed in 24 (55.8%) of the 43 patients who had failed extubation, being performed after the first extubation failure in 19 and after the second extubation failure in 5. One patient remained intubated after the first extubation failure until death. Only 1 patient was extubated for the third time and evolved successfully.

There was a statistically insignificant difference in mortality between the patients who were reintubated because of nonairway problems and those who were reintubated because of airway problems (25.9% vs. 12.5%; p = 0.45). Among the reintubated patients, in-hospital mortality tended to be lower in those who were reintubated within up to 12 h after extubation (14.8% vs. 31.3%; p = 0.26).

Pulmonary complications occurring during the ICU stay were evaluated in 256 of the 311 patients in the cohort, being more common in the extubation failure group than in the extubation success group (65.7% vs. 30.8%; p < 0.001).

On the basis of the extended GOS scores, the functional outcomes at ICU discharge and at hospital discharge were worse in the patients who failed extubation than in those who were successfully extubated. The patients with extubation failure had a lower mean extended

Table 1 - Comparison of morbidity and mortality between patients who were successfully extubated and those who failed extubation.[a]

Variable	Extubation success (n = 268)	Extubation failure (n = 43)	p
Length of ICU stay, days	9 (7-13)	15 (12-19)	< 0.001
Length of ICU stay after the first extubation, days	3.0 (2.0-5.0)	8.5 (5.8-14.0)	< 0.001
Length of hospital stay, days	27.0 (19.2-36.8)	40.0 (24.5-59.5)	0.002
Tracheostomy[b]	5 (1.9)	24 (55.8)	< 0.001
ICU mortality[b]	3 (1.1)	6 (14.0)	< 0.001
In-hospital mortality[b]	12 (4.5)	9 (20.9)	0.001

[a]Values expressed as median (interquartile range), except where otherwise indicated. [b]Values expressed as n (%).

Table 2 - Univariate analysis of the factors associated with mortality in patients with traumatic brain injury.[a]

Variable	Survivors (n = 290)	Death (n = 21)	p
Age, years	35.2 ± 13.5	43.2 ± 16.3	0.012
Male gender[b]	267 (92.1)	20 (95.2)	1.00
GCS score at hospital admission	9.7 ± 3.5	9.8 ± 3.3	0.91
GCS score on the day of extubation	10.7 ± 0.7	10.2 ± 0.8	0.01
Length of ICU stay, days[c]	10.0 (7.0-13.0)	14.0 (9.5-19.5)	0.006
Days on MV before the 1st extubation[c]	7.0 (5-10)	9.0 (5-10.5)	0.17
Type of treatment[b]			
Surgical	216 (74.5)	16 (76.2)	0.86
Conservative	74 (25.3)	5 (27.8)	
Use of NIV after extubation[b]	15 (5.2)	3 (14.3)	0.112
Extubation failure[b]	34 (11.7)	9 (42.9)	0.001

GCS: Glasgow Coma Scale; MV: mechanical ventilation; and NIV: noninvasive ventilation. [a]Values expressed as mean ± SD, except where otherwise indicated. [b]Values expressed as n (%). [c]Values expressed as median (interquartile range).

GOS score at ICU discharge (3.8 ± 2.2 vs. 5.5 ± 1.8; p < 0.001) and at hospital discharge (5.0 ± 2.4 vs. 6.0 ± 2.0; p = 0.036). The proportions of dependent patients at ICU discharge and at hospital discharge were significantly higher in the extubation failure group than in the extubation success group (67.1% vs. 33.3%, p < 0.001, and 43.8% vs. 24.0%, p = 0.018, respectively). Figure 1 shows a comparison between the extubation success group and the extubation failure group in terms of the extended GOS categories at ICU discharge and at hospital discharge.

Table 3 - Multivariate analysis of the risk factors for in-hospital mortality in patients with traumatic brain injury.

Variable	OR	95% CI	p
Age, years	1.04	1.01-1.07	0.019
Extubation failure	4.96	1.86-13.22	0.001

Discussion

The present study examined the association of extubation failure with clinical and functional outcomes in patients with TBI. The patients who failed extubation had longer ICU and hospital stays, higher rates of pulmonary complications, greater need for tracheostomy, worse functional outcome, and higher mortality.

In the present study, the incidence of extubation failure in patients with TBI was found to be 13.8%, which is consistent with the findings of a study evaluating a similar population.[15] The reported incidence of extubation failure varies widely, ranging from 2% to 25%.[16] Because of

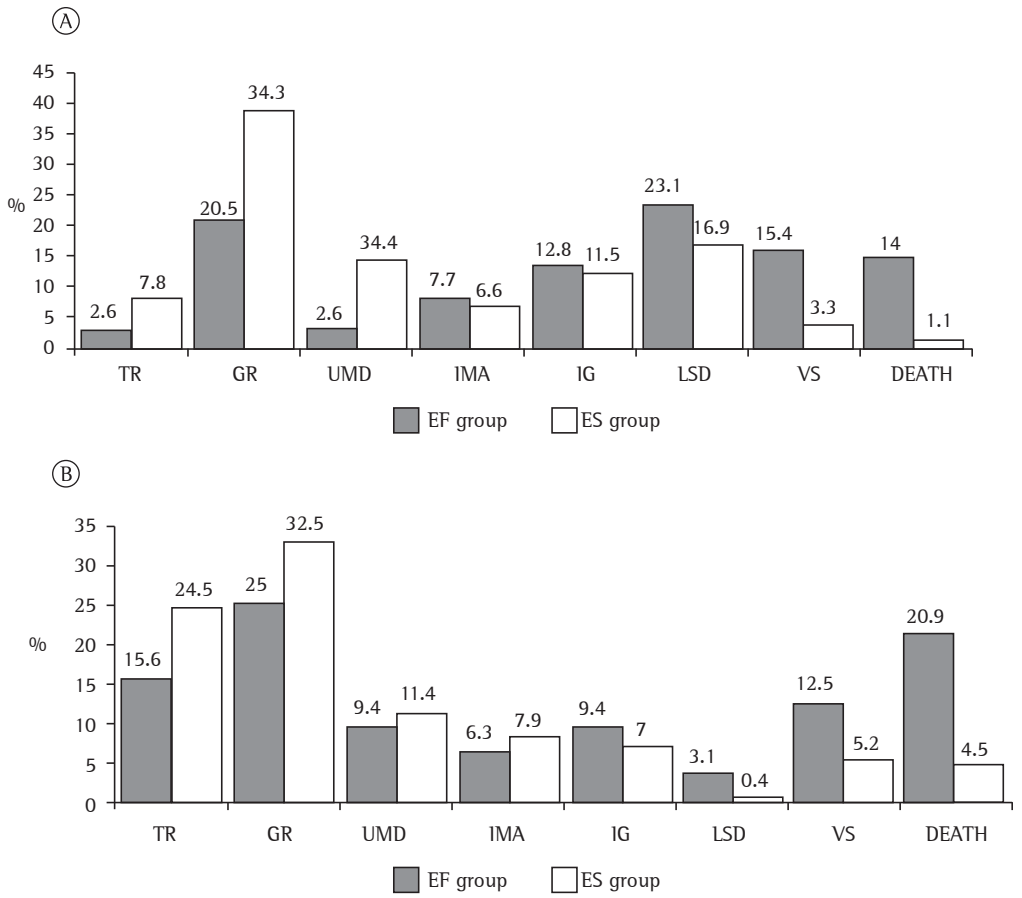

Figure 1 - Comparison of the Glasgow Outcome Scale scores at ICU discharge (in A) and at hospital discharge (B) between the patients in the extubation failure (EF) group and those in the extubation success (ES) group. TR: total recovery; GR: good recovery; UMD: upper moderate disability; LMD: lower moderate disability; USD: upper severe disability; LSD: lower severe disability; and VS: vegetative state.

the different definitions of extubation failure across studies, it can be difficult to compare the reported incidences of extubation failure. In addition, this variation can be partially explained by the heterogeneity of the populations studied. Karanjia et al. studied a heterogeneous cohort of neurological patients and found the incidence of extubation failure to be 6%, which is lower than the incidence found in the present study. This difference is due to the fact that those authors used the total number of intubated patients rather than the total number of extubated patients in order to calculate the incidence of extubation failure.[17]

Extubation failure rates have been reported to be higher in patients with neurological involvement.[11,18] However, the reported incidence is consistent with that found in other populations.[9,19] A recent study suggested that the "optimal" extubation failure rate is 5-10%.[20] In contrast, some authors have reported that extubation failure rates of 10-15% are acceptable.[5] It is not easy to determine the ideal extubation failure rate; however, it can be inferred that rates close to 0% indicate that many patients remained on MV for an unnecessarily long time and that extremely high rates are suggestive of premature withdrawal of MV.

The main reason for reintubation in the present study was respiratory failure, a finding that is consistent with those reported in previous studies.[21,22] We found no association between the reason for reintubation and in-hospital mortality, a finding that corroborates those of Menon et al.[23] In contrast with our results, the results of a study conducted by Epstein et al.[24] showed a higher mortality in patients who were reintubated because of nonairway problems. It is plausible that, in patients who are reintubated because of upper airway obstruction, acute respiratory failure can be immediately corrected, whereas organ dysfunction cannot.

Our univariate analysis showed that the need for NIV after extubation was more common in the patients with extubation failure. It has been suggested that, when used without an appropriate selection, NIV after extubation delays the initiation of appropriate therapy and results in worse outcomes.[25]

In the present study, the patients with extubation failure had unfavorable outcomes. This finding has been reported in previous studies, ICU mortality rates having been reported to be higher in patients who failed extubation than in those who were successfully extubated.[24,26] In addition, we found that the patients who failed extubation had longer ICU and hospital stays, a finding that corroborates previous findings.[7]

In our study sample, the number of patients requiring tracheostomy was substantially higher in the extubation failure group than in the extubation success group. This finding is similar to that reported by one group of authors (66.6% vs. 8.6%).[10] It is possible that extubation failure, when associated with other factors, such as excess pulmonary secretions and reduced level of consciousness, led to the decision of performing a tracheostomy, given that 79% of all tracheostomies were performed after the first extubation failure.

In the present study, in-hospital mortality was found to be approximately five times as high in the patients who failed extubation as it was in those who were successfully extubated, a finding that corroborates those reported in the literature.[21,27] In addition, extubation failure was independently associated with in-hospital mortality in our sample of patients with TBI. In our multivariate analysis, age remained a risk factor for in-hospital mortality even after having been adjusted for extubation failure, a finding that is consistent with previous findings.[28]

Because of its invasive nature, reintubation is associated with increased life-threatening complications. Prolonged MV due to extubation failure can also lead to adverse outcomes. In addition, it is possible that extubation failure is only a marker of greater clinical severity. There is also the possibility that clinical deterioration occurs during the time elapsed between extubation and reintubation.[24] One study[24] showed that patients who were reintubated within up to 12 h after extubation had lower mortality than did those who were reintubated later (24% vs. 51%; $p < 0.05$). In the present study, mortality tended to be lower in the patients who were reintubated within up to 12 h after extubation.

Studies have concluded that the need for reintubation increases the risk of pulmonary complications.[24,29] A case-control study showed a higher incidence of pneumonia in patients requiring reintubation (47% vs. 10%).[29] A prospective study of neurological patients showed higher rates of respiratory complications in patients

who failed extubation than in those who were successfully extubated (85% vs. 15%).[8] In our study, the rate of pulmonary complications was more than twice as high in the patients who failed extubation as it was in those who were successfully extubated.

Another important finding of our study was the association between extubation failure and functional outcome. The association between extubation failure and mortality or that between extubation failure and length of hospital stay has been studied.[7-9,23,26] However, data on the association between extubation failure and physical sequelae are scarce. Cognitive disability, prolonged MV, and longer hospital stays are factors that might be related to a worse functional outcome in patients with TBI and extubation failure. In addition, critical illness polyneuropathy is one of the events that influence the decline in the functional capacity of ICU patients. One study demonstrated that critical illness polyneuropathy was an independent predictor of failure to wean from MV.[30]

The data on functionality reinforce the need for measures to prevent extubation failure, given that functional disability is related to health status and has an impact on activities of daily living. One issue to be addressed in future studies is the long-term monitoring of functional capacity in such patients.

Our study has limitations. Like any observational study, the present study is only a generator of hypotheses; however, it is reasonable to assume that the results obtained are representative of current clinical practice in the intensive care of patients with TBI. Another potential limitation is the fact that the study was conducted in a single center; nevertheless, the incidence of extubation failure was found to be within the range reported in the literature. Finally, we did not assess prognostic scores for severity. This issue was partially resolved by the inclusion of the GCS scores at admission. In addition, the impact of extubation failure on clinical outcomes was found to be consistent with that reported in previous studies. However, we recognize that future studies involving the use of prognostic scores will allow a more accurate determination of the predictive power of extubation failure for mortality in patients with TBI. Despite its limitations, the present study showed that extubation failure is a predictor of poor prognosis in patients with TBI.

In patients with TBI, extubation failure appears to lengthen hospital stays; to increase the frequency of tracheostomy and of pulmonary complications; to worsen functional outcomes; and to increase mortality.

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Risk factors for infection with multidrug-resistant bacteria in non-ventilated patients with hospital-acquired pneumonia*,**

Fatores de risco para multirresistência bacteriana em pneumonias adquiridas no hospital não associadas à ventilação mecânica

Renato Seligman, Luis Francisco Ramos-Lima, Vivian do Amaral Oliveira, Carina Sanvicente, Juliana Sartori, Elyara Fiorin Pacheco

Abstract

Objective: To identify risk factors for the development of hospital-acquired pneumonia (HAP) caused by multidrug-resistant (MDR) bacteria in non-ventilated patients. **Methods:** This was a retrospective observational cohort study conducted over a three-year period at a tertiary-care teaching hospital. We included only non-ventilated patients diagnosed with HAP and presenting with positive bacterial cultures. Categorical variables were compared with chi-square test. Logistic regression analysis was used to determine risk factors for HAP caused by MDR bacteria. **Results:** Of the 140 patients diagnosed with HAP, 59 (42.1%) were infected with MDR strains. Among the patients infected with methicillin-resistant *Staphylococcus aureus* and those infected with methicillin-susceptible *S. aureus*, mortality was 45.9% and 50.0%, respectively (p = 0.763). Among the patients infected with MDR and those infected with non-MDR gram-negative bacilli, mortality was 45.8% and 38.3%, respectively (p = 0.527). Univariate analysis identified the following risk factors for infection with MDR bacteria: COPD; congestive heart failure; chronic renal failure; dialysis; urinary catheterization; extrapulmonary infection; and use of antimicrobial therapy within the last 10 days before the diagnosis of HAP. Multivariate analysis showed that the use of antibiotics within the last 10 days before the diagnosis of HAP was the only independent predictor of infection with MDR bacteria (OR = 3.45; 95% CI: 1.56-7.61; p = 0.002). **Conclusions:** In this single-center study, the use of broad-spectrum antibiotics within the last 10 days before the diagnosis of HAP was the only independent predictor of infection with MDR bacteria in non-ventilated patients with HAP.

Keywords: Pneumonia, bacterial; Drug resistance, bacterial; Cross infection.

Resumo

Objetivo: Identificar fatores de risco para o desenvolvimento de pneumonia adquirida no hospital (PAH), não associada à ventilação mecânica e causada por bactérias multirresistentes (MR). **Métodos:** Estudo de coorte observacional retrospectivo, conduzido ao longo de três anos em um hospital universitário terciário. Incluímos apenas pacientes sem ventilação mecânica, com diagnóstico de PAH e com cultura bacteriana positiva. Variáveis categóricas foram comparadas por meio do teste do qui-quadrado. A análise de regressão logística foi usada para determinar os fatores de risco para PAH causada por bactérias MR. **Resultados:** Dos 140 pacientes diagnosticados com PAH, 59 (42,1%) apresentavam infecção por cepas MR. As taxas de mortalidade nos pacientes com cepas de Staphylococcus aureus resistentes e sensíveis à meticilina, respectivamente, foram de 45,9% e 50,0% (p = 0,763). As taxas de mortalidade nos pacientes com PAH causada por bacilos gram-negativos MR e não MR, respectivamente, foram de 45,8% e 38,3% (p = 0,527). Na análise univariada, os fatores associados com cepas MR foram DPOC, insuficiência cardíaca crônica, insuficiência renal crônica, diálise, cateterismo urinário, infecções extrapulmonares e uso de antimicrobianos nos 10 dias anteriores ao diagnóstico de PAH. Na análise multivariada, o uso de antimicrobianos nos 10 dias anteriores ao diagnóstico foi o único fator preditor independente de cepas MR (OR = 3,45; IC95%: 1,56-7,61; p = 0,002). **Conclusões:** Neste estudo unicêntrico, o uso de antimicrobianos de largo espectro 10 dias antes do diagnóstico de PAH foi o único preditor independente da presença de bactérias MR em pacientes com PAH sem ventilação mecânica.

Descritores: Pneumonia bacteriana; Farmacorresistência bacteriana; Infecção hospitalar.

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Introduction

Hospital-acquired pneumonia (HAP) represents the second major cause of nosocomial infection, accounting for approximately 15% of all hospital-associated infections and supplanted only by urinary tract infection.[1] However, HAP is associated with the highest mortality rate of all nosocomial infections.[2] Mortality related to HAP is estimated to be between 33% and 50%.[3] The attributable costs for HAP are substantial because they are associated with prolonged hospital stay (by 4-9 days).[4]

As a rule, HAP results from microbial invasion of the normally sterile lung parenchyma. Most cases of nosocomial pneumonia are due to microaspiration of contaminated oropharyngeal or gastric secretions. A defect in normal host defenses (e.g., the use of endotracheal intubation), aspiration of a large inoculum of organisms, or aspiration of a particularly virulent organism might contribute to parenchymal infection.[2]

Common pathogens associated with HAP include aerobic gram-negative bacilli, such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* spp. Infections due to gram-positive cocci, such as *Staphylococcus aureus*, particularly methicillin-resistant *S. aureus* (MRSA), have been rapidly emerging. Pneumonia due to *S. aureus* is more common in patients with diabetes mellitus and head trauma, as well as in those hospitalized in ICUs.[3]

The frequency of specific multidrug-resistant (MDR) pathogens causing HAP can vary according to the hospital, population of patients, exposure to antibiotics, and type of ICU patient. That frequency changes over time, emphasizing the need for timely, local surveillance data.[3]

The rates of HAP due to MDR pathogens have increased dramatically in hospitalized patients, especially in ICU and transplanted patients.[5] Data on the mechanisms of antibiotic resistance for specific bacterial pathogens have provided new insights into the adaptability of such pathogens.

The most significant risk factor for HAP is mechanical ventilation. In fact, various authors use the terms "HAP" and "ventilator-associated pneumonia" (VAP) interchangeably. Intubation increases the risk of pneumonia considerably (6- to 21-fold).[1] Previous studies showed other risk factors for HAP (excluding those related to VAP), which emerged from multivariate analyses, including age > 70 years, chronic lung disease, depressed consciousness, aspiration, chest surgery, use of intracranial pressure monitor, use of nasogastric tube, treatment with histamine type-2 receptor (H_2) blockers or antacids, patient transport from the ICU for diagnostic or therapeutic procedures, previous antibiotic exposure (particularly to third-generation cephalosporins), hospitalization during the fall or winter seasons, use of paralytic agents, and underlying illness.[6,7]

In recent years, inadequate HAP treatment, in the vast majority of the cases, has been proven to be due to resistant gram-negative bacteria or MRSA (not considered in the initial empirical regimen), and, since then, therapeutic decision making has not been relying solely on the time of the onset of pneumonia and previous antibiotic use. In the presence of comorbidities, recent use of antibiotics, or in institutionalized patients, the possibility of etiology by MDR germs becomes higher; therefore, the presence of risk factors for MDR germs serves as a basis for the decision making in order to draw up an adequate treatment regimen.[8]

Based on these concerns, the aim of the present study was to identify risk factors for the development of HAP caused by MDR bacteria in non-ventilated patients at a tertiary care teaching hospital.

Methods

This was a retrospective observational cohort study, conducted at the *Hospital de Clínicas de Porto Alegre* (HCPA), a 780-bed tertiary-care teaching hospital. All patients with a diagnosis of HAP and positive microbiological cultures admitted to HCPA between January of 2007 and December of 2009 were included in the study. All of the patients included were aged > 12 years. Patients with HAP with negative microbiological cultures or those diagnosed with VAP were excluded.

The diagnosis of HAP was suspected only when pneumonia symptoms appeared at least 48 h after admission. The diagnosis of pneumonia was established when a patient developed a new and persistent radiographic infiltrate plus two of the following criteria: body temperature ≥ 38.0°C or < 36.0°C; white blood cell count > 11,000 cells/mm^3 or < 4,000 cells/mm^3; and purulent sputum.[3]

The data collected included age, sex, comorbidities (including COPD, congestive heart failure, chronic renal failure, and malignancy), smoking status, immunosuppression, use of H_2 antagonists, use of proton pump inhibitors, use of corticosteroids, use of nasogastric tube, use of a nasogastric feeding tube, dialysis, central vein catheterization, urinary tract catheterization, prophylactic antimicrobial therapy, antimicrobial therapy within the last 10 days before HAP diagnosis, and extrapulmonary infection. The data were collected from standard medical records and compiled into a structured questionnaire. The patients were considered immunosuppressed when chemotherapy was administered within the last 45 days prior to admission, when corticosteroids were used in immunosuppressive doses (prednisone ≥ 1 mg/kg per day or equivalent), or when the patient presented with neutropenia (< 1,000 cells/mm^3).

Antimicrobial treatment was considered adequate on the basis of microbiological results. Adequate antibiotic therapy was defined as the coverage of all of the pathogens isolated from sputum, blood, or pleural fluid cultures by at least one antimicrobial agent administered for HAP, which was determined by the sensitivity pattern in the antibiogram.

The following pathogens were considered MDR on the basis of the knowledge available during the study period: MRSA; extended-spectrum β-lactamase-producing gram-negative Enterobacteriaceae, such as *Klebsiella* spp., *E. coli*, and *Proteus* spp.; *P. aeruginosa* resistant to ceftazidime or carbapenems; other pan-resistant Enterobacteriaceae bacteria or those sensitive only to carbapenems; sulfonamide-resistant *Stenotrophomonas* spp.; *Acinetobacter* spp. resistant to ampicillin, ampicillin/sulbactam, or carbapenems; and vancomycin-resistant *Enterococcus* spp. Other organisms were considered MDR if they were found to be resistant to at least three of the following antibiotic classes: antipseudomonal cephalosporins/penicillins, macrolides, carbapenems, fluoroquinolones, and aminoglycosides.

In 2005, the HCPA Infection Control Commission registered 142 cases of suspected HAP, and 93 cases had positive cultures. Considering a possible frequency of multidrug resistance of 20% in the group who received prior antibiotic treatment and of 5% in the group who did not receive antibiotic treatment, a sample of 140 cases could show significant differences between the two groups adopting a significance level of $p = 0.05$ and a power of $(1 - \beta) = 80\%$. That sample size could be obtained by the search of cases during 18 consecutive months.

The selection of the cases was based on positive bacteriological test results. All of the cases with positive cultures were screened for HAP and described in the hospital medical records. The sputum processing protocol included a pre-analysis in order to validate the gram sample. Sputum samples were considered valid when direct examination revealed fewer than 10 epithelial cells and more than 25 polymorphonuclear cells at low magnification (×100). The cultures were valued only when they were consistent with the findings of the direct examination. Cultures were qualitatively processed in the Microbiology Unit of HCPA Department of Clinical Pathology as part of a routine standard of care. Gram results were available in the electronic medical records within 4 h after sample collection, as were culture results within 72 h after the collection. All of the patients hospitalized for community-acquired pneumonia were excluded from the study.

Categorical variables were compared in the univariate analysis using the chi-square test. For those analyses, two-tailed tests and $p \leq 0.05$ were considered statistically significant. Logistic regression analysis was used in order to determine the relationship between the risk factors and infection with MDR bacteria in the multivariate analysis. Variables with $p \leq 0.15$ were considered significant and were entered into the multivariate model. In the multivariate model, variables with $p \leq 0.05$ were considered significant. The statistical analyses were performed with the Statistical Package for the Social Sciences for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA).

Continuous variables are presented as means and standard deviations, whereas categorical variables are presented as absolute and relative frequencies. For the comparison of continuous variables, the Mann-Whitney U test and the Student's t-test were used depending on variable distribution. For categorical variables, the Pearson chi-square test or the Fisher's exact test was used, as appropriate. Comparisons were made between the groups of patients infected with MDR strains and those infected with non-MDR strains.

The present study was approved by the HCPA Research Ethics Committee, which, considering the nature of the study, waived requirements for informed consent.

Results

During the study period, 529 patients were diagnosed with HAP; 389 patients were excluded because the culture was negative, the culture was found to grow only fungi, or the diagnosis was VAP. The epidemiological characteristics and the clinical status of the 140 patients on admission, as well as the clinical findings at the time of diagnosis, are shown in Table 1.

Of the 140 patients with HAP, 59 (42.1%) were infected with MDR bacteria, whereas 81 (57.9%) were free of MDR strains. There was no significant difference in mortality between the groups infected with MDR and non-MDR bacteria (p = 0.519). According to the univariate analysis, the factors associated with the presence of MDR bacteria in sputum or blood cultures were renal failure, use of urinary catheter, and use of antibiotics within the last 10 days before the diagnosis of HAP.

Of the 140 patients, 52 were infected by *S. aureus*, 38 (64.4%) of whom were infected by MRSA (Table 2); however, the presence of the MRSA phenotype was not a significant determinant of

Table 1- Baseline characteristics of the patients who developed hospital-acquired pneumonia (n = 140).[a]

Variable	Patients with HAP caused by		p
	MDR bacteria (n = 59)	Non-MDR bacteria (n = 81)	
Age, years[b]	63 ± 15	63 ± 14	0.931
Male gender	42 (71.2)	56 (69.1)	0.794
Type of hospitalization			0.677
Clinical	42 (71.2)	55 (67.9)	
Surgical	17 (28.8)	26 (32.1)	
Previous comorbidities	46 (78.0)	63 (77.8)	0.979
COPD	21 (35.6)	19 (23.5)	0.117
Congestive heart failure	12 (20.3)	8 (9.9)	0.081
Renal failure	19 (32.2)	13 (16.0)	0.041
Malignant neoplasia	27 (45.8)	46 (56.8)	0.197
Immunosuppression	14 (25.0)	23 (29.1)	0.598
Extrapulmonary infection	26 (44.8)	24 (30.0)	0.074
Smokers	21 (35.6)	31 (38.3)	0.746
Previous use of medication			
Corticosteroid therapy	22 (37.3)	36 (44.4)	0.396
H_2 receptor antagonists	21 (35.6)	29 (35.8)	0.980
Proton pump inhibitors	33 (55.9)	47 (58.0)	0.805
Invasive procedures			
Tracheostomy	3 (5.1)	6 (7.4)	0.580
Dialysis	9 (15.3)	5 (6.2)	0.077
Central catheter	22 (37.3)	29 (35.8)	0.857
Urinary catheter	38 (64.4)	38 (46.9)	0.040
Nasogastric intubation	6 (10.2)	8 (9.9)	0.955
Nasogastric feeding tube use	32 (54.2)	36 (44.4)	0.252
Septic status			0.469
Sepsis	16 (27.1)	15 (18.5)	
Septic shock	4 (6.8)	7 (8.6)	
Use of antibiotics within 10 days prior to diagnosis	45 (76.3)	38 (46.9)	0.001
Prophylactic antibiotic therapy	4 (6.8)	6 (7.4)	0.887
Mortality during hospitalization	28 (47.5)	34 (42.0)	0.519

HAP: hospital-acquired pneumonia; MDR: multidrug-resistant; and H_2: histamine type 2. [a]Values expressed as n (%), except where otherwise indicated. [b]Values expressed as mean ± SD.

a difference in mortality: 17 of the 37 patients with MRSA-related HAP died (45,9%), whereas 11 of the 22 with non-MRSA-related HAP died (50%; p = 0.763).

Of the 140 patients, 84 had HAP caused by gram-negative bacilli, as a single type of germ or polymicrobial infection; however, the presence of MDR strains was not a significant determinant of a difference in mortality. Of the 24 patients with HAP related to MDR strains, 11 (45.8%) died, whereas, of the 60 patients with HAP caused by non-MDR strains, 23 (38.3%) died (p = 0.527).

In the multivariate analysis, we added four variables (respecting the limit of $p \leq 0.15$), to those included in the univariate analysis (i.e., presence of renal failure, use of urinary catheter, and antibiotic therapy within the last 10 days prior to HAP diagnosis): presence of extrapulmonary infections, dialysis, previous history of COPD, and previous history of congestive heart failure (Table 3). In the multivariate analysis, antibiotic therapy within the last 10 days prior to HAP diagnosis was the only independent predictor of infection with MDR bacteria (OR = 3.45; 95% CI: 1.56-7.61; p = 0.002).

The pattern of resistance in the isolates was as follows: penicillins, in 42.2% of the isolates; cephalosporins, in 33.3%; quinolones, in 26.7%; carbapenems, in 8.9%; and aminoglycosides, in 2.2%. Regarding the antibiotic therapy for MDR bacteria in HAP, 15.6% and 24.4% of the strains, respectively, were resistant to ampicillin/sulbactam and to ciprofloxacin. The resistance rates in the patients with previous antibiotic use within the last 10 days prior to HAP diagnosis are shown in Table 4.

Discussion

In the present single-center study, the use of broad-spectrum antibiotics within the last 10 days before the diagnosis of HAP was the only independent predictor for HAP caused by MDR bacteria. Chronic renal failure and urinary tract catheterization were risk factors for this outcome only in the univariate analysis.

These results are in accordance with those in other studies, which described previous antibiotic therapy as a risk factor for HAP.[9-11] However, in our cohort, age > 70 years, chest surgery, use of nasogastric tube, and H_2 blocker therapy were not independent predictors.

S. aureus and gram-negative microorganisms were the most common etiologic agents in our sample (80.0%). Typical hospital-acquired bacteria were identified in 125 patients (89.3%), whereas 15 (10.7%) presented with common community-acquired microorganisms. Prolonged hospital stay and early colonization of respiratory tract with nosocomial flora could explain these results.[10,12]

The predisposition of *S. aureus* and gram-negative pathogens to develop antibiotic resistance has been demonstrated. Rello et al.[12] observed it when comparing the patients with VAP caused by MRSA and those with VAP caused by methicillin-

Table 2 - Microbiological identification in hospital-acquired pneumonia patients (n = 140).[a]

Microorganism[b]	Patients with HAP caused by		Total
	MDR bacteria	Non-MDR bacteria	
	(n = 59)	(n = 81)	(n = 140)
Staphylococcus aureus	38 (64.4)	14 (17.3)	52 (36.4)
Enterobacter sp.	8 (13.6)	10 (12.3)	18 (12.9)
Klebsiella pneumoniae	7 (11.9)	9 (11.1)	16 (11.4)
Pseudomonas aeruginosa	2 (3.4)	12 (14.8)	14 (10.0)
Escherichia coli	2 (3.4)	10 (12.3)	12 (8.6)
Haemophilus sp.	0 (0.0)	12 (14.8)	12 (8.6)
Acinetobacter sp.	5 (8.5)	3 (3.7)	8 (5.7)
Coagulase-negative Staphylococcus sp.	1 (1.7)	6 (4.9)	7 (5.0)
Enterococcus sp.	0 (0.0)	5 (6.2)	5 (3.6)
Acinetobacter baumannii	2 (3.4)	0 (0.0)	2 (1.4)
Other[c]	0 (0.0)	17 (21.0)	17 (12.1)

HAP: hospital-acquired pneumonia; and MDR: multidrug-resistant. [a]Values expressed as n (%). [b]We identified more than one microorganism in 23 patients (13 patients with MDR bacteria and 10 patients with non-MDR bacteria). [c]*Stenotrophomonas maltophilia, Streptococcus pneumoniae, Citrobacter freundii, Proteus mirabilis, Streptococcus viridans, Citrobacter koseri, Klebsiella oxytoca, Providencia rettgeri*, *Serratia* sp., and *Moraxella* sp.

Table 3 - Risk factors for multidrug-resistant bacteria in hospital-acquired pneumonia.*

Variable	β	Exp(β) OR	CI 95% OR	p
Intercept	−2.264			0.008
COPD	0.864	2.374	(0.982-5.740)	0.055
Congestive heart failure	0.231	1.260	(0.404-3.931)	0.691
Renal failure	0.603	1.828	(0.580-5.759)	0.303
Extrapulmonary infection	0.438	1.550	(0.699-3.440)	0.281
Dialysis	0.486	1.625	(0.367-7.203)	0.523
Urinary catheter	0.322	1.379	(0.618-3.078)	0.432
Use of antibiotics within 10 days prior to diagnosis	1.237	3.447	(1.561-7.610)	0.002

*Multivariate analysis.

Table 4 - Resistance rates in 83 patients with previous antibiotic use within 10 days prior to the diagnosis of hospital-acquired pneumonia.[a]

Antibiotic	Patients with HAP caused by		p
	MDR bacteria	Non-MDR bacteria	
	(n = 45)	(n = 38)	
Penicillins	19 (42.2)	16 (42.1)	0.991
Amoxicillin/clavulanate	6 (13.3)	3 (7.9)	0.427
Ampicillin	4 (8.9)	6 (15.8)	0.336
Ampicillin/sulbactam	7 (15.6)	1 (2.6)	0.047
Oxacillin	1 (2.2)	2 (5.3)	0.460
Penicillin	0	2 (5.3)	0.119
Piperacillin/tazobactam	4 (8.9)	3 (7.9)	0.871
Cephalosporins	15 (33.3)	8 (21.1)	0.213
Cefazolin	2 (4.4)	0 (0.0)	0.188
Cephalexin	0 (0.0)	1 (2.6)	0.274
Cefoxitin	0 (0.0)	1 (2.6)	0.274
Cefuroxime	7 (15.6)	4 (10.5)	0.501
Cefepime	7 (15.6)	2 (5.3)	0.133
Carbapenems	4 (8.9)	5 (13.2)	0.533
Imipenem	3 (6.7)	4 (10.5)	0.113
Meropenem	1 (2.2)	1 (2.6)	0.904
Quinolones	12 (26.7)	6 (15.8)	0.231
Ciprofloxacin	11 (24.4)	4 (10.5)	0.101
Norfloxacin	2 (4.4)	2 (5.3)	0.862
Aminoglycosides: gentamicin	1 (2.2)	3 (7.9)	0.229
Tetracyclines: doxycycline	0 (0.0)	1 (2.6)	0.274
Macrolides: azithromycin	3 (6.7)	0 (0.0)	0.105
Sulfonamides: sulfamethoxazole/trimethoprim	3 (6.7)	4 (10.5)	0.528
Chloramphenicol	0 (0.0)	1 (2.6)	0.274
Clindamycin	5 (11.1)	5 (13.2)	0.775
Vancomycin	5 (11.1)	6 (15.8)	0.531
Metronidazole	6 (13.3)	2 (5.3)	0.215

HAP: hospital-acquired pneumonia; and MDR: multidrug-resistant. [a]Values expressed as n (%).

susceptible *S. aureus*, 100% and 21%, respectively, having received antibiotics a few days prior to the onset of the infection. Similar results were reported by Trouillet et al.,[10] who showed that prolonged hospital stay and prior antimicrobial treatment were risk factors for MRSA pneumonia.

The high rate of resistance to oxacillin corroborates the guidelines established by a Brazilian consensus on pneumonia,[13] whereby all *S. aureus* strains should be considered resistant to oxacillin for the purposes of designing empirical treatment regimens for nosocomial pneumonia,

especially in cases related to mechanical ventilation. In an elegant study designed to compare quantitatively the results of BAL fluid cultures with those of cultures from postmortem lung biopsy samples, Balthazar et al.[14] also found *S. aureus* to be the most common causative agent. Data from one surveillance program in Brazil,[15] however, revealed that, in samples collected in various Brazilian hospitals, *S. aureus* was the second most prevalent microorganism (19.6%), and that approximately half of the strains was MRSA. Carrilho[16] also demonstrated that *S. aureus* was the second most common germ in nosocomial pneumonia in the ICU of a university hospital in the north of the state of Paraná. Korn et al.[17] studied 100 patients admitted to two ICUs and reported that, at the time of admission, 46 were colonized by MRSA, and, after admission, 28 became colonized with the same type of germ, and 16 developed respiratory or urinary infections. The authors found no risk factors in their sample but called attention to the fact that 20% of the patients colonized with MRSA at admission had not been previously admitted to the ICU and had not been transferred from another hospital ward.

In our sample, the exposure to ampicillin/sulbactam significantly increased the risk for MDR bacterial infections—7 cases (15.6%) vs. 1 (2.6%; p = 0.047)—but the use of carbapenems in 9 patients did not demonstrate a trend towards that risk (p = 0.533). Surprisingly, the use of carbapenems did not increase the number of MDR cases, and we attribute that to the small number of patients who used these antimicrobials in our sample.

Even though the use of quinolones doubled the frequency of MDR bacterial infection—12 cases (26.7%) vs. 6 (15.8%)—no statistical significance was found (p = 0.231), possibly because of the small number of specific cases. The limited use of quinolones in hospitalized patients is a preventive measure of the infection surveillance and control committee in our hospital.

Our findings are in accordance with the results of Trouillet et al., who suggested that receiving any fluoroquinolone might be a risk factor for acquiring piperacillin-resistant *P. aeruginosa*.[18] Carmeli et al. also found that previous treatment with ciprofloxacin was a risk factor of the emergence of antibiotic-resistant *P. aeruginosa*.[19]

Harris et al. found that the exposure to piperacillin/tazobactam was the major factor that predisposes to the development of infections with MDR *P. aeruginosa*. The previous exposure to piperacillin/tazobactam was significantly associated with the isolation of piperacillin/tazobactam-resistant *P. aeruginosa* (OR = 8.63; 95% CI: 6.11-12.20; p < 0.0001).[20]

In addition to being intrinsically resistant to various antimicrobial agents, *P. aeruginosa* often develops resistance mechanisms to other antibiotics. This increasing antibiotic resistance makes the treatment of pneumonia caused by *P. aeruginosa* more difficult and more expensive.[21] The emergence of VAP episodes caused by ureido/carboxypenicillin-resistant *P. aeruginosa* was significantly associated with the administration of broad-spectrum antimicrobials, such as ureidopenicillins, carboxypenicillins, or fluoroquinolones, at admission to the ICU.[21] Pneumonias caused by metallo-β-lactamase-producing *P. aeruginosa* result in higher mortality rates. These emerging enzymes hydrolyze virtually all β-lactams.[22]

Based on the results from a surveillance program,[15] *P. aeruginosa* remains the most common type of germ that causes HAP/VAP. These data demonstrate the variability across hospitals and wards, as well as the risk of inadequate treatment by adopting prevalence data from different locations as a basis for the development of empiric treatment protocols.[8]

Besides *S. aureus* strains that are resistant to fluoroquinolones, aminoglycosides, and oxacillin, enterococci increased in importance, and the emergence of strains resistant to penicillin, aminoglycosides, and vancomycin has been described in various North American hospitals and, more recently, in Brazil.[23] In our study, no MDR enterococci have been found.

The duration of exposure to these antibiotics should also be considered. In a case-control study conducted by Paramythiotou et al., among 34 patients infected with MDR *P. aeruginosa*, a previous treatment with ciprofloxacin or imipenem was a significant risk factor for the acquisition of MDR strains only when the duration of the treatment was longer than the median duration of treatment with those antimicrobials.[24]

Antibiotic use, or even overuse, can promote the emergence of resistant bacteria. The administration of combined broad-spectrum antibiotic therapy

can lead to increased mortality in uninfected patients.[25] When a hospital-acquired infection is diagnosed, broad-spectrum antibiotic therapy is often prescribed, usually prior to the availability of microbiological test results because of the possibility of a MDR germ being the etiologic agent. Previous antibiotic use was found to be an independent risk factor for VAP in one study.[26] The etiology of VAP in that population was associated with a high risk of germs resistant to antibiotics. Early and appropriate antimicrobial treatment must be assured. Consequently, the de-escalation of such treatment is the next step, but it is important to achieve the clinical cure in order to avoid persistent MDR microorganisms. The duration of the treatment must be assessed. Observational studies have suggested that early use of broad-spectrum antimicrobials and subsequent de-escalation after microbiological culture results might minimize the emergence of MDR organisms[10,27] and reduce the costs[27] during the treatment of patients with HAP. This strategy was associated with higher antimicrobial adequacy and more favorable outcomes,[28] reducing the overall duration of antimicrobial treatment[29] and mortality rates.[30]

Our study has some limitations. First, we used a retrospective design, and the patients included in the study were not assisted by the research team; we selected patients with positive cultures for aerobic pathogens, and patients who developed HAP but had negative cultures were excluded. Negative results could be a consequence of previous antimicrobial treatment. Second, we did not obtain results from BAL fluid cultures, but only from sputum cultures. Finally, our sample size was adequate to stratify the presence or the absence of MDR bacteria, but it was too small to allow the analysis of the risks implicated in the use of different individual antimicrobial agents.

Among hospital-acquired infections, HAP is the leading cause of death. It can be caused by a wide variety of pathogens, it can be polymicrobial, and it might be due to MDR pathogens. The frequency of MDR bacteria as etiologic agents in HAP is increasing, especially among patients with certain risk factors, such as recent antibiotic therapy, long-term hospitalization, and high frequency of antibiotic resistance in the specific hospital unit.

Regarding HAP prevention bundles, they involve the implementation of various procedures in an attempt to reduce the incidence of HAP among patients at risk, including educational programs, technical measures, surveillance, and feedback. In our study, the use of broad-spectrum antibiotics within the last 10 days before HAP diagnosis was the only independent predictor for infection with MDR bacteria in HAP. This finding is consistent with the Brazilian guidelines for the treatment of HAP and VAP, which state that the prior use of antibiotics in the 15 days preceding the disease is an important risk factor for potentially resistant pathogens.[8]

The development of infection control policies and procedures, with hospital-wide surveillance, as well as the review of antibiotic utilization and its relationship to local antibiotic resistance patterns, together with the development of guidelines for the rational use of antimicrobial therapy, are recommended.

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Impact of pulmonary rehabilitation on quality of life and functional capacity in patients on waiting lists for lung transplantation*

Impacto da reabilitação pulmonar na qualidade de vida e na capacidade funcional de pacientes em lista de espera para transplante pulmonar

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Abstract

Objective: To investigate the impact of a pulmonary rehabilitation program on the functional capacity and on the quality of life of patients on waiting lists for lung transplantation. **Methods:** Patients on lung transplant waiting lists were referred to a pulmonary rehabilitation program consisting of 36 sessions. Before and after the program, participating patients were evaluated with the six-minute walk test and the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). The pulmonary rehabilitation program involved muscle strengthening exercises, aerobic training, clinical evaluation, psychiatric evaluation, nutritional counseling, social assistance, and educational lectures. **Results:** Of the 112 patients initially referred to the program, 58 completed it. The mean age of the participants was 46 ± 14 years, and females accounted for 52%. Of those 58 patients, 37 (47%) had pulmonary fibrosis, 13 (22%) had pulmonary emphysema, and 18 (31%) had other types of advanced lung disease. The six-minute walk distance was significantly greater after the program than before (439 ± 114 m vs. 367 ± 136 m, p = 0.001), the mean increase being 72 m. There were significant point increases in the scores on the following SF-36 domains: physical functioning, up 22 (p = 0.001), role-physical, up 10 (p = 0.045); vitality, up 10 (p < 0.001); social functioning, up 15 (p = 0.001); and mental health, up 8 (p = 0.001). **Conclusions:** Pulmonary rehabilitation had a positive impact on exercise capacity and quality of life in patients on lung transplant waiting lists.

Keywords: Rehabilitation; Lung transplantation; Quality of life; Exercise; Exercise tolerance.

Resumo

Objetivo: Avaliar o impacto de um programa de reabilitação pulmonar na capacidade funcional e na qualidade de vida de pacientes em lista de espera para transplante pulmonar. **Métodos:** Pacientes em lista de espera para transplante pulmonar encaminhados a um programa de reabilitação pulmonar de 36 sessões. Os participantes foram avaliados no início e no final desse com o teste de caminhada de seis minutos (TC6) e com o questionário de qualidade de vida *Medical Outcomes Study 36-item Short-Form Health Survey* (SF-36). O programa de reabilitação pulmonar foi composto por exercícios de fortalecimento muscular, treinamento aeróbico, acompanhamento clínico e psiquiátrico, acompanhamento nutricional, assistência social e palestras educacionais. **Resultados:** Dos 112 pacientes encaminhados, 58 completaram o programa. A média de idade dos participantes foi de 46 ± 14 anos; sendo 52% do sexo feminino. Entre esses pacientes, 37 (47%) eram portadores de fibrose pulmonar, 13 (22%) tinham enfisema pulmonar, e 18 (31%), tinham outras doenças pulmonares em fase avançada. Houve uma melhora significativa na distância percorrida no TC6 ao final do programa (367 ± 136 m vs. 439 ± 114 m; p = 0,001), com um aumento médio de 72 m. Houve aumentos significativos nas pontuações dos seguintes domínios do SF-36: capacidade funcional, 22 pontos (p = 0,001); aspectos físicos, 10 (p = 0,045); vitalidade, 10 (p < 0,001); aspectos sociais, 15 (p = 0,001); e saúde mental, 8 (p = 0,001). **Conclusões:** O programa de reabilitação pulmonar teve um impacto positivo na capacidade de exercício e na qualidade de vida nos pacientes em lista de espera para transplante pulmonar.

Descritores: Reabilitação; Transplante de pulmão; Qualidade de vida; Exercício; Tolerância ao exercício.

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Introduction

Patients with advanced lung disease experience a dyspnea- and fatigue-related reduction in exercise tolerance. In recent decades, numerous strategies associated with pharmacological treatment have been studied to reduce symptoms and improve quality of life in these patients.[1] Pulmonary rehabilitation, which is considered a non-pharmacological intervention with a high level of evidence (grade of recommendation A) in the treatment of COPD, improves exercise tolerance and is fundamentally based on physical training, which, together with the other strategies, aims to relieve and control symptoms, minimize the complications of the disease, and help patients live an active life with few restrictions.[1-6] Some studies have suggested that the benefits of a rehabilitation program are not associated with the stage of disease severity, and that rehabilitation should be recommended at any stage.[4-7]

For patients with advanced lung disease, lung transplantation is a treatment option that has contributed to improving quality of life and increasing survival.[8-10] Recent studies have demonstrated the benefits that pulmonary rehabilitation can bring to patients after lung transplantation.[8,11,12] The benefits of rehabilitation in patients on lung transplant waiting lists are not yet conclusive, because previous studies have involved a small number of patients, heterogeneous samples, and different intervention protocols. Jastrzebski et al.[9] used the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) to assess quality of life in 16 waiting list patients with idiopathic pulmonary fibrosis and 14 waiting list patients with COPD at two time points: at the time of referral for lung transplantation and one year later. Those authors found that there was worsening in the role-physical domain, and that the patients with COPD had worse scores than did those with pulmonary fibrosis. Therefore, pre-transplant pulmonary rehabilitation is essential to minimize loss of functional performance while patients are awaiting transplantation.[13]

The hypothesis of the present study was that patients on lung transplant waiting lists who participate in an individualized, multidisciplinary pulmonary rehabilitation program would experience benefits in terms of both exercise tolerance and health-related quality of life. The objective of the present study was to analyze the impact of a pulmonary rehabilitation program on the functional capacity and quality of life of patients on lung transplant waiting lists.

Methods

This was a prospective study conducted in the Department of Pulmonary Rehabilitation of the Pereira Filho Ward, Department of Lung Diseases of the Santa Casa Hospital Complex in Porto Alegre, Porto Alegre, Brazil. The research project was approved by the Research Ethics Committee of the Santa Casa Hospital Complex in Porto Alegre. All patients gave written informed consent, agreeing to participate in the study.

Between June of 2007 and November of 2010, the study included patients with advanced lung disease who were undergoing optimized drug therapy and were placed on lung transplant waiting lists in accordance with the criteria established in the international guidelines for the selection of lung transplant candidates. [12] Considering the broad base of evidence supporting the recommendation of pulmonary rehabilitation for patients with advanced lung disease, participation in rehabilitation is one of the criteria for remaining on waiting lists and is recommended by the lung transplant team of the Santa Casa Hospital Complex in Porto Alegre. The clinical information about the diagnosis was collected from the medical charts of the patients. The pulmonary function tests were performed in accordance with the technical procedures and the acceptability and reproducibility criteria of the American Thoracic Society/European Respiratory Society and the Brazilian Thoracic Association (BTA). [14-16] The tests were performed in the pulmonary function laboratory of our institution, which is a laboratory certified by the BTA.

The pulmonary rehabilitation program involved the following steps: medical appointments with the transplant team every two months; psychiatric evaluations, nutritional counseling, social assistance, and monthly educational lectures.

The physical training was administered by two physical therapists. The sessions, each lasting 90 minutes, took place three times a week, totaling 36 meetings. The following activities were performed: warming-up, which consisted of breathing exercises (respiratory cycle) associated with arm raising; and muscle strengthening, which was based on arm and leg exercises with an initial load of 30% of one repetition maximum testing and with one set of 10 repetitions per exercise.[17] The load was increased by 0.5 kg every 7 sessions according

to the patient tolerance. Aerobic exercises were performed on a treadmill (Inbrasport, Porto Alegre, Brazil), beginning at 60% of the speed of the patient on the six-minute walk test (6MWT), with a progressive protocol every 6 minutes for the variable time until reaching 30 minutes. The speed was increased by 0.3 km/h every 7 sessions. The completion of all exercises was limited when the patient reported dyspnea or leg fatigue, indicated by a modified Borg scale score greater than 4, and when the SpO_2 reached 92%. At the end of each session, stretching was performed for the major muscle groups involved. During the rehabilitation program, all patients received continuous oxygen therapy in accordance with the medical prescription and were constantly monitored by pulse oximetry. An oxygen flow required to maintain an $SpO_2 \geq 92\%$ was used.

Before and after the 36 sessions, the patients were evaluated by the same physical therapists with the 6MWT, in accordance with the American Thoracic Society recommendations, and the SF-36.[18-20] The modified Borg scale was used for measuring dyspnea and leg discomfort.[21]

Data analysis was performed with the Statistical Package for the Social Sciences, version 14.0 (SPSS Inc, Chicago, IL, USA). Distribution of symmetrical variables was assessed by the Kolmogorov-Smirnov test. Continuous variables are expressed as mean and standard deviation or as median and interquartile range, whereas categorical variables are expressed as absolute and relative frequency.

The study outcomes before and after the rehabilitation sessions were compared with the Student's t-test for paired samples. The chi-square test was used for continuous variables, and the Mann-Whitney U test was used for categorical variables. The level of significance was set at 5%.

Results

During the study period, 112 patients were placed on lung transplant waiting lists and referred for pulmonary rehabilitation. Of those, 54 did not complete the 36 sessions of the program and were excluded from the study. The reasons for not completing the rehabilitation program were as follows: having undergone lung transplantation before the end of the program, 43 patients; having died, 8 patients; having given up transplantation, 2 patients; and having been hospitalized for a long time, 1 patient (Figure 1). Table 1 shows the comparison of demographic and functional characteristics between the 58 patients (53.7%) who completed the program and the 54 (47.3%) who were excluded. The only variable for which there was a significant difference between the groups was age. The patients who underwent the entire program were, on average, 5 years younger than were those who were excluded.

The results obtained before and after the rehabilitation program for the 6MWT variables are shown in Table 2. After completion of the program, there was a mean increase of 72 m in the six-minute walk distance (6MWD), and there was a significant decrease in perceived dyspnea. Resting and post-exercise SpO_2 remained similar after the program, there being no statistically significant difference. The patients walked a greater distance and did not have greater desaturation because of the increased effort, reporting a lesser degree of dyspnea after the rehabilitation program. There was no difference in perceived leg fatigue at rest before and after the sessions; however, after completion of the program, the patients reported less discomfort, this difference being statistically significant.

There were significant point increases in the scores on the following SF-36 domains: physical functioning, up 22 ($p = 0.001$), role-physical, up 10 ($p = 0.045$); vitality, up 10 ($p < 0.001$); social functioning, up 15 ($p = 0.001$); and mental health, up 8 ($p = 0.001$). No statistically significant differences were found for the other domains (Table 3).

Discussion

In the present study, lung transplant candidates who participated in an individualized, multidisciplinary pulmonary rehabilitation program showed significant clinical improvement in the 6MWT and in quality of life. The mean increase of 72 m in the 6MWD and the increase in the SF-36 physical functioning, role-physical, vitality, social functioning, and mental health domain scores, both of which observed after 36 sessions of aerobic exercise training and muscle strengthening, emphasize that pulmonary rehabilitation provides overall benefits to the health of this population.

The benefits of pulmonary rehabilitation in patients with COPD and pulmonary fibrosis have been well documented.[6,21,22] In patients with COPD, rehabilitation has proven to improve exercise tolerance, to reduce dyspnea, to improve

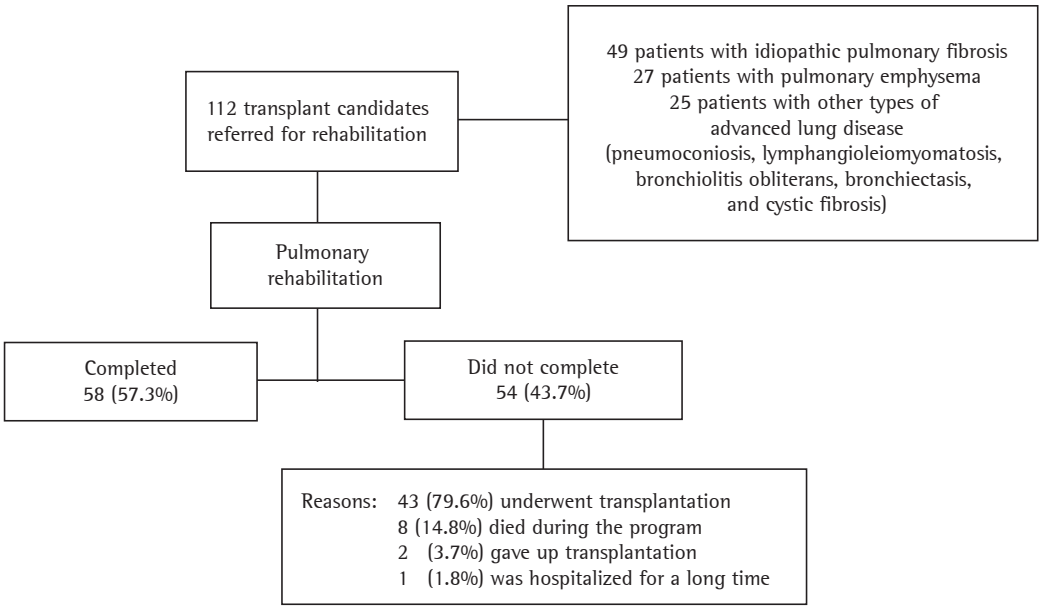

Figure 1 - Flowchart of patient inclusion in the study.

Table 1 - Baseline characteristics of the sample of lung transplant candidates who were prescribed the pulmonary rehabilitation program.[a]

Variable	Participants (n = 58)	Non-participants (n = 54)	p
Demography			
Male gender, n (%)	28 (48)	27 (63)	0.163
Age, years	46 ± 14	51 ± 11	< 0.001
Anthropometry			
BMI, kg/m^2	23 ± 4	24 ± 3	0.162
Diagnosis, n (%)			
Idiopathic pulmonary fibrosis	27(47)	22(51)	0.199
Pulmonary emphysema	13 (22)	14 (32)	
Others[b]	18 (31)	7 (16)	
Pulmonary function[c]			
FVC, L	1.12 ± 0.6	0.95 ± 0.4	0.172
FVC, % of predicted	44.9 ± 16.5	41.1 ± 11.3	0.194
FEV_1, L	0.43 ± 0.62	0.39 ± 0.49	0.853
FEV_1, % of predicted	32.9 ± 15.9	31.6 ± 16.8	0.695
FEV_1/FVC	0.44 ± 0.49	0.34 ± 0.44	0.316
6MWT			
6MWD, m	367 ± 136	330 ± 135	0.992
6MWD, % of predicted	56.6 ± 22.6	48.7 ± 24.8	0.082
PASP, mmHg	44.8 ± 17.3	42.9 ± 17.1	0.580

BMI: body mass index; 6MWT: six-minute walk test; 6MWD: six-minute walk distance; and PASP: pulmonary artery systolic pressure. [a]Values expressed as mean ± SD, except where otherwise indicated. [b]Lymphangioleiomyomatosis, bronchiolitis obliterans, and pneumoconiosis. [c]Post-bronchodilator pulmonary function tests.

quality of life, and to reduce the use of health resources. As adjuvant treatment to surgical programs, such as lung volume reduction surgery, rehabilitation plays an important role in the preparation of these patients for the procedure, facilitating postoperative recovery.[1,23]

In the present study, most patients had pulmonary fibrosis and emphysema. In a study

Table 2 - Comparison of the six-minute walk test variables before and after the pulmonary rehabilitation program (n = 58).[a]

Variable	Pulmonary rehabilitation program			p
	Before	After	Δ[b]	
6MWD, m	367 ± 136	439 ± 114	72 (50-95)	0.001
6MWD, % of predicted	56,6 ± 22,6	75,5 ±16,6	19 (58-92)	0.001
Resting SpO_2 , %	95 ± 2	94 ± 3	2 (1-2)	0.001
Post-exercise SpO_2 , %	80 ± 9	80 ± 9	0 (–2 to 2)	0.940
Modified Borg scale				
Resting dyspnea	0 (0–2)[c]	0 (0–0)[c]	–1 (–1 to 0)	0.001
Post-exercise dyspnea	5 (3–7)[c]	4 (3–5)[c]	–1 (–2 to 0)	0.001
Leg fatigue at rest	0 (0–0)[c]	0 (0–0)[c]	0 (0–0)	0.129
Leg fatigue after exercise	3 (0–5)[c]	2 (0–3)[c]	–1 (–2 to 0)	0.011

Δ: variation (measurement after the rehabilitation program – measurement before the rehabilitation program); and 6MWD: six-minute walk distance. [a]Values expressed as mean ± SD, except where otherwise indicated. [b]Values expressed as mean (95% CI). [c]Values expressed as median (interquartile range).

Table 3 - Comparison of the domains of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) before and after the pulmonary rehabilitation program (n = 58).[a]

Variable	Pulmonary rehabilitation program			p
	Before	After	Δ[b]	
Physical functioning	20 (10-35)	45 (30-55)	22 (17-26)	< 0.001
Role-physical	0 (0-25)	06 (0-50)	10 (1-19)	0.045
Bodily pain	62 (41-90)	74 (51-9)	6 (–1 to 14)	0.055
General health	30 (20-52)	36 (22-52)	4 (–2 to 9)	0.151
Vitality	57 (38-75)	65 (53-81)	10 (5-14)	< 0.001
Social functioning	50 (25-75)	64 (50-87)	15 (8-21)	< 0.001
Role-emotional	33 (0-100)	66 (0-100)	12 (–1 to 25)	0.087
Mental health	82 (64-88)	84 (79-92)	8 (4-13)	0.001

Δ: variation (measurement after the rehabilitation program – measurement before the rehabilitation program). [a]Values expressed as median (interquartile range), except where otherwise indicated. [b]Values expressed as mean (95% CI).

in which 30 patients with idiopathic pulmonary fibrosis were compared with 15 control group patients who did not undergo rehabilitation, those who underwent pulmonary rehabilitation obtained an increase of 46.3 m (95% CI: 8.3-84.4; $p < 0.05$) in the 6MWD.[24] A study involving 13 patients with idiopathic pulmonary fibrosis showed that, after a pulmonary rehabilitation program, there was a reduction in perceived dyspnea, as measured by the Borg scale, from 3.0 ± 1.4 to 2.5 ± 1.4 ($p < 0.01$).[25] Although, in the present study, we did not analyze the underlying diseases separately, we found a significant improvement in the functional capacity and quality of life of the patients who completed the rehabilitation program.

In a prospective cohort study involving 376 patients on lung transplant waiting lists, the baseline 6MWD was analyzed as a predictor of survival in that population. Those authors found that post-transplant survival increased significantly as the 6MWD values increased in comparison with baseline values. In addition, they found that this relationship is similar in all types of lung disease; this reveals the possibility that rehabilitation programs in the pre-transplant phase can provide a favorable impact during hospitalization. The patients in the present study had a higher mean 6MWD after the rehabilitation program, which allows us to infer a higher probability of post-transplant survival.[26,27]

All of our patients underwent continuous training on a treadmill, i.e., a conventional program. A randomized clinical trial investigated different modes of exercise (interval vs. continuous) in lung transplant candidates and found that there was an increase in the 6MWD in the two groups studied, with a greater reduction in dyspnea occurring in the group receiving interval training.[13] In another study, a different mode of training, i.e., Nordic walking with ski poles, was used for twelve weeks in a pulmonary rehabilitation program in lung transplant candidates. Those

authors observed a significant increase in mean 6MWD (310.2 m vs. 372.1 m; $p < 0.05$) and improvement in the SF-36 social functioning domain ($p < 0.05$), demonstrating that the type of training was safe and feasible.[28]

Most of the current pulmonary rehabilitation programs, designed for lung transplant candidates, comply with the general recommendations for pulmonary rehabilitation, with a weekly frequency of two to three sessions per week, over a period of six to eight weeks. These programs include aerobic training, arm and leg muscle strengthening, and also an educational component, which, in addition to the aspects of the disease that are commonly addressed, needs to include issues relevant to the procedure itself, educating patients regarding immunosuppressive drugs, rejection, infections, and complications so that they can adopt a new lifestyle.[1,3,11,25]

Considering that, of the 112 patients referred to our program, most completed it, it should be emphasized that many of the excluded patients from the analysis were excluded because they underwent transplantation. The excellent adherence to the program in our study population can be explained by the fact that pulmonary rehabilitation is included in the preoperative treatment plan for this group of patients who are highly motivated for surgery. Patients who are preparing for lung transplantation represent a selected group of individuals with advanced chronic respiratory disease and often remain on waiting lists for long periods of time. Since maintaining health status, exercise capacity, and quality of life are key factors for a highly complex surgical procedure, ongoing maintenance of these patients in a rehabilitation program would be a desirable strategy.[11,25,27] In this context, a determining factor in the success of rehabilitation programs would be patient adherence to scheduled sessions.[4] A study involving 711 patients referred for pulmonary rehabilitation demonstrated that 31.8% of those patients did not attend the programs and that, of those who did, 29.1% were non-adherent. Using a logistic regression model, those researchers observed that use of long-term oxygen therapy and living alone were independent factors for non-attendance. In addition, being a current smoker, performing poorly on the shuttle test, and hospitalizations were independent predictors of poor adherence.[29]

Since this group of patients is only one of the several groups that use pulmonary rehabilitation, we have established a rotation strategy for those remaining on waiting lists for long periods of time. This strategy, which provides access to rehabilitation opportunities for all, was based on a study in which the authors concluded that the benefits of a rehabilitation program on the indices of anxiety, depression, quality of life, and exercise capacity persisted over 24 months in patients with COPD.[30]

Among the limitations of our study is the lack of a control group, the use of which was considered by us, in the preparation of the protocol, to be an unethical strategy, given that various studies have emphasized the importance of rehabilitation in advanced lung disease. The fact that cardiopulmonary exercise testing was not used might have underestimated the training strategy of these patients, preventing them from further improving their exercise capacity. Another factor that can be considered a limitation is the lack of an analysis of the emotional aspects of these patients, who view transplantation as their last chance of improving their disease outcome.

The findings of the present study allow us to conclude that the individualized, multidisciplinary pulmonary rehabilitation program was beneficial for patients on lung transplant waiting lists. The patients who participated in the program showed significant clinical improvement after 36 physical training sessions, as well as showing improvement in the 6MWD and in quality of life, which underscores the need for rehabilitation programs at facilities performing complex surgical procedures, such as lung transplantation.

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Characteristics of tuberculosis in the state of Minas Gerais, Brazil: 2002-2009*

Características da tuberculose no estado de Minas Gerais entre 2002 e 2009

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Abstract

Objective: To analyze the profile of tuberculosis cases reported between 2002 and 2009 in the state of Minas Gerais, Brazil, according to sociodemographic, clinical, and laboratory characteristics, as well as to comorbidities and mortality. **Methods:** This was a descriptive, epidemiological study based on data obtained from the Brazilian Case Registry Database and the Brazilian Mortality Database for the 2002-2009 period. **Results:** There were 47,285 reported cases of tuberculosis, corresponding to a mean incidence of 22.3/100,000 population. The individuals diagnosed with tuberculosis were predominantly in the 20- to 49-year age bracket and male (62.4% and 67.0%, respectively). Individuals with a low level of education accounted for 18.5% of the cases. New cases, cases of recurrence, and cases of retreatment accounted for 83.7%, 5.7%, 5.7%, respectively. The rates of cure and treatment noncompliance were 66.2% and 11.2%, respectively; multidrug-resistant tuberculosis was identified in 0.2% of the cases; and the mortality rate was 12.9%. The directly observed treatment, short-course (DOTS) strategy was applied in 21.8% of the cases. Sputum smear microscopy and culture were performed in only 73.9% and 12.9% of the cases, respectively. Chest X-rays were performed in 90.5% of the cases. Pulmonary tuberculosis was the predominant form (in 83.9%). Comorbidity with alcoholism, HIV infection, and diabetes mellitus were identified in 17.2%, 8.3%, and 3.8%, respectively. **Conclusions:** During the study period, the numbers of new cases, cases of treatment noncompliance, and deaths were high, comorbidities were common, and there was a failure to perform adequately basic tests for the diagnosis of tuberculosis. Multidisciplinary approaches, expanded use of the DOTS strategy, better knowledge of the distribution of tuberculosis, and improvements in the databases are needed in order to achieve better control of the disease in the state of Minas Gerais.

Keywords: Tuberculosis/epidemiology; Tuberculosis/mortality; Information systems.

Resumo

Objetivo: Analisar o perfil de casos de tuberculose no estado de Minas Gerais entre 2002 e 2009, segundo características sociodemográficas, clínicas e laboratoriais, assim como presença de comorbidades e mortalidade. **Métodos:** Estudo epidemiológico descritivo com levantamento de dados dos casos notificados no Sistema de Informação de Agravos de Notificação e Sistema de Informação de Mortalidade entre 2002 e 2009. **Resultados:** Foram notificados 47.285 casos de tuberculose nos anos estudados, com média de incidência 22,3/100.000 habitantes. Os indivíduos com tuberculose eram predominantemente da faixa etária de 20-49 anos (62,4%), do sexo masculino (67,0%) e tinham baixa escolaridade (18,5%). Casos novos, de recidiva e de retratamento representaram, respectivamente, 83,7%, 5,7% e 5,7% do total de casos. As proporções de cura, abandono do tratamento e tuberculose multirresistente foram, respectivamente, 73,1%, 11,2% e 0,2%, enquanto o coeficiente de mortalidade foi 12,9%. O tratamento diretamente observado (TDO) foi administrado em 21,8% dos casos. A baciloscopia e a cultura de escarro somente foram realizadas em 73.9% e 12,9% dos casos, respectivamente. A radiografia de tórax foi realizada em 90,5% dos casos. A forma pulmonar prevaleceu (83,9%). A comorbidade com alcoolismo, infecção pelo HIV e diabetes mellitus foi identificada em 17,2%, 8,3% e 3,8% dos casos, respectivamente. **Conclusões:** No período estudado, o número de casos novos, de abandono e de óbitos foi elevado, as comorbidades foram relevantes, e os exames básicos não foram realizados adequadamente para o diagnóstico da tuberculose. São necessários o trabalho multiprofissional, ampliação da estratégia TDO, maior conhecimento da distribuição da tuberculose em Minas Gerais e melhorias nos bancos de dados para que haja um melhor controle da doença no estado.

Descritores: Tuberculose/epidemiologia; Tuberculose/mortalidade; Sistemas de informação.

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Introduction

Even with the advancement of medicine, tuberculosis remains the infectious disease that causes the greatest number of deaths among adults worldwide. It is estimated that one third of the world population is infected with *Mycobacterium tuberculosis* and that, each year, the bacillus makes approximately 9.4 million people ill, causing 1.7 million deaths. In 2009 in Brazil, there were 71,686 reported new cases and approximately 4,800 reported deaths, which means that Brazil ranks 19th among the 22 countries that are estimated to account for 80% of all cases of tuberculosis worldwide.[1,2]

In recent years, the Brazilian National Ministry of Health has encouraged tuberculosis control, on the basis of the targets set by the World Health Organization (WHO): diagnose at least 70% of the expected cases; properly treat 100% of the diagnosed cases; cure at least 85% of those cases; and maintain treatment noncompliance at acceptable levels (up to 5%). Among the Brazilian states, Minas Gerais ranks 5th in terms of the number of reported cases.[2]

Minas Gerais is one of the 27 federative units in Brazil and has a territorial extent of 586,528.29 km^2. With a population of 19,595,309 people, it is the second most populous state in Brazil, with a population density of 32.73 people/km^2 and 853 cities. The cities in the state of Minas Gerais account for 51.5% of the cities in southeastern Brazil and for 15.5% of the cities in Brazil. The state is subdivided into 28 Regional Health Management Districts and currently has 25 priority cities for tuberculosis control. In addition, Minas Gerais has 3,553 Family Health Program Teams, who serve 829 cities.[3,4]

Some diseases can favor the development of tuberculosis. The three chief comorbidities among those related to tuberculosis are HIV infection, alcoholism, and diabetes mellitus (DM). The epidemiological profile of tuberculosis has been changed by HIV over the years. Tuberculosis/HIV co-infection has caused an increase in mortality, changing resistance to antituberculosis drugs and the risk of transmission due to treatment noncompliance.[5,6]

Studies have shown that DM can favor the development of tuberculosis and account for over 10% of tuberculosis cases due to immunosuppression, and that the risk of developing tuberculosis is approximately three times higher in patients with DM than in those without.[7,8] This therefore justifies the need for increasing efforts to identify and treat diabetic patients with latent *M. tuberculosis* infection before the disease becomes active.[7,9] Alcoholism is also associated with pulmonary tuberculosis, leading to a higher risk of developing the disease and to treatment difficulties.[10]

Given this context, knowledge of the characteristics of tuberculosis could contribute to the development of new strategies for the control of this disease in accordance with the targets set by the WHO. Therefore, the objective of the present study was to analyze the profile of tuberculosis between 2002 and 2009 in the state of Minas Gerais according to sociodemographic, clinical, and laboratory characteristics, as well as to comorbidities and mortality.

Methods

This was a descriptive, epidemiological study based on data regarding reported cases of tuberculosis by city of residence obtained from the Brazilian National Ministry of Health *Sistema de Informação de Agravos de Notificação* (SINAN, Brazilian Case Registry Database) for the 2002-2009 period in the state of Minas Gerais. The present study was approved by the Ethics Committee of the Federal University of Minas Gerais (Protocol no. ETIC 216-08).

All cases reported in the period were included, and 341 cases were excluded because of missing or unknown data, such as age, gender, city of residence, and previous treatment.

Incidence, defined on the basis of the tuberculosis cases registered in the SINAN, was calculated by dividing the mean rate of new cases of tuberculosis by the mean population estimate.

We analyzed sociodemographic characteristics (gender, age, and level of education), clinical characteristics (disease form, type of admission, and outcome), and laboratory characteristics (sputum smear microscopy results, sputum culture results, chest X-ray findings, and tuberculin skin test [TST] results), as well as comorbidities (HIV infection, DM, and alcoholism). The reference values used for the analysis of the TST results were as follows: negative, an induration of 0 to 4 mm; weakly positive, an induration of 5 to 9 mm; and strongly positive, an induration $\geq$ 10 mm,[11] as described in the SINAN.

Data on the population (per 1,000 people) were obtained from the Brazilian Institute of Geography and Statistics, according to estimates and the 2010 census.[3]

The analysis of the clinical characteristics involved disease form (pulmonary, extrapulmonary, and disseminated forms), type of (new case, recurrence, readmission after treatment noncompliance, and transfer), and outcomes (cure, treatment noncompliance, transfer, a change in diagnosis, multidrug-resistant (MDR) tuberculosis, and death). Mortality data were obtained from the *Sistema de Informação de Mortalidade* (SIM, Brazilian Mortality Database).

The data obtained were entered into a database with the use of TabWin 3.5, which is made available by the Information Technology Department of the Brazilian National Ministry of Health, and the analyses were performed with the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA), and OpenEpi, version 2.3. We performed a descriptive analysis of the information obtained from this database, including a description of the population, frequency distributions, and statistical measures of the selected characteristics. Interval estimation was performed by using confidence intervals for binomial proportions based on the Wilson test score method.[12]

Results

During the study period, there were 47,285 reported cases of tuberculosis. The mean incidence rate was 22.3/100,000 population (Figure 1).

The 20- to 49-year age group had the greatest number of tuberculosis cases, which corresponds to 29,526 cases (62.4%), followed by the over-65-year age group (5,356 cases; 11.3%). Males predominated (31,690 cases; 67.0%; Table 1).

Regarding the level of education, those who had had less than 9 years of schooling had the highest incidence (9,288 cases; 18.5%), followed by those who had had less than 5 years of schooling (8,267 cases; 16.5%; Table 1).

Regarding the type of admission, the distribution was as follows: new case, in 39,581 cases (83.7%); recurrence, in 2,686 cases (5.7%), readmission after treatment noncompliance, in 2,697 cases (5.7%); transfer, in 1,980 cases (4.2%); and no data, in 341 cases (0.7%; Figure 2).

The directly observed treatment, short-course (DOTS) strategy was applied in 10,317 cases (21.8%).

Of the reported cases, 53.8% had a positive first sputum smear and 26.1% did not undergo sputum smear microscopy. Of the patients who underwent culture, 2,743 (66.7%) had positive results. However, 41,227 patients (87.1%) did not undergo the test. Chest X-rays were performed

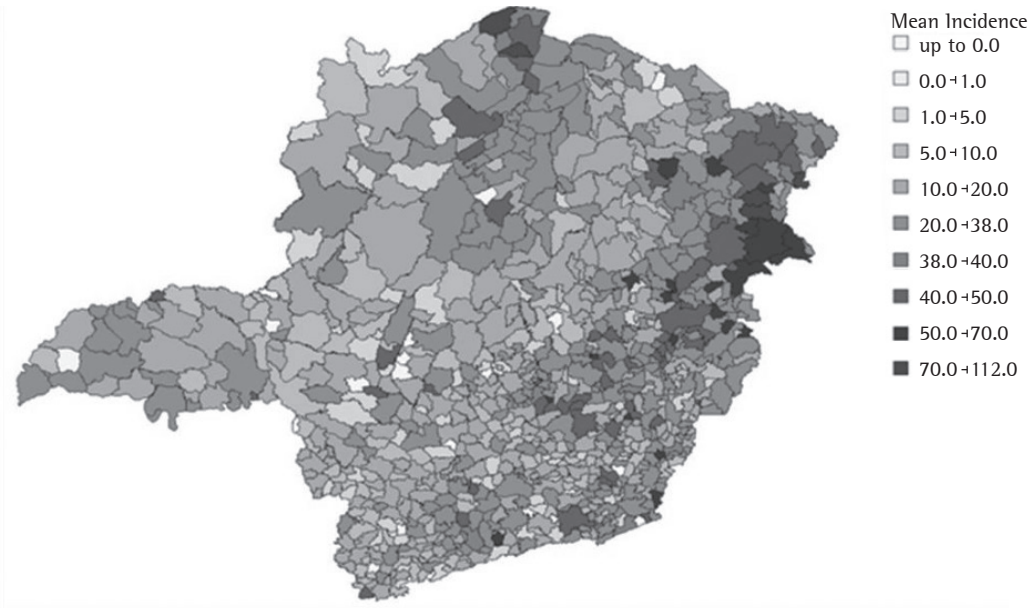

Figure 1 - Spatial distribution of the mean incidence of tuberculosis in the state of Minas Gerais, Brazil, by city, 2002-2009. Source: SINAN-MG (Brazilian Case Registry Database-Minas Gerais).

in 42,343 (89.5%) of the reported cases, and 38,495 (81.4% of the total number of cases) were considered to be cases of suspected tuberculosis.

Table 1 - Frequency of tuberculosis by age bracket, gender, and level of education, Minas Gerais, Brazil, 2002-2009.

Variable	n	%	95% CI
Age bracket, years			
< 1	266	0.6	0.5-0.7
1-4	356	0.7	0.6-0.8
5-9	420	0.9	0.8-1.0
10-14	549	1.2	1.1-1.3
15-19	2,055	4.3	4.2-4.5
20-34	13,757	29.0	28.7-29.5
35-49	15,769	33.4	32.9-33.8
50-64	8,757	18.5	18.2-18.9
65-79	4,286	9.1	8.8-9.3
≥ 80	1,070	2.3	2.1-2.4
Gender			
Male	31,690	67.0	66.6-67.4
Female	15,595	33.0	32.6-33.4
Level of education			
Illiterate	4,097	8.7	8.4-8.9
≤ 9 years of schooling	20,102	42.5	42.1-43.0
High school (incomplete/ complete)	5,254	11.1	10.8-11.4
College (incomplete/ complete)	1,706	3.6	3.4-3.8
Unknown/no data	16,126	34.1	-

Source: SINAN-MG (Brazilian Case Registry Database-Minas Gerais).

In 37,044 cases (78.3%), TST was not performed. Considering the total number of cases, the TST results were as follows: negative, in 5.4%; weakly positive, in 1.9%; and strongly positive, in 11.6% (Table 2).

The pulmonary, extrapulmonary, and disseminated forms of tuberculosis were found in 39,669 (83.9%), 8,509 (18.0%), and 1,973 (4.2%) of the cases, respectively. Among the patients with pulmonary tuberculosis, 33,505 (80.5%) of the 41,642 results were positive on the first and second smears, confirming the diagnosis of the pulmonary form of the disease, and, for those under 15 years of age, the proportion was 6.9% (479/6,989). Overall, the most common comorbidity was alcoholism, in 8,112 cases (17.2%), followed by HIV infection, in 3,915 (8.3%), and DM, in 1,786 (3.8%). Comorbidity of pulmonary tuberculosis with alcoholism, HIV infection, and DM was identified in 15.0%, 4.5%, and 3.2% of the cases, respectively.

According to the data collected from the SINAN, outcomes were as follows: cure, in 34,611 cases (73.1%); treatment noncompliance, in 5,311 cases (11.2%); transfer, in 2,558, (5.4%); a change in diagnosis, in 1,334 (2.8%); MDR tuberculosis, in 79 (0.2%); and no data/unknown, in 2,715 (5.7%; Figure 3). A total of 677 deaths were reported, and the mortality rate was 3.5% (677/19,220,578).

According to data collected from the SIM, there were 2,488 deaths from tuberculosis, of which 2,215 (89.0%) were from pulmonary tuberculosis, 143 (5.8%) were from miliary tuberculosis, 58 (2.3%) were from central nervous

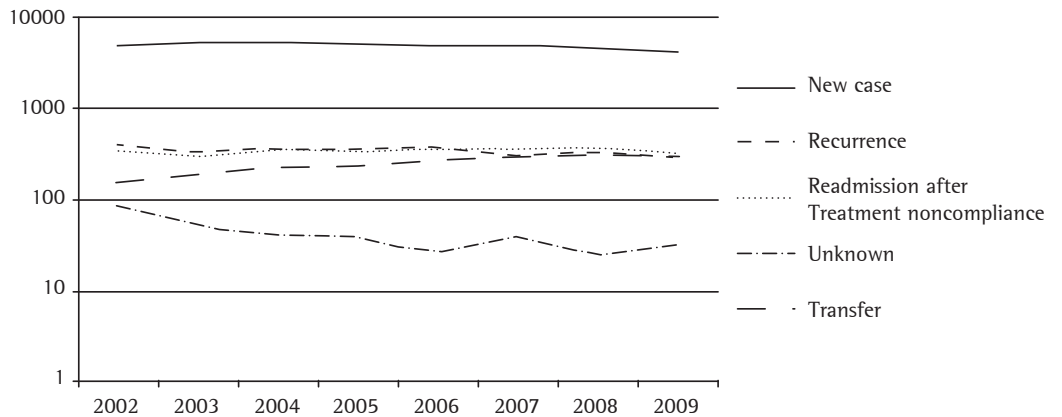

Figure 2 - Profile of tuberculosis by type of admission, Minas Gerais, Brazil, 2002-2009. Source: SINAN-MG (Brazilian Case Registry Database-Minas Gerais). Number of cases on a logarithmic (log_{10}) scale.

Table 2 - Frequency of testing among the cases diagnosed with tuberculosis, Minas Gerais, Brazil, 2002-2009.

Test	n	%	95% CI
1st sputum smear			
Positive	25,461	53.8	53.4-54.3
Negative	9,497	20.1	19.7-20.4
Not performed	12,323	26.1	25.7-26.5
Unknown/no data	4	-	-
2nd sputum smear			
Positive	6,077	27.3	26.7-27.9
Negative	3,236	14.5	14.1-15.0
Not performed	12,943	58.1	57.5-58.8
Unknown/no data	25,029	-	-
Sputum culture			
Positive	2,743	5.8	5.6-6.0
Negative	1,370	2.9	2.7-3.0
In progress	1,941	4.1	3.9-4.3
Not performed	41,227	87.2	86.9-87.5
Unknown/no data	4	-	-
Chest X-ray			
Suspicious	38,495	82.3	81.9-82.6
Normal	3,284	7.0	6.8-7.2
Pathologies other than tuberculosis	564	1.2	1.1-1.3
Not performed	4,453	9.5	9.2-9.8
Unknown/no data	489	-	-
Tuberculin skin test			
Negative	2,551	5.5	5.3-5.7
Weakly positive	904	1.9	1.8-2.1
Strongly positive	5,485	11.9	11.6-12.2
Not performed	37,044	80.6	80.2-80.9
Unknown/no data	1,301	-	-

Source: SINAN-MG (Brazilian Case Registry Database-Minas Gerais).

system tuberculosis, and 72 (2.9%) were from tuberculosis in other organs. The mortality rate was 12.9% (2,488/19,220,578).

Discussion

The mean incidence (defined on the basis of the reported cases alone) in the state of Minas Gerais for the study period was 22.3/100,000 population, which means that Minas Gerais ranks 24th among the Brazilian states[13] and has met the millennium development goal for tuberculosis incidence, which is to reduce incidence to 25.6 cases per 100,000 population by 2015.[13] However, an analysis of the distribution of the disease by city reveals a different scenario, since 92 cities had incidence rates equal to or greater than the national average of 38.3/100,000 population. This demonstrates that, in the state of Minas Gerais, prioritization should not be restricted to the metropolitan areas singled out by the tuberculosis control program, given that high incidence rates are found in smaller cities.

In the present study, tuberculosis predominated in the economically active population (i.e., those aged 20-49 years) and in individuals over 65 years of age, especially in males, at a ratio of 2:1, with a low level of education, which is in agreement with the findings of other studies.[2,13]

Regarding the type of admission, new cases accounted for 83.7%, and, as shown in Figure 2, nearly all types of admission remained stable during the eight-year study period. In addition, it is of note that the calculated incidence is decreasing mainly because of the increase in the

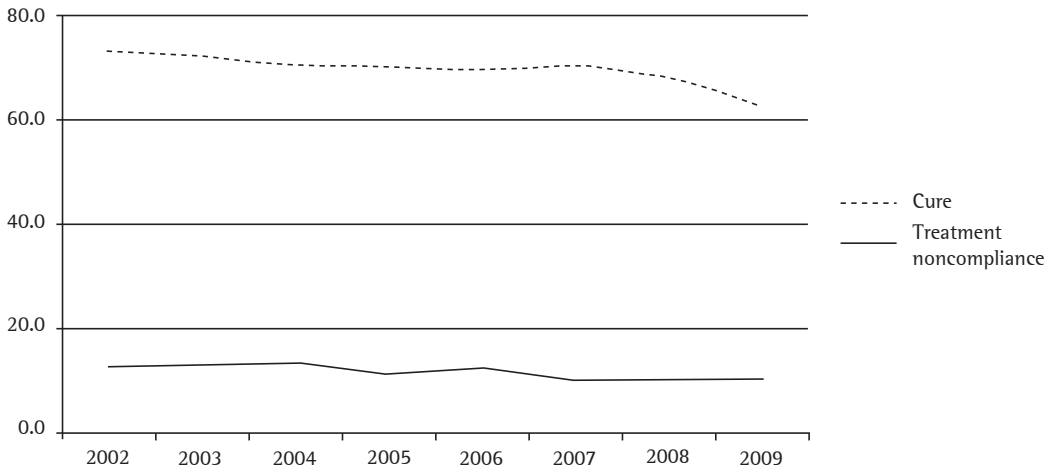

Figure 3 - Profile of tuberculosis by outcome (cure and treatment noncompliance), Minas Gerais, Brazil, 2002-2009. Source: SINAN-MG (Brazilian Case Registry Database-Minas Gerais).

population, given that the absolute number of new cases has not decreased significantly over time. In order to reduce the number of new cases effectively, it is necessary to develop a process that can identify areas with different needs and measures, where the tuberculosis control program will invest in the surveillance of patients with respiratory symptoms and in the identification of the population at risk for latent tuberculosis. When such cases are identified and correctly treated, there will be a true reduction in the number of new cases.

For readmission after treatment noncompliance, the reported rate was only 5.7%; however, the rate of treatment noncompliance during the study period was 11.2%. This shows that the noncompliant patients did not return for another treatment. Active surveillance of these cases should be incorporated into the routine practice of the Family Health Program Teams.

The Brazilian National Tuberculosis Control Program, in accordance with the WHO recommendation, has set a target cure rate of 85% and a target noncompliance rate of up to 5% for pulmonary tuberculosis.[2] According to the reported tuberculosis outcomes in the state of Minas Gerais (Figure 3), little has been achieved in terms of cure (66.2%) and noncompliance (11.8%), which underscores the need for the implementation and expanded use of the DOTS strategy, the coverage of which was low.[13]

We found that approximately 30% of the patients did not undergo sputum smear microscopy, which shows that this test is not routinely requested by health care workers. Since sputum smear microscopy is an inexpensive and easy-to-perform test that is needed for screening patients with respiratory symptoms, one realizes the ineffectiveness of the tuberculosis control measures, given that pulmonary tuberculosis was the most common form (in 84%), as shown in other studies.[2] Even for the patients who underwent the test, the positivity rate (53.8%) is found to be lower than the 2009 nationwide rate (64%), which underscores the need to implement quality control measures in the laboratories in the state of Minas Gerais.[2]

The results show that most patients did not undergo sputum culture (87.2%). Although sputum culture is a more complex, more expensive test that takes longer to perform and is less accessible, it is of fundamental importance to the evaluation of smear-negative cases of pulmonary tuberculosis. Culture allows not only diagnosis but also mycobacterial identification and drug resistance determination, especially for patients with comorbidities, such as alcoholism, HIV infection, and DM. It is of fundamental importance to determine the resistance profile of the strains circulating in the state of Minas Gerais because of the high rate of noncompliance (11.9%), primarily aiming at providing appropriate treatment.[4,9,10,13] The low incidence of MDR tuberculosis (0.2%) could be underestimated, given that most cases did not undergo sputum culture or susceptibility testing.

Chest X-ray, which is an extremely important tool in the investigation of pulmonary tuberculosis and in the identification of atypical presentations in immunocompromised patients, was the most commonly performed procedure (in 90.5%). Suggestive findings are indispensable in order to request bacteriological examination (sputum smear microscopy and culture),[13] which was not observed in this study, since sputum smear microscopy and culture were performed in only 73.9% and 12.9% of the cases, respectively. It should also be emphasized that a failure to perform culture precludes the correct identification of the bacterial species, as well as preventing the determination of drug resistance in order to define treatment.

In the study population, TSTs were requested in 80.6% of the cases and seem to have been used as a diagnostic parameter, given that bacteriological examination was not requested.

The high prevalence of comorbidities, such as alcoholism, HIV infection, and DM, shows the need for follow-up by a multidisciplinary team because of the possibility of a worsening of the diseases, as well as for measures, such as the DOTS strategy, at primary health care clinics in order to prevent noncompliance.[5-7,9,10]

Pulmonary tuberculosis was more common than was extrapulmonary tuberculosis when related to all comorbidities evaluated (alcoholism, HIV, and DM). Of those patients with pulmonary tuberculosis, 80.4% had two positive sputum smears, which shows the good sensitivity of sputum smear microscopy. However, for patients under 15 years of age, the positivity rate of sputum smear microscopy was only 6.8% of the cases of pulmonary tuberculosis, which might be related

to smear-negative lesions and to the difficulty in expectorating.[8]

According to the reported data from the SIM and the SINAN, there was a large difference in terms of mortality (12.9% vs. 3.5%), which shows a large difference between the databases, justifying the need for measures that will enable data availability in a consistent and updated manner on the same platform automatically. Mortality is one of the main assessment measures of the tuberculosis control program, and the target set by the WHO is that mortality should be reduced to less than 5% by 2015. Therefore, strategies should be developed to allow interaction between reporting programs, with cross-referencing of data, allowing improved data reliability.

Currently, epidemiological methods have been used for assessing the distribution of *M. tuberculosis* in a given community. These methods include the molecular biology techniques known as restriction fragment length polymorphism[14,15] and mycobacterial interspersed repetitive units,[16,17] which allow the assessment of recent infection (active surveillance) or late infection (surveillance of an at-risk population), as well as spoligotyping, which assesses the distribution of *M. tuberculosis* strains.[15,16] Therefore, investments can be better targeted at the surveillance of individuals with respiratory symptoms or individuals with comorbidities who require preventive treatment of latent infection.

One of the limitations of this study was the use of secondary data, which might affect the quality of results.[18]

In conclusion, during the study period, the numbers of new cases, cases of treatment noncompliance, and deaths from tuberculosis were high, comorbidities were common, and there was a failure to perform basic tests for the adequate diagnosis of tuberculosis in the state of Minas Gerais. Therefore, it is necessary that there be a joint effort involving health care providers and administrators, as well as the civil society and its organized segments, in the fight against tuberculosis. In addition, expanded use of the DOTS strategy; management of tuberculosis/HIV co-infection and MDR tuberculosis; and better knowledge of the distribution of the disease, with the improvement and combination of the data in the SIM and the SINAN; as well as epidemiological studies and studies on the molecular profiles of *M. tuberculosis*, are needed in order to achieve better control of the disease in the state of Minas Gerais.

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Performance comparison between the mycobacteria growth indicator tube system and Löwenstein-Jensen medium in the routine detection of Mycobacterium tuberculosis at public health care facilities in Rio de Janeiro, Brazil: preliminary results of a pragmatic clinical trial*

Comparação do desempenho do sistema *mycobacteria growth indicator tube* e meio Löwenstein-Jensen na detecção de rotina de *Mycobacterium tuberculosis* em unidades do sistema único de saúde no Rio de Janeiro: resultados preliminares de um ensaio clínico pragmático

Adriana da Silva Rezende Moreira, Gisele Huf, Maria Armanda Vieira, Leila Fonseca, Monica Ricks, Afrânio Lineu Kritski

Abstract

In view of the fact that the World Health Organization has recommended the use of the mycobacteria growth indicator tube (MGIT) 960 system for the diagnosis of tuberculosis and that there is as yet no evidence regarding the clinical impact of its use in health care systems, we conducted a pragmatic clinical trial to evaluate the clinical performance and cost-effectiveness of the use of MGIT 960 at two health care facilities in the city of Rio de Janeiro, Brazil, where the incidence of tuberculosis is high. Here, we summarize the methodology and preliminary results of the trial.
(ISRCTN.org Identifier: ISRCTN79888843 [http://isrctn.org/])

Keywords: Controlled clinical trial; Tuberculosis; Diagnostic tests, routine.

Resumo

Em razão da recomendação da Organização Mundial da Saúde sobre o uso do sistema *mycobacteria growth indicator tube* (MGIT) 960 para o diagnóstico de tuberculose e da falta de evidências sobre o impacto clínico de sua incorporação em sistemas de saúde, um ensaio clínico pragmático está sendo conduzido para avaliar o desempenho clínico e a relação custo-efetividade do MGIT 960 em duas unidades do Sistema Único de Saúde na cidade do Rio de Janeiro, que tem uma elevada incidência de tuberculose. Apresentamos aqui, de forma sintética, o método e resultados preliminares do ensaio.
(ISRCTN.org Identifier: ISRCTN79888843 [http://isrctn.org/])

Descritores: Ensaio clínico controlado; Tuberculose; Testes diagnósticos de rotina.

Rapid diagnosis of tuberculosis is essential for reducing the length of time for which the chain of transmission is maintained and, therefore, the number of individuals infected by those with the disease. Sputum smear microscopy has low sensitivity, and the major problem with culture for mycobacteria is the long incubation period required.[1,2] New tests, despite the high cost, can represent a breakthrough in the fight against the disease, especially in HIV-infected patients, or in patients treated at hospital level.[3]

In 2008, the World Health Organization[4] recommended the use of solid media, such as the mycobacteria growth indicator tube (MGIT) system, because, in studies of diagnostic accuracy, the MGIT 960 system (Becton Dickinson, Sparks, MD, USA) has shown results similar to those observed with the use of the gold standard—

* Study carried out under the auspices of the Academic Tuberculosis Program, Federal University of Rio de Janeiro School of Medicine *Hospital Universitário Clementino Fraga Filho, Instituto de Doenças do Tórax* – HUCFF-IDT, Clementino Fraga Filho University Hospital/Thoracic Diseases Institute – Rio de Janeiro, Brazil.Correspondence to: Afrânio L. Kritski. Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rua Rodolpho Paulo Rocco, 255, Ilha do Fundão, CEP 21541-912, Rio de Janeiro, RJ, Brasil.
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Löwenstein-Jensen (LJ) solid medium,—whether in the detection of *Mycobacterium tuberculosis* or in the identification of strains resistant to the two most important drugs in the first-line antituberculosis treatment regimens—rifampin and isoniazid. In addition, the time to a positive result for MGIT 960 is shorter (10-15 days) than that for the test performed on LJ, which ranges from 20 to 40 days.

Typically, when diagnostic kits are validated by the US Food and Drug Administration or by European regulatory agencies, the regulatory agencies in developing countries tend to approve those kits for marketing, provided that the same items contained in the products marketed in the country of origin are included in the usage instrument (directions for use). However, in recent years in Brazil, researchers affiliated with the Brazilian Tuberculosis Research Network have proposed that, before new diagnostic methods related to diseases of public health impact are granted approval, are available in the national market, and, especially, are used in the *Sistema Único de Saúde* (SUS, Brazilian Unified Health Care System), they be evaluated in terms of their clinical performance and cost-effectiveness, under routine conditions, through practical clinical trials. Through such studies, it is possible to evaluate interventions under conditions that are as close as possible to those under which such interventions are applied in clinical practice, supporting decision making, as opposed to so-called explanatory clinical trials, which are conducted under more controlled conditions and seek to answer questions about whether and how an intervention works, a requirement for products to be approved and marketed. Because practical studies are developed under routine conditions, they do not complicate the usual practice and do not compete with routine activities, thereby being inexpensive and securing voluntary collaboration from the team.[5]

The Brazilian Tuberculosis Research Network, with support from the Brazilian National Ministry of Health, have conducted a practical clinical trial to evaluate the clinical performance and cost-effectiveness of the use of MGIT 960 at two health care facilities in the city of Rio de Janeiro, Brazil, where the incidence of tuberculosis is high (85/100.000 population). The present study was motivated by the following considerations: the World Health Organization has recommended the use of MGIT 960 for the diagnosis of tuberculosis; to our knowledge, the literature provides no data on the evaluation of the clinical impact of the use of this diagnostic method or on the economic analysis of its use in health care systems[6]; this diagnostic method has not yet been used in the SUS in Brazil. The present study involved inpatients at the *Universidade Federal do Rio de Janeiro* (UFRJ, Federal University of Rio de Janeiro) *Hospital Universitário Clementino Fraga Filho* (HUCFF, Clementino Fraga Filho University Hospital) and outpatients at a secondary care facility—the Rio de Janeiro Municipal Department of Health *Policlínica de Guadalupe* (PG, Guadalupe Polyclinic). A cost-effectiveness analysis is currently under way. Below, we summarize the methodology and preliminary results of the clinical trial. The research project was approved by the UFRJ Research Ethics Committee (Protocol no. 020/07), and the clinical trial is registered with the identifier ISRCTN79888843.

At the two study sites, the main inclusion criterion was suspicion of tuberculosis in over-16-year-olds; those who were already being treated for tuberculosis were excluded. The MGIT 960 system was compared with the traditional method (LJ). The primary outcome was a change in the initial approach (initiation or discontinuation of treatment) within two months after inclusion of the patient in the study. The participants were randomized, and there was no blinding, with the exception of the outcome assessors. Measures were taken to ensure concealment of the randomization.

At the HUCFF and at the PG, respectively, 427 and 266 patients with suspected tuberculosis were randomized between April of 2008 and October of 2010 and between April of 2008 and July of 2009. At both sites, the randomization process was successful in producing groups with similar sociodemographic and clinical characteristics. At the HUCFF, the study population consisted of inpatients, whereas, at the PG, it consisted of outpatients. The mean age of the participants was slightly higher at the HUCFF than at the PG (51 vs. 45), as was the proportion of male participants (55% vs. 50%). In addition, presumptive identification of tuberculosis, performed by an experienced, well-trained nurse at inclusion in the study, was much greater at the HUCFF than at the PG (20% vs. 4%). The preliminary results are shown in Table 1.

Table 1 - Performance comparison between the mycobacteria growth indicator tube 960 system and Löwenstein-Jensen solid medium at the Clementino Fraga Filho University Hospital and at the Guadalupe Polyclinic, Rio de Janeiro, Brazil.[a]

Variable	HUCFF		PG	
	MGIT	LJ	MGIT	LJ
	(n = 214)	(n = 213)	(n = 134)	(n = 132)
Positive smear result	6 (2.8)	10 (4.7)	29 (21.6)	24 (19.0)
Positive culture for *M. tuberculosis*	25 (11.7)	20 (10.0)	38 (28.3)	31 (23.5)
Time to result, days[b]	10.7 ± 5.7 (4-25)	31.7 ± 8.9 (19-49)	10.6 ± 7.0 (2-31)	29.5 ± 8.9 (14-55)

HUCFF: *Hospital Universitário Clementino Fraga Filho* (Clementino Fraga Filho University Hospital); PG: *Policlínica de Guadalupe* (Guadalupe Polyclinic); MGIT: mycobacteria growth indicator tube; and LJ: Löwenstein-Jensen. [a]Values expressed as n (%), except where otherwise indicated. [b]Values expressed as mean ± SD (range).

Some relevant aspects were observed. Sputum smear microscopy was ineffective for the inpatients at the HUCFF, who were, in general, paucibacillary. The results seem to indicate an advantage for the MGIT in the two study sites, given that the reporting of the results to the attending physician occurred sooner. At present, the final analysis of the clinical performance of the tests in terms of patient-centered outcomes (morbidity, mortality, length of hospital stay, unnecessary medication use, and, in patients diagnosed with tuberculosis, bacteriological conversion and pharmacological treatment response) is under way.

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Lung cysts in chronic paracoccidioidomycosis*

Cistos pulmonares na paracoccidioidomicose crônica

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Abstract

On HRCT scans, lung cysts are characterized by rounded areas of low attenuation in the lung parenchyma and a well-defined interface with the normal adjacent lung. The most common cystic lung diseases are lymphangioleiomyomatosis, Langerhans cell histiocytosis, and lymphocytic interstitial pneumonia. In a retrospective analysis of the HRCT findings in 50 patients diagnosed with chronic paracoccidioidomycosis, we found lung cysts in 5 cases (10%), indicating that patients with paracoccidioidomycosis can present with lung cysts on HRCT scans. Therefore, paracoccidioidomycosis should be included in the differential diagnosis of cystic lung diseases.

Keywords: Paracoccidioidomycosis; Cysts; Multidetector computed tomography.

Resumo

Os cistos pulmonares na TCAR são caracterizados por áreas arredondadas de baixo coeficiente de atenuação no parênquima pulmonar com uma interface bem definida com o pulmão adjacente normal. As doenças pulmonares císticas mais comuns são linfangioleiomiomatose, histiocitose de células de Langerhans e pneumonia intersticial linfocítica. Em uma análise retrospectiva de achados de TCAR em 50 pacientes com diagnóstico de paracoccidioidomicose crônica residual, observou-se a presença de cistos pulmonares em 5 casos (10%), mostrando que pacientes com paracoccidioidomicose podem apresentar cistos pulmonares na TCAR. Portanto, essa infecção deve entrar no diagnóstico diferencial das doenças císticas pulmonares.

Descritores: Paracoccidioidomicose; Cistos; Tomografia computadorizada multidetectores.

Lung cysts are rounded, well-circumscribed spaces surrounded by an epithelial or fibrous wall. On HRCT scans, lung cysts are characterized by rounded areas of low attenuation (air content) in the lung parenchyma and a well-defined interface with the normal adjacent lung.[1] The most common cystic lung diseases are lymphangioleiomyomatosis, Langerhans cell histiocytosis, and lymphocytic interstitial pneumonia.[1-3] Paracoccidioidomycosis, however, does not currently feature on the list of differential diagnoses of cystic parenchymal lung diseases.

Paracoccidioidomycosis primarily affects the lung and is the most common systemic mycosis in Brazil.[4-6] Caused by the dimorphic fungus *Paracoccidioides brasiliensis*, chronic paracoccidioidomycosis affects mainly males in their economically productive years (30-60 years of age).[6] Similarly to tuberculosis and histoplasmosis, paracoccidioidomycosis is acquired by inhalation of viable propagules that undergo reactivation in adults, causing the chronic form of the disease, the primary target of which is the respiratory system.[4,7] In infected tissues of immunocompetent individuals, innate immunity induces a granulomatous inflammatory reaction in an attempt to inhibit the proliferation of the fungus and prevent its dissemination to other organs.[8] Tuder et al. described, in addition to the presence of granulomas, dense fibrosis and reticulin fiber proliferation even in areas where there were no granulomas in chronically injured lungs.[9] The chronic form of lung involvement is progressive and typically manifests as a bilateral, diffuse reticulomicronodular interstitial infiltrate on X-rays, correlating with the pathophysiology

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of the disease, which begins in the mediastinal lymph nodes and disseminates to the periphery of the lung via the lymphatic vessels.[4,6,7] Residual parenchymal scarring might be present in more than half of the individuals after antifungal treatment.[10,11] However, to our knowledge, no studies have described the incidence of lung cysts in this condition.

The chest X-ray abnormalities in patients with chronic paracoccidioidomycosis are often multiple and nonspecific, the most common patterns being linear and reticular opacities, nodules of different sizes, ill-defined opacities, air-space consolidation, and cavities.[12,13] In endemic areas, the finding of a "butterfly wing" pattern, with symmetrical opacities in the middle lung regions, associated with emphysema, should suggest that diagnosis.[13] In chronic paracoccidioidomycosis, architectural distortion, paracicatricial emphysema, and bronchiectasis are also common manifestations that reflect the residual fibrotic changes of this disease.[7,10]

Because HRCT allows a more detailed evaluation of the type of lesion, disease extent, and therapeutic response, it has gained popularity in the evaluation of patients with paracoccidioidomycosis.[14] Abnormal HRCT findings occur in more than 90% of patients with chronic paracoccidioidomycosis, and ground-glass opacities, consolidations, nodules, masses, cavities, septal thickening, reversed halo sign, emphysema, and fibrotic changes are reported to be the most prevalent findings. However, despite the epidemiological significance of paracoccidioidomycosis in Latin America, few studies have attempted to describe the chest HRCT findings of this disease.[7,15,16]

According to Funari et al., who studied 42 patients with chronic paracoccidioidomycosis (with or without a history of antifungal treatment), the most common CT findings are interlobular septal thickening (in 88%), nodules (in 83%), traction bronchiectasis (in 83%), peribronchovascular interstitial thickening (in 78%), paracicatricial emphysema (in 68%), centrilobular opacities (in 63%), and intralobular lines (in 59%). These changes are often seen in combination, tend to be bilateral and symmetrical, and involve all lung zones.[7] Gasparetto et al., reviewing 148 HRCT scans from patients with paracoccidioidomycosis, reported the presence of the reversed halo sign in 10% of the patients with active infection with *P. brasiliensis*.[17] Souza et al. evaluated 77 untreated patients and found ground-glass opacities (in 58.4%), centrilobular nodules (in 45.5%), nodules (in 41.6%), parenchymal bands (in 33.8%), cicatricial emphysema (in 33.8%), interlobular septal thickening (in 31.2%), and architectural distortion (in 29.9%). The findings were distributed predominantly in the peripheral region (in 53%) and in posterior regions (in 88%), involving all lung zones.[15] Extrapulmonary findings in the thorax are uncommon and include tracheal, pleural, lymph node, and osseous involvement.[18]

Our study, conducted in the outpatient clinics of the departments of pulmonology and infectious diseases of the University of São Paulo School of Medicine *Hospital das Clínicas*, showed that lung cysts are another possible CT pattern related to paracoccidioidomycosis.

The study was a reanalysis of 50 CT scans from patients who had previously been evaluated from the radiological and functional standpoint.[19] In this reevaluation, the presence of lung cysts, a CT change that had not been described previously, was of note. We studied patients diagnosed with chronic paracoccidioidomycosis and treated for more than six months in whom the skin lesions resolved, microbiological test results were negative, and anti-*P. brasiliensis* antibody titers, as determined by counterimmunoelectrophoresis, were low (< 1:4 or a drop of at least 4 dilutions).[5] Patients with lung cancer or respiratory coinfections (tuberculosis or other chronic infections) were excluded. Of the 50 patients studied, 47 were male and 3 were female. Ages ranged from 33 to 73 years (mean, 56.9 ± 9.7 years). In all patients, the diagnosis was confirmed by microbiological analysis (direct visualization or culture of the lesions) or by histopathology. The study and the content of the consent form were approved by the Ethics Committee for the Analysis of Research Projects of the Clinical Board of the University of São Paulo School of Medicine *Hospital das Clínicas* (Protocol no. 870/06). All study participants gave written informed consent.

The HRCT scans were obtained with a Philips Brilliance CT 40 multislice scanner (Philips Medical Systems, Cleveland, OH, USA) by using the following parameters: collimation, 8 × 3; increment, 1.6 mm; rotation time, 0.75; voltage, 120 Kv; amperage, 150 mAs/image; and a 7.5-mm reconstruction interval with 7.5-mm increments. Fifty-seven 7.5-mm CT slices and two hundred and ten

3.3-mm slices were obtained. Image slices at maximum inhalation and maximum exhalation were obtained for all patients. The changes were classified in accordance with the latest Brazilian Thoracic Association guidelines.[1] All analyses were independently performed by a radiologist specializing in chest CT and by a pulmonologist specializing in interstitial diseases, both of whom were blinded to the clinical data of the patients. In cases of disagreement, the final results were obtained by consensus.

Lung cysts were found in 5 cases (10% of the patients): in 1 of the cases, there was a single cyst in the right lower lobe; and in the other 4, there were two or more parenchymal cysts with no preferential location (Figure 1).

The clinical and demographic characteristics, as well as the number of lung cysts, of the 5 patients are shown in Table 1.

The present study is, to our knowledge, the first to describe the presence of parenchymal cysts in patients with chronic paracoccidioidomycosis.

Multiple mechanisms can explain the formation of cysts in various lung diseases. These mechanisms would include vascular occlusion followed by ischemia and necrosis, bronchial dilatation, smooth muscle cell proliferation, and even a check-valve mechanism in small airways, which, because of inflammatory cell infiltration and subsequent centrilobular fibrosis, would lead to bronchial obstruction and dilatation downstream of the lesion.[2,3,20] It can be speculated that, in paracoccidioidomycosis, centrilobular fibrosis, with involvement of the small airways and small vessels[9,16] would cause bronchial obstruction and distal airway dilatation, similarly to the check-valve mechanism identified in bronchiolitis.[21] Another possible explanation would be the presence of peribronchial nodules or granulomas associated with mycosis, promoting dilatation of a small airway, with the consequent formation of lung cysts, similarly to what is observed in Langerhans cell histiocytosis.[2,3] Another plausible explanation would be that the cysts or pneumatoceles would result from an inflammatory process leading to central necrosis and elastic recoil of the adjacent lung tissue, with localized air expansion, whether in the airways or in the lung interstitium, as occurs in other infectious diseases, such as staphylococcal pneumonia.[3]

Finally, we must consider the high level of smoking in the study population, which would

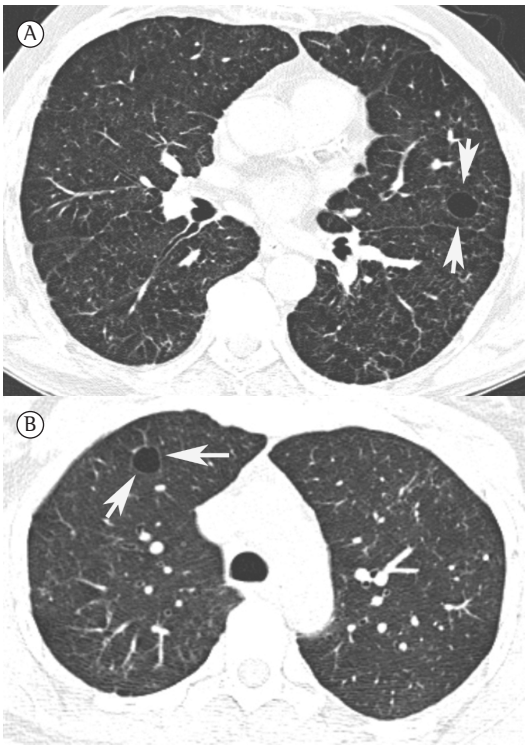

Figure 1 - HRCT scans. In A, HRCT scan slice at the level of the aortic arch showing a thin-walled cyst in the right lung of a 41-year-old female patient (arrows). Also note faint reticular and nodular opacities in the lung, which are probably residual in nature. In B, HRCT scan slice at the level of the lower lobes showing a thin-walled cyst in the left lung of a 68-year-old male patient (arrows). Note the presence of faint reticular opacities predominantly in the posterior regions.

Table 1 - Clinical and demographic characteristics, as well as number of lung cysts, of the patients studied.[a]

Variable	Result
Age, years	55.0 ± 9.2
Body mass index, kg/m^2	23.9 ± 3.6
Current or former smoking[b]	5 (100)
Active smokers[b]	3 (60)
Smoking history, pack-years	46.6 ± 30.9
Treatment duration, months	16.7 ± 8.5
CIE, titration[c]	1:2 (0-1:4)
Lung cysts, n	
Patient 1	2
Patient 2	3
Patient 3	1
Patient 4	multiple
Patient 5	multiple

CIE: serology with counterimmunoelectrophoresis. [a]Values expressed as mean ± SD, except where otherwise indicated. [b]Values expressed as n (%). [c]Value expressed as median (interquartile range).

make it possible to attribute the formation of the cysts to a smoking-related disease, such as Langerhans cell histiocytosis and desquamative interstitial pneumonia. However, no other characteristics related to the cysts and suggesting those diagnoses were found on the HRCT scans from those 5 patients.

In conclusion, patients with chronic paracoccidioidomycosis can present with lung cysts on HRCT scans. Therefore, paracoccidioidomycosis should be included in the differential diagnosis of cystic lung lesions.

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Smoke inhalation injury during enclosed-space fires: an update*

Lesão por inalação de fumaça em ambientes fechados: uma atualização

Ana Carolina Peçanha Antonio, Priscylla Souza Castro, Luiz Octavio Freire

Abstract

In view of the tragic fire at a nightclub in the city of Santa Maria, Brazil, which culminated in the sudden death of 232 young people, we decided to review the literature regarding smoke inhalation injury caused by enclosed-space fires, which can be divided into direct thermal damage, carbon monoxide poisoning, and cyanide poisoning. Such injuries often call for immediate orotracheal intubation, either due to acute airway obstruction or due to a reduced level of consciousness. The diagnosis and the severity of the thermal injury can be determined by fiberoptic bronchoscopy. The levels of gases and gas by-products in the bloodstream should be assessed as rapidly as possible, even while still at the scene of the incident. First responders can also treat carbon monoxide poisoning, with immediate administration of oxygen at 100%, as well as cyanide poisoning, with oxygen therapy and hydroxocobalamin injection.

Keywords: Smoke inhalation injury; Carbon monoxide; Cyanides.

Resumo

Aproveita-se o trágico incêndio ocorrido em uma boate na cidade de Santa Maria, RS, que culminou na morte imediata de 232 jovens, para revisarmos a literatura com relação à lesão por inalação de fumaça em ambientes fechados, que pode ser dividida em dano térmico direito, intoxicação por monóxido de carbono e intoxicação por cianeto. Essas condições frequentemente levam à necessidade de intubação orotraqueal imediata, seja por obstrução aguda de vias aéreas, seja por depressão do nível de consciência. O diagnóstico e a gravidade da injúria térmica podem ser determinados pela fibrobroncoscopia. Quanto aos envenenamentos, a dosagem dos gases ou de seus subprodutos na corrente sanguínea é possível e deve ser realizada ainda na cena do incidente. Da mesma maneira, o tratamento da intoxicação por monóxido de carbono consiste na administração imediata de oxigênio a 100%, enquanto o da intoxicação por cianeto consiste em oxigenoterapia e hidroxicobalamina injetável como antídoto.

Descritores: Lesão por inalação de fumaça; Monóxido de carbono; Cianetos.

Introduction

In the early hours of January 27, 2013, 232 young adult victims died immediately during the fire at a nightclub in the city of Santa Maria, Brazil. Of the survivors, 88 were admitted to the ICU with severe smoke inhalation injury (SII) and varying percentages of total body surface area (TBSA) burned, as well as with other injuries, most of which were of moderate severity. This was the second largest fire death toll in the history of Brazil. The health care facilities in the state of Rio Grande do Sul joined forces in order to optimize victim assistance, meeting with international authorities periodically in order to exchange experiences. In view of these facts, it is necessary to review and update the literature regarding adults with SII caused by enclosed-space fires, including direct thermal damage to the airways, hydrogen cyanide (HCN) poisoning, and carbon monoxide (CO) poisoning.

In a model to estimate burn-related mortality, SII, together with age > 60 years and > 40% TBSA burned, is an independent factor for mortality. In the presence of only one of those factors, the burn mortality rate is 3%, increasing to

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33% and 90%, respectively, when two and all of those factors are present.[1]

It is impossible to predict the pathophysiological interactions of all toxins produced by smoke, especially if we consider the wide variety of pyrolysis components and the unpredictable rate of by-product formation, depending on the temperature, area, and composition of the environment. During a fire, the concentration of oxygen (O_2) typically drops to 10-15%, at which point death from asphyxia occurs.[2,3] Between 60% and 80% of all sudden deaths occurring at the scene of a fire are attributed to smoke inhalation.[4] The classic scenario is an enclosed-space fire, with loss of consciousness in the presence of facial burns or large TBSA burns.[5]

Didactically, SIIs can be classified into three types: 1) upper airway thermal injury involving the mouth, oropharynx, and larynx; 2) lower airway and parenchymal injury caused by chemicals and particulate matter originating from smoke; and 3) metabolic asphyxiation, whereby certain smoke constituents impede tissue O_2 delivery, tissue O_2 consumption, or both.[5] The immediate management of SII victims should focus primarily on the ABCDE of trauma.[3]

For thermal injury itself, we searched the Medline database using the following search strategy: "Smoke Inhalation Injury"(Mesh) AND ("2003/02/14"(PDat) : "2013/02/10"(PDat) AND "humans"(MeSH Terms) AND English(lang) AND "adult"(MeSH Terms). A total of 127 references were retrieved. After having read the titles and abstracts, we excluded 97 references, because they were outside the scope of the present review. For CO poisoning, we used the following strategy: "Carbon Monoxide Poisoning"(Mesh) AND "Burns"(Mesh) AND ("2003/02/28"(PDat) : "2013/02/24"(PDat) AND "humans"(MeSH Terms) AND English(lang). A total of 34 references were retrieved. After having read the abstracts, we excluded 28 of those references because the settings of the studies in question were other than fires. For HCN poisoning, we used the following search strategy: (english(Language) AND ("2001"(PDAT) : "2013"(PDAT))) AND (("burns"(MeSH Terms) OR "burns"(All Fields)) AND ("cyanides"(MeSH Terms) OR "cyanides"(All Fields) OR "cyanide"(All Fields)) AND ("poisoning"(Subheading) OR "poisoning"(All Fields) OR "poisoning"(MeSH Terms)) AND ("therapy"(Subheading) OR "therapy"(All Fields) OR "treatment"(All Fields) OR "therapeutics"(MeSH Terms) OR "therapeutics"(All Fields))). A total of 24 references were retrieved. After having read the abstracts, we excluded 8 of those references because the studies in question did not involve adult burn patients in a hospital setting. Subsequently, we included some specific review articles on the topics of interest.

Airway inhalation injury

Upper airway inhalation injury resulting in obstruction within the first 12 h after the incident is caused by direct thermal damage, chemical irritation, or both. The resulting pathophysiological changes are not due to the burn per se; the smoke itself, which is far more capable of carrying heat than is dry air, can overwhelm the ability of the upper airways to dissipate extreme heat. Nor is the carbonaceous material present in the smoke able to damage the lung parenchyma, although it can serve as a vehicle for other damaging agents.

Up to one third of all SII victims can present with acute upper airway obstruction.[6] Direct thermal injury to the face and airways is always indicative of a difficult airway; however, prophylactic establishment of a definitive airway is not mandatory in such cases. Ideally, all victims suspected of having inhaled smoke should undergo fiberoptic bronchoscopy in order to determine whether the laryngeal edema is severe enough and whether there is injury below the glottis. A retrospective study conducted in a burn referral center evaluated 41 patients, 8 of whom underwent orotracheal intubation (OTI), and showed a high correlation between the need for OTI and the presence of facial burns and soot in the oral cavity but no correlation between the need for OTI and the classic signs and symptoms, i.e., stridor, dysphonia, dysphagia, and sialorrhea.[7] Nevertheless, prophylactic OTI is recommended for all patients with extensive burns, i.e., those with more than 40% TBSA burned.[5]

Fiberoptic bronchoscopy is the gold standard for the diagnosis of airway inhalation injury. In addition, fiberoptic bronchoscopy is often used for airway hygiene, removing particulate matter, mucus plugging obstructing bronchi, and the large quantity of inflammatory secretion that forms because of cellular necrosis (Figure 1).[5,6] Furthermore, fiberoptic bronchoscopy can predict the evolution of patients from a respiratory standpoint. Bronchoscopic grading through the abbreviated injury score (AIS), whereby thermal

injury to the airway is classified as 0 (no injury), 1 (mild injury), 2 (moderate injury), 3 (severe injury), or 4 (massive injury), was associated with decreased PaO_2/FiO_2 within the first 24 h after ICU admission in a retrospective cohort of 32 patients with extensive burns.[8] Another study showed that, in patients with extensive burns, a higher AIS at admission correlated with a longer duration of mechanical ventilation (a median of 3 days for grade 0 and of 23 days for grade 4), a trend toward a greater frequency of tracheostomy, and a longer ICU stay.[9] A retrospective cohort study showed an absolute reduction of 27% in survival in patients with an AIS of 2-4 in comparison with those with an AIS of 0 or 1.[10]

Classically, imaging tests such as chest X-rays and CT scans have little or no value in the diagnosis of SII.[5,6] A retrospective analysis of 44 patients admitted to a burn referral center showed that chest CT scans taken within the first 24 h after admission have prognostic value in predicting the composite outcome of pneumonia, ARDS, and death.[11]

Serial repetition of fiberoptic bronchoscopy after the diagnosis has been established remains controversial among experts. In the literature, there are no prospective or intervention studies specifically examining this issue. In the USA, a study of 624 patients with SII receiving different treatment regimens showed no conclusive (statistically significant) results regarding the aggressive use of fiberoptic bronchoscopy, although there seemed to be a slight trend toward shorter hospital stays in those who underwent more than one procedure during their hospital stays.[12]

Appropriate fluid resuscitation is the cornerstone of treatment of patients with extensive burns.[13] However, in the literature, conflicting opinions exist regarding the presence of concomitant SII, which are due to the fear that significant worsening of lung compliance might lead to irreversible hypoxemia.[5] Nevertheless, a retrospective cohort study showed that the presence of SII increases the need for fluid resuscitation by approximately 34%.[14] One group of authors found no correlation between increased fluid requirements and the AIS, i.e., the severity of the initial injury.[10]

The management of patients with thermal injury to the airways is basically supportive. As

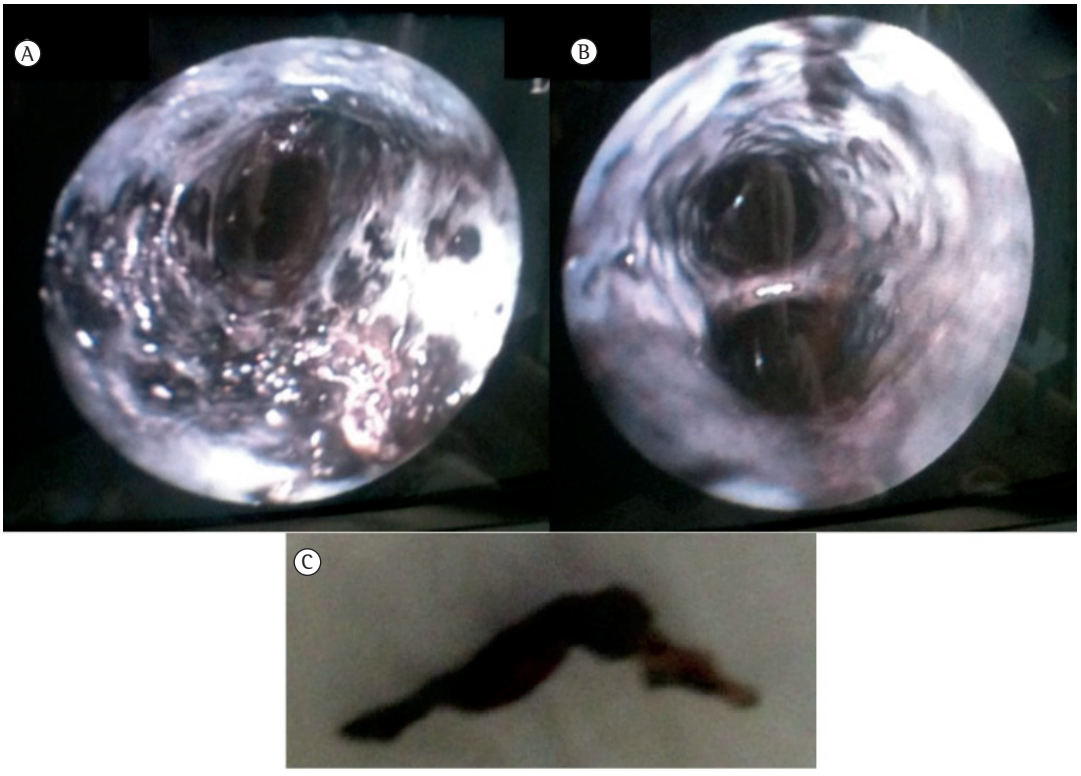

Figure 1 - In A and B, severe thermal injury in a patient with extensive burns. In C, particulate matter extracted from the airway.

in any other context, a protective ventilatory strategy is recommended, with a tidal volume of 4-8 mL/kg of predicted weight and a plateau airway pressure of less than 30 cmH_2O. No other strategy is recommended.[13]

When high-frequency oscillatory ventilation was used as a rescue therapy for patients who developed ARDS after extensive burns, the group of patients with airway inhalation injury showed a poor response, showing prohibitive levels of hypercapnia, possibly due to the impossibility of nebulizer use.[15] A randomized clinical trial comparing protective ventilation and high-frequency oscillatory ventilation in a sample of 62 patients with extensive burns, in whom the prevalence of SII was 37%, showed no differences between the two groups regarding the primary outcome measure "number of ventilator-free days"; however, the need for rescue ventilation was more common in the group of patients receiving low tidal volume ventilation.[16] A quasi-experimental trial including 18 patients with severe ARDS (12 of whom had SII) showed that prone positioning improves oxygenation.[17] Finally, a meta-analysis of the use of extracorporeal membrane oxygenation in burn patients with varying degrees of airway involvement concluded that the current literature is insufficient to support or oppose the use of the technique in such patients.[18]

In a case series of 37 patients with SII, noninvasive mechanical ventilation was used as initial ventilatory support; 6 patients (16.2%) required emergency OTI, and another 16 (43.7%) subsequently required invasive mechanical ventilation over the course of 29 days of follow-up. The mortality rate in the case series was 13.5%. The authors concluded that noninvasive ventilation can be used as initial ventilatory support in patients with SII provided that they are conscious and hemodynamically stable.[19]

Thermal injury triggers an intense inflammatory reaction in the airways, with activation of procoagulant factors and release of oxygen free radicals. This explains the close association between thermal injury and the development of ARDS. One of the first studies to evaluate the therapeutic role of inhaled heparin and N-acetylcysteine in adults retrospectively analyzed 62 patients who had received the combination therapy during the first 72 h of admission and concluded that, although there was an improvement in the PaO_2/FiO_2 ratio, the therapy had no long-lasting effect and did not affect clinical outcomes, which did not differ between the treated and untreated groups.[20] However, a population-based nested case-control study conducted in the following year showed significant improvements in hypoxemia and lung compliance in the group receiving the combination therapy, as well as showing a significant reduction in mortality even after 150 days of follow-up, the number needed to treat being 3.[21] A systematic review of 11 experimental studies and 3 clinical studies recommended the use of nebulized heparin in patients with thermal injury to the airways, on the basis of improved survival and a higher number of ventilator-free days.[22]

Pneumonia is one of the most common complications of SII, its incidence being approximately 30%,[23-25] particularly in patients over 60 years of age, those with more than 20% TBSA burned, those with an AIS above 3, and those with CO poisoning and hypoxemia at presentation.[25] Prevention and treatment strategies are similar to those employed in the management of nosocomial pneumonia.

As in any other critically ill patient, early extubation is recommended. The timing of tracheostomy has yet to be well established; however, some authors have suggested that tracheostomy be performed within up to 7 days after initiation of mechanical ventilation.[26]

Long-term follow-up of 52 patients who were victims of a fire in a subway station in Korea in 2003 showed significant improvements in FVC and FEV_1 within 3 months after the incident and complete remission in the following 3 months, the small group of patients receiving corticosteroid therapy having shown no improvement.[27]

CO poisoning

It is known that CO is an asphyxiant, colorless, odorless, tasteless, and non-irritating gas,[28] which is produced by the incomplete combustion of hydrocarbons.[29,30] Its concentration in the atmosphere is generally less than 0.001%.[31] A CO concentration of only 1% is enough to cause serious injury because CO is rapidly absorbed by the pulmonary epithelium and has high affinity for hemoglobin,[30] which can be 200-250 times higher than that of O_2.[31] Of all SII-related deaths, CO poisoning accounts for 80%, and most occur within the first 24 h after exposure.[32]

Carboxyhemoglobin (COHb) is an extremely stable complex, and COHb production decreases oxyhemoglobin saturation and shifts the hemoglobin dissociation curve to the left, reducing the release of O_2 to tissues.[31,33] In addition, competitive inhibition with the cytochrome oxidase complex, principally P-450, prevents the use of O_2 to generate energy.[34] Additional mechanisms include CO binding to myoglobin, impairing O_2 storage in muscle, and brain lipid peroxidation.[35] Brain lipid peroxidation after CO exposure is similar to post-ischemic reperfusion and is mediated by changes in cerebral blood flow and oxidative damage by free radicals.[33]

As is the case for most toxins, the extent of the injury caused by CO poisoning depends on the CO concentration, exposure duration, and comorbidities in the exposed individual.[35] The clinical symptoms of CO poisoning are nonspecific and suggestive of many differential diagnoses. Patients can present with tachycardia and tachypnea as compensatory mechanisms for cellular hypoxia. Headache, nausea, and vomiting are common symptoms. Syncope, presyncope, and convulsions result from cerebral vasodilation and cellular hypoxia and can also cause brain edema. Angina, acute pulmonary edema, and arrhythmias can result from the increased cardiac output that follows. Patients with cardiovascular disease and those with lung disease can experience symptom exacerbation. The classic findings of cherry-red lips, cyanosis, and retinal hemorrhages are rare.[31]

Many exposed individuals show no acute signs of cerebral involvement; however, delayed neuropsychiatric sequelae have been described and can occur within 3-240 days after exposure. The estimated incidence is 10-30%. Cognitive changes, personality changes, Parkinsonism, agnosia, apraxia, incontinence, dementia, and psychosis have been reported and can persist for one year or more. In such patients, cranial CT and magnetic resonance imaging can show characteristic changes, which include bilateral necrosis of the globus pallidus, cerebral cortex, hippocampus, or substantia nigra.[29,31,33]

The diagnosis of CO poisoning is based on a history of CO exposure and on consistent physical examination findings.[28] It is possible to measure COHb levels by co-oximetry of a blood sample.[33] Pulse oximetry cannot distinguish between COHb and oxyhemoglobin at the wavelengths that are commonly employed by most devices.

The severity of the symptoms appears to correlate better with exposure duration than with COHb levels. These values can be low or even undetectable depending on the time elapsed between exposure and measurement.[28,30,31] The levels of COHb do not predict the degree of neurological sequelae.[28] Nonsmokers rarely present with COHb levels above 1.5%, whereas smokers can present with COHb levels as high as 5%. Levels of COHb above 10-15% are consistent with CO poisoning.[33]

After the diagnosis of CO poisoning has been confirmed, electrocardiography is recommended. A more detailed assessment, with measurement of cardiac biomarkers, is warranted in patients with electrocardiographic changes, those with symptoms suggestive of myocardial ischemia, those over 65 years of age, and those with a history of or risk factors for heart disease.[29,36,37]

Most patients can be evaluated and treated as outpatients. Hospitalization should be considered for patients with severe poisoning, severe comorbidities, or associated injuries.[31]

The treatment of CO poisoning is based on O_2 supplementation, ventilatory support, and cardiac monitoring.[29] In cases of CO poisoning, O_2 plays a role in increasing gas exchange reserve, reversing the effect of hypoxic gas inhalation, and in dissociating CO from its binding sites.[34] Patients with CO poisoning should receive O_2 therapy at high concentrations (ideally at 100%) for 6-12 h, because this reduces the half-life of CO.

The mean half-life of COHb is 320 min in young healthy volunteers ventilated on room air. The administration of O_2 at 100% and 1 atm reduces the half-life of COHb to 80.3 min, whereas the administration of O_2 at 3 atm reduces the half-life of COHb to 23.3 min.[29] Hyperbaric O_2 therapy (HBOT) is recommended by most toxicologists when COHb levels are higher than 25. Ideally, HBOT should be initiated within 6 h after CO exposure, and there is no proven benefit for patients receiving HBOT more than 12 h after CO exposure. However, HBOT is not widely available or risk-free.[29,31,33] There are 7 randomized clinical trials comparing HBOT and normobaric O_2 therapy. Those studies were examined in a systematic review, and, to date, there has been no conclusive evidence that HBOT reduces the incidence of neurological sequelae; in addition to have yielded conflicting results,

those studies are highly heterogeneous in terms of design, methodology, protocol, study population, and analysis.[35,38]

Data regarding the prognosis of patients with CO poisoning are inconclusive and contradictory. Approximately 30% of all patients with severe CO poisoning can have a fatal outcome. Indicators of poor prognosis include altered state of consciousness at presentation, advanced age, underlying cardiovascular disease, metabolic acidosis, and structural abnormalities on CT scans or magnetic resonance images.[29]

HCN poisoning

A highly volatile compound, HCN is formed by the incomplete combustion of carbonaceous and nitrogenous materials during a fire, including cotton, silk, wood, paper, plastics, sponges, acrylics, and synthetic polymers in general.[4,39] In addition, the recycling of pyrolysis products in enclosed spaces increases the rate of HCN formation, and the lack of ventilation in the environment can increase that rate by up to 10 times.[4]

Notable for its ability to bind to iron ions, HCN is carried through the bloodstream by red blood cells. In the intracellular environment, HCN binds to the enzyme cytochrome c oxidase a, completely blocking the respiratory cycle and, consequently, the formation of ATP. Therefore, profound lactic acidosis occurs, death occurring within minutes after exposure to large doses.[3,4,40]

After being absorbed, HCN rapidly disappears from the bloodstream, its alpha half-life ranging from 1 h to 3 h, its beta half-life being 44 h, and its peak concentration being difficult to measure.[3] Therefore, a blood sample should be obtained as early as possible, even while still at the scene of the accident, and treatment should be initiated before laboratory test results are known, the results being released within 2 h, on average.

The diagnosis of HCN poisoning remains a challenge and is essentially based on a high clinical suspicion. The initial manifestations reflect respiratory and neurological stimulation resulting from the blockade of cellular respiration, including hyperventilation, headache, nausea, vomiting, palpitations, and anxiety. Subsequently, convulsions, bradycardia, and hypotension occur, culminating in respiratory arrest and cardiovascular collapse.[4,40] Because very few patients survive, reports of neurological sequelae are rare. However, mild CO poisoning is recognized as a cause of permanent neurological injury, ranging from extrapyramidal manifestations of varying intensity to a persistent vegetative state progressing over the years.[40]

Serum HCN concentrations above 0.5 mg/L are related to acute poisoning.[39] There is some correlation between serum HCN levels and symptom severity; in general, serum levels of 0.5-1 mg/L are mild, serum levels of 2-3 mg/L are moderate, and serum levels above 3 mg/L are lethal.[4]

Plasma lactate concentrations above 90 mg/dL or 10 mmol/L correlate with HCN poisoning.[3,4] A small case series of patients with HCN poisoning unrelated to smoke inhalation showed that serum lactate levels above 8 mmol/L have a sensitivity of 94%, a specificity of 74%, a positive predictive value of 98%, and a negative predictive value of 98% for predicting serum HCN levels > 1 mg/L.[41] A reduced arterial-venous O_2 difference is also observed, being generally lower than 10 mmHg, which explains the absence of cyanosis. Because there is no correlation between COHb levels and HCN levels, it is impossible to predict concomitant poisoning.[4]

For decades, a cyanide antidote kit was available in the USA and consisted of a combination of three drugs, namely inhaled amyl nitrite, intravenous sodium nitrite (both drugs being capable of generating methemoglobin, which diverts HCN from the mitochondrial cytochrome), and intravenous sodium thiosulfate for 30 min (which binds to free HCN via the enzyme rhodanese and forms thiocyanate, which is cleared by the kidneys). The kit has a slow onset of action and causes hypotension, as well as inducing methemoglobinemia, which can be harmful to smoke inhalation victims with suspected CO poisoning.[39]

According to a European expert consensus published in 2012[4] and a North American review of prehospital care,[3] the drug of choice for the treatment of patients with suspected HCN poisoning is hydroxocobalamin, a drug that has recently been made available by the Ministry of Health, which binds to HCN to form cyanocobalamin, which is excreted in urine. Hydroxocobalamin is a drug with a rapid onset of action, reaching therapeutic levels in the cerebrospinal fluid within approximately 30 min after administration. Minor adverse effects have been reported, including hypertension, reflex bradycardia, and urticaria-like rashes, as well as

reddish skin and urine.[40] In a prospective cohort study, the preemptive use of hydroxocobalamin (5 g diluted in 100 mL of distilled water and infused for 15-20 min, with the possibility of repeating the same dose in cases of coma or persistent hemodynamic instability) resulted in the survival of 67% of the patients with HCN poisoning from smoke inhalation.[42]

The role of HBOT in the adjunctive treatment of concomitant CO and HCN poisoning is controversial. The physiological rationale is based on a greater induction of nitric oxide formation in the bloodstream, nitric oxide competing with HCN for the binding to the enzyme cytochrome c oxidase a.[40] A quasi-experimental study showed no reduction in blood concentrations of HCN after HBOT in SII victims.[43]

It is recommended that all SII victims presenting with a decreased level of consciousness (Glasgow coma scale score ≤ 13) or signs of hemodynamic instability and respiratory failure be empirically treated with hydroxocobalamin in a prehospital environment. In cases of cardiac arrest attributed to HCN poisoning, it is possible to administer a double dose immediately or repeat the standard dose. When referred to the emergency room, patients for whom the antidote was not initially indicated but who show elevated levels of lactate during a 2-h observation period should also receive the antidote.[4] Patients diagnosed with brain death due to HCN poisoning are candidates for organ donation.[3]

Final considerations

Enclosed-space fires should raise the suspicion of SII associated with loss of consciousness, facial burns, and large TBSA burns. Treatment is basically supportive, consisting of immediate O_2 therapy, rapid administration of an antidote, and protective mechanical ventilation. The use of inhaled heparin in victims of thermal injury is recommended by some experts. In such patients, the use of HBOT is highly controversial, as is the use of additional ventilation modes. In addition to immediate management, individuals with SII should be extubated as soon as possible, and attention should be paid to the possibility of early tracheostomy.

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Pneumothorax as a complication of lung volume recruitment*,**

Pneumotórax como complicação associada ao recrutamento do volume pulmonar

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Abstract

Lung volume recruitment involves deep inflation techniques to achieve maximum insufflation capacity in patients with respiratory muscle weakness, in order to increase peak cough flow, thus helping to maintain airway patency and improve ventilation. One of these techniques is air stacking, in which a manual resuscitator is used in order to inflate the lungs. Although intrathoracic pressures can rise considerably, there have been no reports of respiratory complications due to air stacking. However, reaching maximum insufflation capacity is not recommended in patients with known structural abnormalities of the lungs or chronic obstructive airway disease. We report the case of a 72-year-old woman who had poliomyelitis as a child, developed torsion scoliosis and post-polio syndrome, and had periodic but infrequent asthma attacks. After performing air stacking for 3 years, the patient suddenly developed a pneumothorax, indicating that this technique should be used with caution or not at all in patients with a known pulmonary pathology.

Keywords: Barotrauma; Pneumothorax; Insufflation.

Resumo

O recrutamento do volume pulmonar envolve técnicas de insuflações pulmonares profundas para se atingir a capacidade de insuflação máxima em pacientes com fraqueza da musculatura respiratória, a fim de aumentar o pico de fluxo da tosse e assim auxiliar a manutenção da patência de vias aéreas e melhorar a ventilação. Uma dessas técnicas é o empilhamento de ar, na qual se utiliza um ressuscitador manual para insuflar os pulmões. Embora as pressões intratorácicas possam aumentar consideravelmente, não há relatos de complicações por empilhamento de ar. Entretanto, atingir a capacidade de insuflação máxima não é recomendado em pacientes com anormalidades na estrutura pulmonar ou doença obstrutiva crônica das vias aéreas. Relatamos o caso de uma paciente de 72 anos que teve poliomielite quando criança, desenvolveu escoliose de torção e síndrome pós-pólio e tinha exacerbações de asma periódicas, mas infrequentes. Após realizar empilhamento de ar por 3 anos, a paciente subitamente desenvolveu pneumotórax, mostrando que essa técnica deve ser utilizada com cuidado ou não ser utilizada por pacientes com patologia pulmonar conhecida.

Descritores: Barotrauma; Pneumotórax; Insuflação.

Introduction

Lung volume recruitment (LVR) is a dynamic physiologic process used to reopen collapsed aveoli; augment voice volume and duration; prevent (micro)atelectasis; preserve or improve respiratory compliance; and augment cough flows to facilitate continued use of noninvasive ventilation (NIV). When deeply insufflated air volumes are followed by coughing, cough flows can be greatly increased, facilitating the expulsion of bronchial secretions. In patients with decreased respiratory muscle function due to neuromuscular disease or chest wall deformity, air stacking has been recommended as a method for deep lung insufflation (Chart 1). With this technique, a manual resuscitator is used to deliver volumes of air that the glottis holds to volumes greater than VC until the maximum insufflation capacity (MIC) is reached.[1] The intrathoracic pressures are thereby elevated. Despite sometimes achieving transpulmonary pressures of 80 cmH_2O,[2,3] the

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Chart 1 - Recommendations and complications for air stacking/deep passive lung insufflation.

Reference	Prerequisites	Indications	Relative contraindications[a]	Complications
Toussaint et al.[7]	Clinical stability; ability to follow directions	VC > 0.558 L and MEP > 11 cmH_2O to increase PCF ≥ 3 L/s with AS[b]	Tracheostomy; bulbar weakness[c]; history of pneumothorax; symptomatic low cardiac output	None mentioned
Bach et al.[3,8]	No cognitive impairment; adequate patient cooperation	Indicated for all NMD patients with diminishing VC; VC < 70% of predicted	Primary lung and airway disease; medical instability (e.g. tachypnea)	No barotrauma or other complications reported—over 1,000 patients in the last 28 years
Dwight et al.[4]				Duodenal rupture (LI with one-way valve)
Sancho et al.[9]		PCF < 4.25 L/s		None mentioned
Tzeng et al.[10]	Dedicated care provider	VC < 1.5–2.0 L or < 50% of predicted; PCF < 4.5 L/s	Chronic lung disease[d]; substance abuse; pulmonary emphysema; bronchiectasis	None mentioned

PCF: peak cough flow; AS: air stacking; LI: lung insufflation; NMD: neuromuscular disease. [a]Exclusion criteria in the studies. [b]VC and MEP of at least 0.56 L and 11 cmH_2O, respectively, are mandatory to elevate PCF > 3 L/s using AS. [c]AS cumbersome or impossible; passive lung insufflation remains feasible, according to Bach et al.[8] [d]Defined as chronic abnormalities in chest X-ray and SpO_2 < 95% or FEV_1/FVC ratio two standard deviations less than normal.

technique is considered to be safe, because complications have been seldom reported.[4,5] We report the case of a chronically ventilator dependent patient who presented with severe respiratory distress almost a day after she experienced acute chest pain and dyspnea while stacking air. We discuss the findings and the possible consequences of management, as well as suggest future recommendations.

Case report

A 72-year-old woman who had poliomyelitis as a child developed scoliosis and post-polio syndrome, which led to chronic respiratory failure at age 54. She had been on nocturnal ventilatory assistance for 15 years, resulting in normal blood gases during the day. She had a history of bronchial asthma and a 20 pack-year smoking history, having quit smoking 30 years prior. Because of ineffective peak cough flows registered in 2005, she was taught how to stack air. Thus, she gradually improved her assisted as well as her spontaneous peak cough flows (PCF, Table 1). After having used air stacking uneventfully for nearly 3 years, the patient suddenly experienced a sharp pain during deep inflation one morning in June of 2008. The pain, which was located in her back and on her right side, was accompanied by acute dyspnea. She began ventilation earlier that evening to alleviate dyspnea. The following morning, she was referred to the emergency room and presented with worsening respiratory distress. She required emergent intubation and invasive ventilation before a diagnostic work-up could be initiated. Subsequently, blood gas analysis results were as follows: pH, 6.99; $PaCO_2$, 127.5 mmHg; bicarbonate, 29.0 mmol/L; base excess, −8.4 mmol/L; PaO_2, 101.3 mmHg; and SaO_2, 92%. A chest X-ray revealed right-sided pneumothorax (Figure 1). Immediately after chest tube drainage her respiratory distress resolved and she was successfully extubated. In order to minimize pleural air leakage during positive pressure ventilation, we considered to temporarily discontinue nocturnal NIV, but she could not tolerate sleeping without NIV. Four days later, the lung had completely expanded and talcum pleurodesis was performed. After healing of the pleurodesis (16 days later) the patient was oxygen dependent during spontaneous breathing and she was discharged home on long-term oxygen therapy for 15 hours daily. During nocturnal NIV the use of oxygen was not indicated. The patient discontinued air stacking.

Nine months later (April 1st, 2009), the patient visited the outpatient clinic. She was slightly

Table 1 - Lung volume recruitment and pulmonary function during admissions due to asthma exacerbation.

Variables, 1991-2009	1991	1994 (3 mo. after the start of NIV)		2006	2008 (1.5 mo. before the incident)	April 1, 2009
Pulmonary function						
VC, L (%)	1.00 (37)	1.32 (49)		1.2 (51)		
FEV_1, L (%)	0.70 (30)	0.92 (41)		0.6 (34)		
Albuterol	0.80 (34)			0.7 (38)		
FEV_1/VC, %	70	70		51		
Albuterol, %	78			58		
TLC, L (%)	3.00 (65)	3.38 (74)		3.47 (77)		
ITGV, L (%)	2.30 (90)			2.53 (99)		
Raw, $kPa.L^{-1}.s$ (n)	0.56 (0.3)	0.57 (0.3)				
Blood gas analysis	arterial	arterial		capillary	capillary	capillary
pH	7.37	7.39		7.40	7.42	7.44
PCO_2, mmHg	52	48.0		45	44	51
Bic, mmol/L	31	30		27.9	28.0	31.6
PO_2, mmHg	52	61		61	61	59
SO_2, %	85	90		91	91	90
SpO_2, %				95	94	93
Variables, 2004-2009	2004	2005		2006	2007	2009
LVR-related measurements		(prior to the start of AS)	(3 mo. after the start of AS)			
PCF unassisted, L/s	2.20	2.25	2.50	3.08	2.83	--
PCF after MIC, L/s		2.75	3.50	4.08	4.00	--
RR, min^{-1}		16	18	22	16	20-24

mo.: months; NIV: noninvasive ventilation; incident: acquisition of pneumothorax; ITGV: intrathoracic gas volume; Raw: airway resistance; Bic: bicarbonate; PCO_2: carbon dioxide tension; PO_2: oxygen tension; SO_2: oxygen saturation; LVR: lung volume recruitment; PCF: peak cough flow; and MIC: maximum insufflation capacity.

hypercapnic, without wheezing, and used O_2 1 L/min during spontaneous respiration (Table 1). The patient did not report having experienced chest pain, backache, or sudden dyspnea.

Discussion

To our knowledge, this is the first report of pulmonary barotrauma/volutrauma caused by LVR using air stacking. Although it seems prudent to avoid LVR when patients have a history of recent pneumothorax, pulmonary emphysema, or bronchiectasis, barotrauma and volutrauma have seldom been reported as complications of air stacking. We identified only one report of intestinal barotrauma as a complication of passive lung insufflation via a manual resuscitator with a one-way valve in a nine-month-old infant with neuromuscular weakness.[4] Recently, Suri et al. reported two cases of pneumothorax (possibly resulting from volutrauma) associated with daily use of mechanical insufflation-exsufflation via a cough-assist device and NIV. Although one of those patients resumed using the cough-assist device without recurrence of pneumothorax, the second patient died of acute-on-chronic congestive heart failure after re-expansion of the collapsed lung.[5]

Our patient used neither a one-way valve for air stacking nor a cough-assist device for maximum lung insufflation. Her symptoms of pain and dyspnea occurring during air stacking suggest a causal connection. A pneumothorax suggests a pleural (i.e., peripheral alveolar) lesion, a bleb, or an emphysematous bulla (Figure 1). It remains unknown how often milder forms of alveolar damage, such as pulmonary interstitial emphysema or subclinical pneumothorax, occur as a consequence of deep insufflation of the lungs. Although rare, the clinical course in our patient clearly shows that potentially life-threatening complications can develop. However, we still feel that, after having weighed the pros and cons at that time (in 2005), there were no reasons to

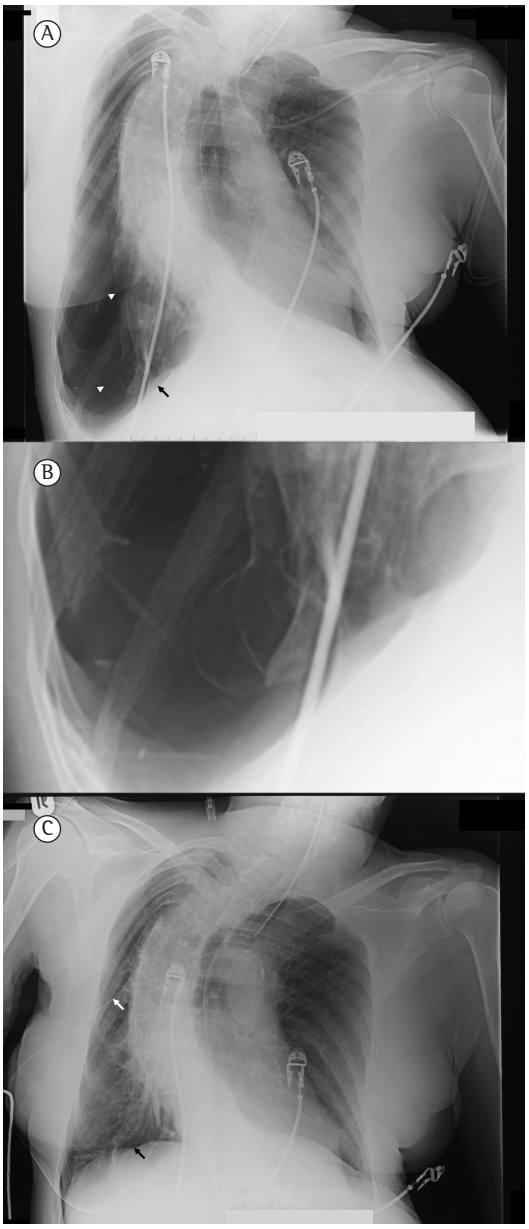

Figure 1 - In A, a chest X-ray, taken at admission, shows right-sided pneumothorax. Notice the total collapse of the lung (upper white arrowhead), diaphragmatic bullae (lower white arrowhead), and widened intercostal spaces. The black arrow shows the depressed right hemidiaphragm. In B, a detail of the right lower lobe reveals inflated bullae in the collapsed lung. In C, a chest X-ray, taken an hour after the first one (A) and immediately after chest tube drainage (white arrow) shows the normal position of the hemidiaphragm (black arrow).

withhold air stacking for deep lung insufflation in this patient. In fact, the patient met several of the criteria for being trained in the use of and using this LVR technique (Chart 1), which improved her PCF and might have prevented respiratory deterioration for a period of 3 years. A PCF > 2.7 L/s is considered minimal for airway secretion clearance, whereas a PCF > 4.5 L/s is needed in order to achieve such clearance during respiratory tract infections. In retrospect, this complication might have been aggravated by her stable bronchial asthma, which occasionally caused airflow limitation. However, even though the patient had asthma attacks, they were infrequent (only four hospitalizations in 18 years), and she did not meet the criteria for a diagnosis of COPD[6]; nor was she suffering from chronic asthma. In addition, since a pneumothorax would have been expected to induce a hypercapnic exacerbation in the presence of COPD, the fact that, following chest tube drainage, she immediately could be extubated and maintained spontaneous respiration, argues against concomitant airflow limitation. Furthermore, her DLCO was normal (after correction for her restricted alveolar ventilation—92% of the predicted value), which excludes parenchymatous pulmonary disease. Moreover, her former smoking habit and the use of NIV might have put her at risk for developing a pneumothorax, as may have her severe scoliosis. Presumably, the use of nocturnal NIV following the incident and the delay in seeking medical attention might have contributed to the severity of the clinical condition at presentation. Despite the use of nocturnal NIV oxygen was needed after pleurodesis to keep her sufficiently oxygenated during spontaneous breathing. The daytime hypercapnia noted nine months after discharge might have been caused by progressive restriction due to pleurodesis or the use of oxygen.

Although LVR is considered safe for individuals with normal lungs and the risk-benefit ratio of LVR, after thousands of patient-hours of use, is still favorable, this event raises concern as to whether the indiscriminate use of LVR is advisable in all patients with restrictive respiratory disease, especially in older patients, who might have an undiagnosed pulmonary pathology resulting in structural abnormalities. In addition, patients should be advised of the warning symptoms of possible complications of LVR in order to avoid a delay in seeking medical attention and to ensure immediate access to medical care.

We therefore recommend that patients with restrictive respiratory disorders who develop chest pain or backache with acute dyspnea during or

following LVR be referred for urgent diagnostic evaluation to exclude pulmonary barotrauma. In certain cases, and depending on the medical history, diagnostic imaging of the chest should be considered prior to LVR, especially in elderly individuals and in those with known risk factors for a parenchymatous pulmonary pathology or with a history of pulmonary disease.

Acknowledgments

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Alveolar hemorrhage after parenteral injection of industrial silicone

Hemorragia alveolar após injeção parenteral de silicone industrial

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To the Editor:

A previously healthy 24-year-old male-to-female transsexual presented with a 48-h history of dyspnea, fever, and signs of severe hypoxemia (SpO_2, 72%). The patient reported having undergone an illegal procedure 10 days prior, when industrial liquid silicone had been injected into her buttocks for cosmetic purposes. The patient had previously received silicone breast implants. After admission, the patient rapidly evolved to severe respiratory failure and required mechanical ventilation. During intubation and throughout the period on mechanical ventilation, pulmonary bleeding was observed. Her hemoglobin level was 6 g/dL (hematocrit, 18%), and she was given a blood transfusion. Her platelet count, partial thromboplastin time, and prothrombin time were all normal.

Chest CT scans showed patchy, bilateral ground-glass opacities, suggestive of alveolar hemorrhage, and bibasilar consolidations (Figure 1). Mild bilateral pleural effusion was also observed. Ultrasound examination of the site of the injection showed no abnormal liquid collection that would require drainage or any other type of surgical intervention. Because of the severe hypoxemia, bronchoscopy and BAL were not performed. Blood cultures were negative throughout the treatment period.

The patient was given a diagnosis of silicone pulmonary embolism with alveolar hemorrhage, which was initially treated with mechanical ventilation, accompanied by methylprednisolone pulse therapy, together with a 14-day course of empirical antimicrobial therapy (with oxacillin and ceftriaxone). The evolution was favorable, her hemoglobin level gradually returning to a value that was within the normal range (11.4 g/dL). On post-admission day 14, she was extubated and her SpO_2 was 91%. On post-admission day 21, her overall health status was good and she was discharged.

Silicone is the chemical and commercial name for polydimethylsiloxane (dimethicone), an organic compound comprising a chain of alternating silicon and oxygen atoms bonded to other organic groups. The chemical state of the polymer—gel (elastomer), liquid, or solid—is determined by the number of cross-links in the molecule.[1] It has been long considered an inert compound with good thermal stability, favoring its use in medicine in various implantable devices. In its pure form, silicone has been used in cosmetic and esthetic procedures for the last five decades, and it is known to produce minimal tissue reactions and no significant immune response, although, in many countries, it is approved only for use in breast augmentation devices and is prohibited as an injectable liquid.[2] However, the widespread underground practice of industrial liquid silicone injection within the transsexual community worldwide has produced various cases featuring a variety of severe reactions, mainly involving the lungs and the central nervous system.[2,3] That is probably related to impurities present in, or the adulteration of, industrial silicone, which can provoke subcutaneous infection (cellulitis) and distant mass formation due to silicone migration, as well as nodules, necrosis, granulomatous hepatitis, regional lymphadenopathy, and lung injury due to pulmonary embolization, alveolar hemorrhage, pneumonitis, and acute respiratory distress syndrome.[3]

The lung injury seen in some individuals who have received silicone injections appears to be triggered by pulmonary embolism. The embolism might be related to the high pressure promoted by the injection of large amounts of the product, local massage in order to accommodate the content, regional migration, or direct

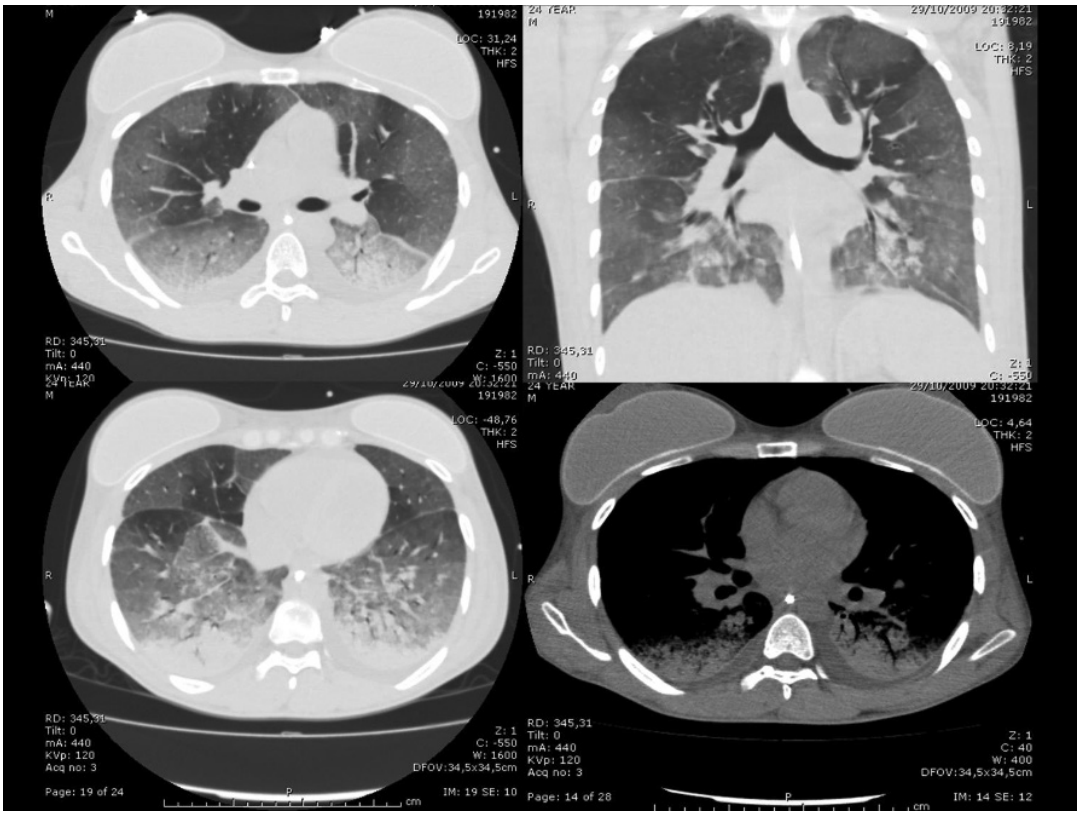

Figure 1 - Chest CT scans showing patchy, bilateral ground-glass opacities suggestive of alveolar hemorrhage, bibasilar consolidations, and mild bilateral pleural effusion.

intravascular injection. Histological examination can show distended capillary vessels filled with homogeneous, clear globular material that resists staining (presumably silicone), macrophages showing cytoplasmic inclusions of the same substance, with a pathologic pattern ranging from the mere presence of vascular emboli to congestion, hemorrhage, acute pneumonitis, and diffuse alveolar damage.[4]

The pneumonitis seen after silicone injection can be acute or latent. The acute form, in which the symptoms appear within the first few days (in some cases as early as two hours after the injection), is more common. In the latent form, symptoms appear 6-13 months after injection.[5] Mortality can be as high as 24%.[6] There appears to be a relationship between mortality and the total amount of embolized material.[6] For cases in which there are neurological manifestations, the prognosis is poor.

In the present case, the clinical evolution was quite typical of the acute form of the condition (with dyspnea, cough, fever, and signs of hypoxemia), and pronounced alterations were seen on chest X-rays and CT scans. The images were quite suggestive of alveolar filling. The presence of bleeding during intubation and the decrease in hemoglobin levels were indicative of hemorrhage.[4] Lung biopsy was unnecessary because of the history of silicone injection, and the clinical and radiological aspects were highly suggestive of alveolar hemorrhage. Ventilatory support treatment was established. Due to the rapid evolution to respiratory failure, we administered methylprednisolone pulse therapy, despite the fact that there is no clinical evidence in the literature to support its use in such cases.

The case presented here highlights the risk of serious complications resulting from the clandestine use of silicone injections for cosmetic purposes. Despite the severity of the clinical status of the patient at admission, the clinical evolution was favorable. A history of illicit cosmetic procedures involving silicone, especially industrial liquid silicone,

should be considered in cases of acute pulmonary involvement in previously healthy adults.

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Pulmonary capillary hemangiomatosis: an uncommon cause of pulmonary hypertension

Hemangiomatose capilar pulmonar: uma causa incomum de hipertensão pulmonar

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To the Editor:

We read with interest the recent publications in the Brazilian Journal of Pulmonology highlighting the prevalence of pulmonary hypertension (PH) in Brazil, particularly as a complication of sickle cell anemia[1] and schistosomiasis,[2] and discussing the role of imaging methods in the evaluation of this disease.[3-5] We would like to report another uncommon cause of PH, pulmonary capillary hemangiomatosis (PCH), and describe the important role of imaging methods in establishing the diagnostic suspicion of this condition.

A 25-year-old male nonsmoker presented to the pulmonology department with a three-month history of rapidly progressive dyspnea. Physical examination revealed digital clubbing, and he was tachypneic and cyanotic, requiring supplementary oxygen. Heart auscultation and chest examination were unremarkable, and examination of the abdomen revealed a slightly enlarged liver. A transesophageal echocardiogram showed enlargement of the main pulmonary artery and right heart chamber. Arterial blood gas analysis showed the following results: pH, 7.46; $PaCO_2$, 26.6 mmHg; and PaO_2, 51.8 mmHg. A chest X-ray showed dilatation of the main and central pulmonary arteries with a nonspecific interstitial infiltrate. Chest CT angiography allowed us to exclude pulmonary embolism and revealed diffuse centrilobular ground-glass opacities (GGOs) and marked dilatation (36 mm) of the main pulmonary artery (Figure 1). The GGOs were bilateral and symmetrical, with no thickening of the interlobular septa. On a pulmonary function test, DLCO was 20%. Anticoagulation therapy with heparin was started and initially improved the symptoms slightly. Pulmonary catheterization demonstrated a mean pulmonary artery pressure of 65 mmHg and a negative vasoactive intestinal peptide result. The pulmonary artery occlusion pressure was 13 mmHg, and cardiac output was 2.9 L/min. Because of the diagnostic suspicion of PCH, the patient was placed on the waiting list for lung transplantation. Despite the treatment with heparin and furosemide, the condition of the patient gradually deteriorated, and he died two months after admission. An autopsy revealed prominent dilation of the right heart chambers and of the pulmonary artery, as well as diffuse alveolar hemorrhage. Microscopic examination of the lungs showed well-demarcated areas with dense proliferation of capillary channels within alveolar walls and surrounding walls of pulmonary venules and veins, which supported the diagnosis of PCH (Figure 2).

The PH syndrome is a heterogeneous group of conditions with the common feature of pulmonary artery involvement, resulting in increased pulmonary vascular resistance, hypertrophy, and right ventricular dilatation that can lead to significant cardiac dysfunction (cor pulmonale) and death. Currently, PH is defined as a resting mean pulmonary artery pressure $\geq$ 25 mmHg, as measured by right heart catheterization.[5,6]

PCH is an extremely rare cause of primary PH and occurs most commonly in adults aged 20-40 years, but it has been reported to occur in all age groups and shows no sex predilection. The clinical presentation of PCH is very nonspecific and most frequently includes dyspnea and fatigue. Other complaints are chest pain, chronic cough, peripheral edema, cyanosis, and syncope.[3] Hemoptysis can be a very useful sign in order to differentiate PCH from pulmonary veno-occlusive disease (PVOD), because it is not found in PVOD.

On chest X-rays, PCH appears as diffuse or bibasilar reticulonodular opacities. Signs of pulmonary arterial hypertension (PAH), such as enlarged central pulmonary arteries and dilatation on the right side of the heart, can also be present. CT scans can show diffuse, ill-defined, centrilobular GGOs and signs consistent with PAH

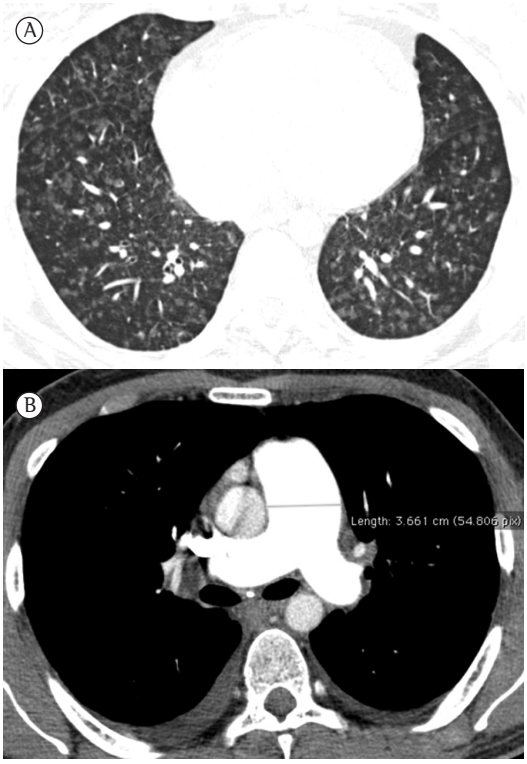

Figure 1 - In A, HRCT scan showing diffuse centrilobular ground-glass opacities. In B, chest CT angiography image demonstrating marked dilatation of the main pulmonary artery (diameter, 36 mm) and bilateral pleural effusion.

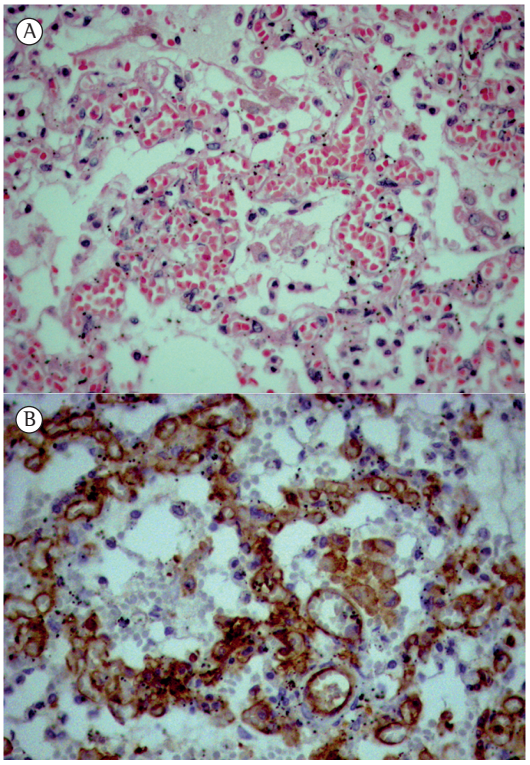

Figure 2 - In A, photomicrograph showing alveolar septal thickening with intense capillary proliferation (H&E; original magnification, ×400). In B, photomicrograph showing capillaries of the alveolar walls with marked CD31 positivity (immunohistochemistry; magnification, ×400).

(main pulmonary artery diameter > 3 cm).[4,5] The association of centrilobular GGOs with the findings mentioned above is an important clue for differentiating PCH from classic causes of this GGO pattern, such as viral infections and acute hypersensitivity pneumonitis. PCH and PVOD should be suspected in patients with PAH associated with hemoptysis or hemorrhagic pleural effusion and interstitial lung infiltrates.

The final diagnosis of PCH is made by lung biopsy. Open lung biopsy is the most accurate method, but various patients do not have the necessary clinical conditions to undergo such a procedure. Transbronchial biopsy has been considered a highly risky procedure due to the possibility of bleeding. The proliferation of capillary channels within alveolar walls is the main histological characteristic of PCH.[6] No specific treatment other than lung transplantation is available.

In conclusion, PCH is an extremely rare cause of primary PH and has a poor prognosis. This condition must be considered when a patient with PAH presents hemoptysis or hemorrhagic pleural effusion and interstitial lung infiltrates, especially in the presence of centrilobular GGOs and sparse, smoothly thickened interlobular septa. Currently, biopsy is the only method to confirm the diagnosis of PCH.

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Aspergillus fumigatus fungus ball in the native lung after single lung transplantation

Bola fúngica por *Aspergillus fumigatus* no pulmão nativo após transplante unilateral de pulmão

Fernando Ferreira Gazzoni, Bruno Hochhegger, Luiz Carlos Severo, José Jesus Camargo

To the Editor:

A 49-year-old woman underwent right lung transplantation due to pulmonary emphysema, with favorable evolution in the early postoperative period. A year later she was readmitted to our department with productive cough. During that admission, the patient was treated for cytomegalovirus pneumonia and received broad-spectrum antibacterial therapy.

At outpatient follow-up, cavities appeared in the native lung, which gradually increased in size. Ten months later, she was admitted for the resection of a hyperinflated cavity. Chest X-rays showed an increase in the cavity in the left upper lobe with herniation of the lung and compression of the transplanted lung. Chest HRCT at various positions showed a round mass with soft tissue density within a lung cavity that moved when the patient changed position, thus strengthening the hypothesis of a fungus ball (Figure 1). Bullectomy was performed, and the histopathologic examination showed fungal colonization by *Aspergillus fumigatus* in emphysematous bullae and bronchiectasis. She was treated with itraconazole and had a satisfactory response.

Lung transplantation has become an acceptable treatment option for many end-stage lung diseases and could be single or double.[1,2] However, *Aspergillus* sp. infections continue to be an important cause of morbidity and mortality in these patients. *Aspergillus* sp. is an ubiquitous fungus that can cause clinical entities of varying severity, such as asymptomatic colonization, aspergilloma, tracheobronchitis, active parenchymal disease, and angioinvasive aspergillosis.[1-6]

Airway colonization is a common occurrence in such patients because of the exposure of the transplanted lung to the environment and impaired local host defenses, including mucociliary clearance. In addition, colonization of the native lung, which commonly occurs in end-stage lung disease, is an important source of post-transplantation aspergillosis in single lung transplantation recipients. *Aspergillus* sp. colonization has also been related to cytomegalovirus infection and chronic rejection.[1-4]

Patients who undergo unilateral transplantation are often older and have a higher prevalence of COPD as an underlying disease, a condition that might predispose to airway colonization by *Aspergillus* sp.[1-3]

The most accurate way to perform the diagnosis is the demonstration of characteristic, acute branching, broad, septate hyphae showing zones of growth in biopsy/surgical/autopsy specimens and positive cultures for *Aspergillus* sp.[3,5,6]

Our patient presented with *Aspergillus fumigatus* fungal ball (aspergilloma) in emphysematous bullae and bronchiectasis in the native lung 26 months after transplantation, with a satisfactory response to medical and surgical treatment. She also had a history of cytomegalovirus infection one year after transplantation as another risk factor. The diagnosis was made through imaging and evaluation of surgical specimens. In fact, aspergilloma affecting the native lung in single lung transplantation recipients has been reported only rarely in retrospective studies.[3,4]

Aspergilloma is characterized by *Aspergillus* sp. infection without tissue invasion. It leads to the conglomeration of intertwined fungal hyphae mixed with mucus and cellular debris within a pre-existing pulmonary cavity, bulla, or ectatic bronchus. The most common underlying causes are tuberculosis and sarcoidosis. Although patients might remain asymptomatic, the most common clinical manifestation is hemoptysis.[5,6] Risk factors for a poor prognosis of aspergilloma include the severity of the underlying lung disease, increase in size or in the number of lesions on

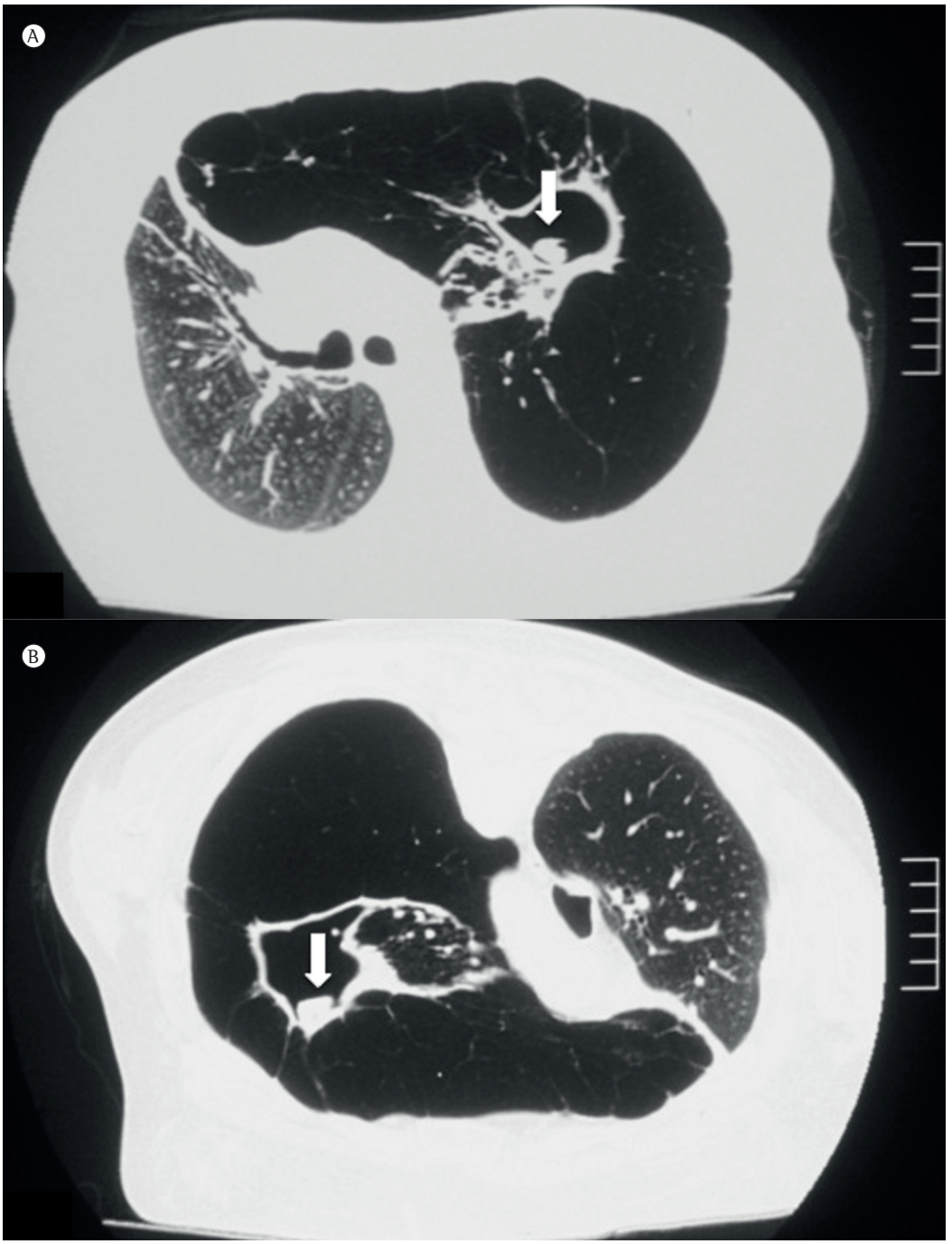

Figure 1 - Axial HRCT scans. In A, cavitary lung lesion in the left upper lobe filled with an opacity resembling a fungus ball (arrow). In B, a scan after moving the patient from the supine position to the prone position, demonstrating the motility of the mass (arrow).

chest X-rays, immunosuppression (including transplantation), increasing Aspergillus-specific IgG titles, recurrent large volume hemoptysis, and sarcoidosis. This highlights the importance of radiological findings, cultures, reviews of the level of immunosuppression, and environmental factors for the early diagnosis and prevention of further complications, such as angioinvasive disease. Treatment should be considered only when patients become symptomatic, usually with

hemoptysis. There is no consensus on the best treatment approach; however, surgical resection of the cavity and removal of the fungus ball are usually indicated in patients with recurrent hemoptysis if their pulmonary function is sufficient to allow surgery.[4-6]

On CT scans and X-rays, aspergillomas are characterized by the presence of a round or oval mass with soft tissue density within a lung cavity. The mass can be separated from the wall of the cavity by an air space of variable size, resulting in the "air crescent" sign. The aspergilloma usually moves when the patient changes position, as was seen in our case. Another finding of aspergillomas is the thickening of the cavity wall and adjacent pleura, which might be the earliest radiological sign.[5,6]

In summary, the susceptibility of the native lung to *Aspergillus* sp. infections might be an additional factor to be considered in choosing the ideal transplantation procedure. In cases of single lung transplantation, radiological and clinical attention is especially directed to the transplanted organ. However, the native lung, structurally damaged, can be a nidus for *Aspergillus* sp. and provide a source of infection.

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Pleuropulmonary complications related to pulmonary instillation of activated charcoal

Complicações pleuropulmonares relacionadas à instilação pulmonar de carvão ativado

Luiz Felipe Nobre, Edson Marchiori, Daniel Yared Forte, Gláucia Zanetti

To the Editor:

Recently, Bairral et al.[1] described the interesting case of a 20-year-old female patient who attempted suicide by ingesting lead shot. She was treated with atropine and received 50 g of activated charcoal (AC) diluted in 400 mL of mannitol administered through a gastric tube. A few hours later, the patient vomited, as well as experiencing a decreased level of consciousness and agonal respiration. At bronchoscopy, blackish material mixed with food debris was obtained, characterizing the occurrence of aspiration of the material. Imaging studies revealed bilateral alveolar opacities.

We would like to report our experience of a case of attempted suicide in which the pulmonary and pleural complications were due not to aspiration, but to direct instillation of AC into the airways. The patient was a 23-year-old female who was admitted to the hospital approximately one hour and a half after the ingestion of 200 mg of paroxetine. Upon her arrival, she was in a coma and underwent gastric lavage with a solution of 1.5 L of AC. The patient immediately developed dry cough and dyspnea. A chest X-ray showed right pleural effusion, and, during thoracentesis, there was discharge of black fluid, identified as AC (Figure 1). A CT scan showed pleural effusion and consolidation in the right lower lobe, both of which exhibited high density (attenuation values of approximately 130 HU), as well as pneumothorax (Figure 2). These findings raised the suspicion of direct instillation of AC into the lungs due to placement of the nasogastric tube within the patient's airway. At bronchoscopy, there was discharge of black material from the right lower lobe. An air leak was noted from the chest tube, suggesting bronchopleural fistula. The patient underwent thoracoscopy and pleural lavage. Fifteen days later, the fistula closed, and the patient was discharged from the hospital. Some of the data on this case have been reported in a previous publication.[2]

Most of the complications related to treatment with AC result from aspiration of gastric content, as has been reported by Bairral et al.,[1] rather than from direct aspiration of AC. Occasionally, the nasogastric tube can be mistakenly inserted into the trachea, and there can occur direct administration of AC into the airways. Another complication related to direct instillation of charcoal into the airways is pleural involvement. Findings of pleural effusion, presence of charcoal in the collected fluid, and pneumothorax associated with bronchopleural fistula are probably secondary to instillation of a large amount of AC solution into the distal airways.[3] Pleural rupture caused by the nasogastric tube, rupture of a subpleural bulla after aspiration (with consequent development of a bronchopleural fistula), and perforation of the esophagus, with formation of an esophagopleural fistula, are possible mechanisms for pleural involvement.[4]

The incidence of inadvertent insertion of the nasogastric tube into the trachea and the distal airways ranges from 0.3% to 15%.[5] Physical examination is often not a good predictor of incorrect positioning of the tube, especially in unconscious patients. In general, the positioning of the tube is initially assessed by fluid aspiration or by air insufflation and auscultation of the abdomen. These maneuvers can provide false-positive results.[6] The position of the tube should be verified radiographically before the administration of AC.[3]

In conclusion, in patients treated with AC, a CT finding of high-density material in the lung parenchyma or the pleural cavity is strongly suggestive of accidental instillation of the product into the airways.

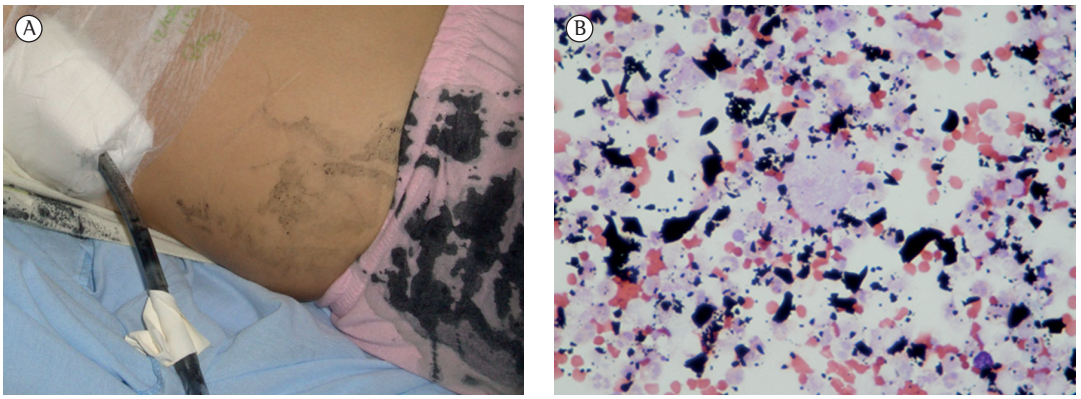

Figure 1 - In A, photograph of the patient, which was taken after placement of the chest tube, showing the presence of blackish fluid (discharged during the procedure) in the tube. In B, photomicrograph of the pleural fluid showing the presence of charcoal particles (H&E; magnification, ×400).

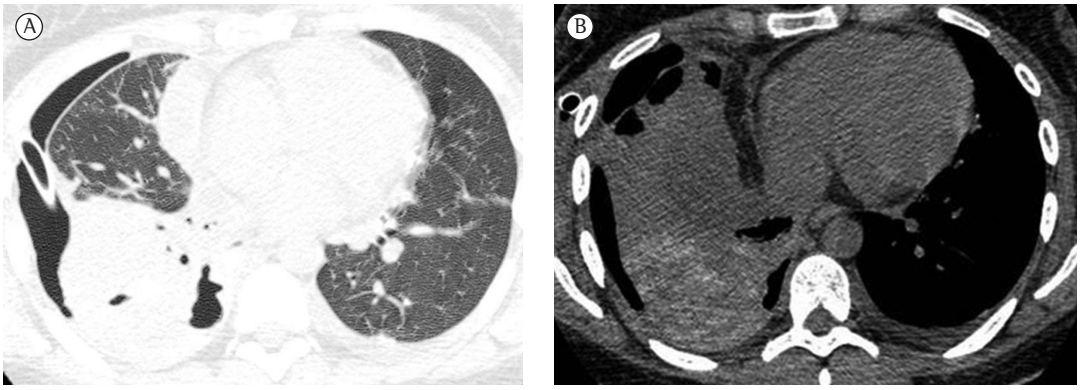

Figure 2 - Chest CT scan. In A, slice on lung window showing right hydropneumothorax, which had been drained, as well as parenchymal consolidation. In B, slice on mediastinal window showing high-attenuation areas within the consolidation, measuring approximately 130 HU.

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Erratum

This corrects the article "Mortality due to respiratory diseases in the elderly after influenza vaccination campaigns in the Federal District, Brazil, 1996-2009" pages 198-204.

In J Bras Pneumol. 2013;39(2):198-204, Scoralick FM, Piazzolla LP, Pires LL, Neri C, Kummer WP. Mortality due to respiratory diseases in the elderly after influenza vaccination campaigns in the Federal District, Brazil, 1996-2009, the correct names of the authors are Francisca Magalhães Scoralick, Luciana Paganini Piazzolla, Liana Lauria Pires, Cleudson Nery de Castro e Wladimir Kummer de Paula (Scoralick FM, Piazzolla LP, Pires LL, Castro CN, Kummer WP).

Instructions for Authors

The Jornal Brasileiro de Pneumologia (J Bras Pneumol, Brazilian Journal of Pulmonology) ISSN-1806-3713, published once every two months, is the official organ of the *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Society) for the publication of scientific papers regarding Pulmonology and related areas.

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The accuracy of all concepts presented in the manuscript is the exclusive responsibility of the authors. The number of authors should be limited to six, although exceptions will be made for manuscripts that are considered exceptionally complex. For manuscripts with more than six authors, a letter should be sent to the Journal describing the participation of each.

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Abstract: The abstract should present the information in such a way that the reader can easily understand without referring to the main text. Abstracts should not exceed 250 words. Abstracts should be structured as follows: Objective, Methods, Results and Conclusion. Abstracts for review articles and case reports may be unstructured.

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Keywords: Three to six keywords in Portuguese defining the subject of the study should be included as well as the corresponding keywords in English. Keywords in Portuguese must be based on the Descritores em Ciência da Saúde (DeCS, Health and Science Keywords), published by Bireme and available at: http://decs.bvs.br, whereas keywords in English should be based on the National Library of Medicine Medical Subject Headings (MeSH), available at: http://www.nlm.nih.gov/mesh/MBrowser.html.

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Legends: Legends should accompany the respective figures (graphs, photographs and illustrations) and tables. Each legend should be numbered with an Arabic numeral corresponding to its citation in the text. In addition, all abbreviations, acronyms, and symbols should be defined below each table or figure in which they appear.

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2. Singer M, Lefort J, Lapa e Silva JR, Vargaftig BB. Failure of granulocyte depletion to suppress mucin production in a murine model of allergy [abstract]. Am J Respir Crit Care Med. 2000;161:A863.

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Theses

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Electronic publications

6. Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

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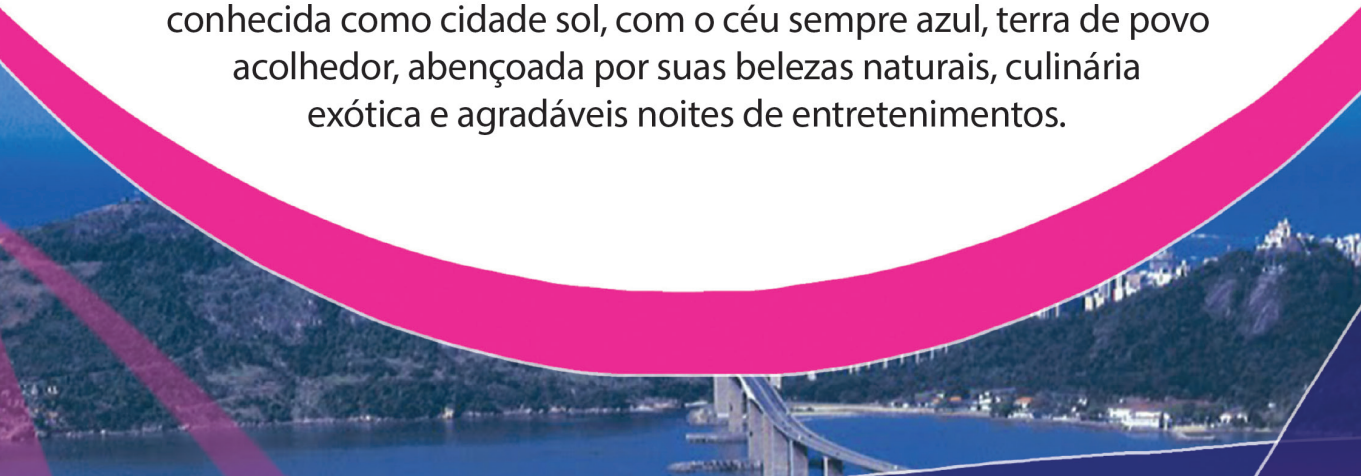
Tudo pronto para o IX Congresso Brasileiro de Asma, V congressos Brasileiros de DPOC e Tabagismo. A capital capixaba receberá, de 21 a 24 de agosto grandes nomes da pneumologia nacional e internacional que discutirão os temas de maior interesse do profissional da área. O evento acontece no Centro de Convenções de Vitória, localizado a Rua Constante Sodré, 157 - Bairro Santa Lúcia – Vitória – ES. O Congresso contará com cursos pré congressos no dia 21, conferencias, mesas redondas sem falar nas discussões dos principais temas e relatos de caso. Todos os detalhes tem sido trabalhados de modo a englobar profissionais de todas as regiões do país e também aos jovens especialistas. Aproveite para rever ou conhecer a cidade, uma ilha encantadora, conhecida como cidade sol, com o céu sempre azul, terra de povo acolhedor, abençoada por suas belezas naturais, culinária exótica e agradáveis noites de entretenimentos.



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A evolução no tratamento da asma[1-6]

Nada melhor que
máxima flexibilidade.

200 / 400 mcg

12 mcg

Mesmo dispositivo inalatório

O uso combinado com Fluir permite e facilita o Step Up e o Step Down.[7,8]

OXIMAX®:CONTRAINDICAÇÕES: contra-indicado em pacientes com hipersensibilidade conhecida ao furoato de mometasona ou à lactose. INTERAÇÕES MEDICAMENTOSAS: A co-administração de OXIMAX com o cetoconazol, um potente inibidor da enzima CYP3A4, pode aumentar os níveis plasmáticos de furoato de mometasona durante administração concomitante.

OXIMAX® (furoato de mometasona). **INDICAÇÕES:** indicado para o controle e na profilaxia da asma de qualquer intensidade, inclusive no tratamento dos pacientes asmáticos dependentes de corticosteróides inalatórios ou sistêmicos, e de pacientes asmáticos não-dependentes de corticosteróides, porém inadequadamente controlados com outros esquemas de tratamento. **PRECAUÇÕES E ADVERTÊNCIAS:** Durante os estudos clínicos, ocorreu o desenvolvimento de infecções localizadas de boca e faringe com Candida albicans. Poderá haver o desencadeamento de um episódio de broncoespasmo com aumento imediato de sibilos após a dose. É necessário cuidado especial com pacientes em processo de transição de corticosteróides sistemicamente ativos para OXIMAX. OXIMAX não é um broncodilatador e não é indicado para o alívio rápido do broncoespasmo ou de outros episódios agudos de asma. Durante esses episódios, os pacientes poderão precisar de terapia com corticosteróides orais. OXIMAX não deve ser utilizado durante a gravidez, nem por mães que estejam amamentando, a menos que o benefício justifique o risco potencial à mãe, ao feto ou ao bebê. **REAÇÕES ADVERSAS:** As reações adversas mais comuns são cefaléia, rinite alérgica, faringite, infecção do trato respiratório superior, sinusite, candidíase oral, dismenorreia, dor músculo esquelética, dor lombar e dispepsia. **POSOLOGIA:** OXIMAX destina-se ao uso em adultos e em crianças a partir de 12 anos. A dose inicial recomendada na terapia com OXIMAX para a maioria dos pacientes, independentemente de terem sido anteriormente tratados apenas com broncodilatadores ou corticosteróides inalatórios, é de 400 µg uma vez por dia, aplicados com o dispositivo. Alguns pacientes podem ser mais adequadamente controlados com 400 µg administrados em duas doses diárias (200 µg duas vezes por dia). A redução da dose para 200 µg uma vez por dia pode ser uma alternativa para a manutenção eficiente em alguns pacientes. MS 1.7287.0488. **VENDA SOB PRESCRIÇÃO MÉDICA. SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.** Mais informações à disposição da classe médica no departamento científico da Mantecorp. Distribuição exclusiva à classe médica. (MB-OXI5). **Referências bibliográficas:** 1) Nayak AS, et al. Once-daily mometasone furoate dry powder inhaler in the treatment of patients with persistent asthma. Ann Allergy Asthma Immunol. 2000;84(4):417-24. 2) D'Urzo A. Mometasone furoate dry-powder inhaler for the control of persistent asthma Expert Opin Pharmacother. 2007;8(16):2871-84. 3) Sharpe M, Jarvis B. Inhaled mometasone furoate: a review of its use in adults and adolescents with persistent asthma. Drugs. 2001;61(9):1325-50. 4) Price D, et al. Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study. BMC Pulm Med. 2010;10:1. 5) Navaratnam P, et al. The impact of adherence and disease control on resource use and charges in patients with mild asthma managed on inhaled corticosteroid agents. Patient Prefer Adherence. 2010;4:197-205. 6) Bula do produto: Oximax, 2012. 7) Global initiative for asthma. GINA. Global strategy for asthma management and prevention. Updated 2010. Available from: http://www.ginasthma.com 8) Bacharier LB, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. Allergy. 2008;63(1):5-34.

FLUIR® - fumarato de formoterol diidratado. Indicações: profilaxia e no tratamento da broncoconstrição em pacientes com doença obstrutiva reversível das vias aéreas. **CONTRAINDICAÇÕES:** Hipersensibilidade a algum dos componentes da fórmula. **PRECAUÇÕES E ADVERTÊNCIAS:** Cuidado especial e supervisão, com ênfase particular nos limites da dose, serão necessários quando coexistirem as seguintes condições: doença cardíaca isquêmica, arritmias cardíacas, especialmente bloqueio atrioventricular de terceiro grau, descompensação cardíaca grave, estenose subvalvular aórtica idiopática, cardiomiopatia obstrutiva hipertrófica, tireotoxicose, prolongamento suspeito ou conhecido do intervalo QT (QTc > 0,44 seg). Recomenda-se controle adicional de glicose sangüínea em pacientes diabéticos. O uso de Fluir durante a gravidez deve ser evitado, salvo se não existir alternativa mais segura. As mães em tratamento com FLUIR não devem amamentar. **INTERAÇÕES MEDICAMENTOSAS:** Fármacos como quinidina, disopiramida, procainamida, fenotiazínicos, anti-histamínicos e antidepressivos tricíclicos podem ser associados com prolongamento do intervalo QT e com aumento do risco de arritmia ventricular. A administração concomitante de outros agentes simpatomiméticos pode potencializar os efeitos indesejáveis. FLUIR não deve ser administrado juntamente com bloqueadores beta-adrenérgicos (incluindo-se colírios). **REAÇÕES ADVERSAS:** tremores; palpitações; cefaléia; agravamento do broncoespasmo. Outros- Reações de hipersensibilidade, como hipotensão grave, urticária, angioedema, prurido e exantema. Edemas periféricos, irritação conjuntival e edema de pálpebra, alteração do paladar e náuseas. **POSOLOGIA:** Terapia de manutenção regular: Adultos – inalação de 1 a 2 cápsulas (12 a 24 mcg), duas vezes por dia. Crianças acima de 5 anos – inalação de uma cápsula (12 mcg), duas vezes por dia. MS 1.7287.0497. **VENDA SOB PRESCRIÇÃO MÉDICA.** Julho/2011. (MB-FLU10). **SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO. JUNHO/13**

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Mantecorp Farmasa
Respiratória

vacina pneumocócica 13-valente (conjugada). **Indicações:** A vacina pneumocócica 13-valente (conjugada) é indicada para a prevenção de doença invasiva, pneumonia e otite média causadas pelo *Streptococcus pneumoniae* dos sorotipos 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F e 23F em lactentes e crianças e para adultos com 50 anos ou mais para a prevenção de doença pneumocócica (incluindo pneumonia e doença invasiva), pelos mesmos sorotipos. **Contraindicações**: A vacina pneumocócica 13-valente (conjugada) está contraindicada para pacientes hipersensíveis a qualquer dos componentes da vacina, incluindo o toxoide diftérico. **Advertências:** Doenças menores, como infecção respiratória leve, com ou sem febre de baixo grau, em geral não constituem contraindicações para a vacinação. A decisão de administrar ou adiar a vacinação devido a uma doença febril atual ou recente depende em grande parte da severidade dos sintomas e de sua etiologia. A administração da vacina pneumocócica 13-valente (conjugada) deve ser adiada em indivíduos sofrendo de doença febril aguda severa. Como ocorre com qualquer vacina, a vacina pneumocócica 13-valente (conjugada) pode não proteger todos os indivíduos que receberem a vacina contra a doença pneumocócica. **Precauções:** Como ocorre com todas as vacinas pediátricas injetáveis, o possível risco de apneia deve ser considerado ao administrar a série de imunização primária em lactentes prematuros. A necessidade de monitoramento por no mínimo 48 horas após a vacinação deve ser considerada para lactentes muito prematuros (nascidos ≤ 30 semanas de gestação) que permaneçam hospitalizados no momento da administração recomendada. Uma vez que o benefício da vacinação é elevado neste grupo de lactentes, a vacinação não deve ser suspensa ou adiada. *Gravidez:* Categoria de risco C: Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista. Não se sabe se os antígenos da vacina ou os anticorpos são excretados no leite materno. A segurança e a eficácia da vacina pneumocócica 13-valente (conjugada) em crianças com menos de 6 semanas ou após 6 anos não foram estabelecidas. A vacina pneumocócica 13-valente (conjugada) mostrou-se segura e imunogênica na população geriátrica. **Reações adversas:** Lactentes e Crianças com 6 Semanas a 5 Anos de Idade: Reação muito comum: diminuição do apetite, irritabilidade, sonolência/aumento do sono, sono inquieto/diminuição do sono, febre, qualquer eritema, endurecimento/tumefação ou dor/sensibilidade no local da vacinação, eritema ou endurecimento/tumefação no local da vacinação 2,5 cm – 7,0 cm (após dose em crianças entre 1 e 2 anos e crianças mais velhas [2 a 5 anos de idade]). Reação comum: diarreia, vômitos, erupção cutânea, febre acima de 39°C, eritema ou endurecimento/tumefação no local da vacinação 2,5 cm – 7,0 cm (após série em lactentes), dor / sensibilidade no local da vacinação interferindo com o movimento. Adultos com 50 Anos de Idade ou Mais: Reação muito comum: diminuição do apetite, cefaleias, diarreia, erupção cutânea, dor generalizada nas articulações recente/agravada, dor muscular generalizada recente/agravada, calafrios, fadiga, eritema no local da vacinação, endurecimento/inchaço no local da vacinação, dor/sensibilidade no local da vacinação, limitação do movimento do braço. Reação comum: vômitos, febre. **Interações Medicamentosas:** A vacina pneumocócica 13-valente (conjugada) pode ser administrada com qualquer um dos seguintes antígenos de vacina, seja de modo monovalente ou em vacinas combinadas: difteria, tétano, pertussis acelular ou de célula inteira, *Haemophilus influenzae* tipo b, poliomielite inativada, hepatite B, meningococo do sorogrupo C, sarampo, caxumba, rubéola e varicela. Estudos clínicos demonstraram que as respostas imunológicas e os perfis de segurança das vacinas administradas não foram afetados. Em estudos clínicos, quando a vacina pneumocócica 13-valente (conjugada) foi administrada concomitantemente, porém em um local ou por via diferente, com vacina de hepatite A ou de rotavírus, não foi observada alteração nos perfis de segurança para estes lactentes. A vacina pneumocócica 13-valente (conjugada) pode ser administrada com a vacina inativada trivalente contra influenza (VIT). A resposta imune para vacina pneumocócica 13-valente (conjugada) quando administrada concomitantemente com a VIT foi menor comparada à sua administração isolada. O significado clínico disto é desconhecido. Não foram realizados estudos para avaliar a resposta imune da vacina pneumocócica 13-valente (conjugada) quando administrada concomitantemente a outras vacinas além da VIT. **Posologia:** A dose é 0,5 mL, administrada por via IM, com cuidado para evitar a aplicação em nervos e vasos sanguíneos ou suas proximidades. Para lactentes até 6 meses de idade, a série de imunização recomendada consiste em três doses de 0,5 mL cada, com aproximadamente 2 meses de intervalo, seguidas por uma quarta dose de 0,5 mL aos 12-15 meses de idade, no mínimo 2 meses após a terceira dose. A idade usual para a primeira dose corresponde a 2 meses de idade, mas esta pode ser administrada mais cedo com 6 semanas de idade. A imunização para lactentes acima de 6 meses e crianças não vacinadas previamente: lactentes entre 7 e 11 meses devem receber 2 doses com intervalo mínimo de 4 semanas e uma dose de reforço entre 12 e 15 meses no mínimo 2 meses após a dose anterior; crianças entre 12 e 23 meses devem receber duas doses com intervalo de 2 meses; e crianças de 24 meses a 6 anos incompletos devem receber uma dose. Para adultos com 50 anos de idade ou mais a recomendação é uma dose única de 0,5 mL. VENDA SOB PRESCRIÇÃO MÉDICA. SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO. **MS – 1.2110.0277.** Para informações completas, consulte a bula do produto (PRV13_12). Documentação científica e informações adicionais estão à disposição da classe médica mediante solicitação. Wyeth Indústria Farmacêutica Ltda. Rua Alexandre Dumas, 1.860, São Paulo – SP – CEP 04719-904 Tel.: 08000-160625. www.wyeth.com.br.

CONTRAINDICAÇÕES: A VACINA PNEUMOCÓCICA 13-VALENTE (CONJUGADA) ESTÁ CONTRAINDICADA PARA PACIENTES HIPERSENSÍVEIS A QUALQUER DOS COMPONENTES DA VACINA, INCLUINDO O TOXOIDE DIFTÉRICO. **INTERAÇÕES MEDICAMENTOSAS:** LACTENTES E CRIANÇAS COM 6 SEMANAS A 5 ANOS DE IDADE: VACINA PNEUMOCÓCICA 13-VALENTE (CONJUGADA) PODE SER ADMINISTRADA COM QUALQUER UMA DAS SEGUINTES VACINAS: VACINAS CONTRA DIFTERIA, TÉTANO E *PERTUSSIS* (DTP) OU DIFTERIA, TÉTANO E *PERTUSSIS* ACELULAR (DTPA); *HAEMOPHILUS INFLUENZAE* TIPO B (HIB); VACINA CONTRA POLIOMIELITE INATIVADA; HEPATITE B; VACINA MENINGOCÓCICA C (CONJUGADA); SARAMPO, CAXUMBA E RUBÉOLA (MMR) E VARICELA. ADULTOS COM 50 ANOS DE IDADE OU MAIS: A VACINA PNEUMOCÓCICA 13-VALENTE (CONJUGADA) PODE SER ADMINISTRADA COM A VACINA INATIVADA TRIVALENTE CONTRA INFLUENZA (VIT).

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Internacionalmente comercializada como
Prevenar 13
vacina pneumocócica 13-valente (conjugada)

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A PRIMEIRA E ÚNICA VACINA PNEUMOCÓCICA CONJUGADA INDICADA PARA ADULTOS COM[1,2] 50+

...PARA A PREVENÇÃO DE PNEUMONIA E DOENÇA PNEUMOCÓCICA INVASIVA

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