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HIGHLIGHT

Sleep and intensive care

Lung transplantation

Imaging and COPD

A CIDADE MARAVILHOSA TE ESPERA DE BRAÇOS ABERTOS PARA NOSSO PRÓXIMO ENCONTRO

XXXVIII CONGRESSO BRASILEIRO DE PNEUMOLOGIA E TISIOLOGIA
IX CONGRESSO LUSO-BRASILEIRO DE PNEUMOLOGIA
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Imaging and COPD

Bruno Hochhegger[1,2]

COPD involves destruction of alveolar septa in the lungs, associated with small airway dilation that is partially irreversible.[1] The first process leads to loss of surface area for gas exchange (restrictive component), whereas the second process is detrimental to an adequate respiratory cycle (obstructive component). COPD is an entity that has remarkable relevance in public health practice, because of its high prevalence and because it is associated with the occurrence of lung cancer and reduced life expectancy and quality of life.[2]

A diagnosis of COPD is based on a combination of clinical findings and changes in pulmonary function tests, especially spirometry. A Tiffeneau index (FEV_1/FVC ratio) lower than 70% after a bronchodilator test is considered a diagnostic criterion for the disease.[1-4] In addition, the classification of the Global Initiative for Chronic Obstructive Lung Disease groups patients into severity classes, in order to systematize the therapeutic approaches.[3] However, the relationship between FEV_1 and symptoms has proven to be limited,[4] there being dissociation between Global Initiative for Chronic Obstructive Lung Disease classes and symptom severity in many patients.[4,5]

Currently, the attempt to divide COPD patients into several groups has been extensively explored in the literature. The term phenotype in COPD is defined as "a unique combination of disease or attributes that describes differences between individuals with COPD and how they are related to clinically meaningful outcomes". Among all phenotypes described in the literature, three are associated with prognosis and particularly with variable response to currently available therapies. They are as follows: the exacerbator phenotype; the COPD/asthma overlap phenotype; and the emphysema/hyperinflation overlap phenotype. The expectation is that the identification of the particularities of the different COPD phenotypes will help us offer a more tailored treatment, so that patient characteristics and disease severity can be the key to choosing the best treatment option.[5]

In this context, imaging is essential for the characterization of emphysema. In the opinion of various authors, the quantification of emphysema with conventional radiological imaging is flawed.[3-7] For this reason, CT has gained great importance in the imaging assessment of pulmonary emphysema. Various studies have been devoted to CT detection of emphysema, to investigating the correlation between CT and pathologic examination findings of emphysema, and to CT quantification of emphysema.[8] One of the major advantages of CT is that it allows the pathologic classification of pulmonary emphysema. The current pathologic classification of emphysema was proposed by Reid,[8] being based on the acinar distribution of emphysema, and it is divided into four major groups: centroacinar; paraseptal or periacinar; panacinar; and irregular. However, the distribution of these findings in the lung parenchyma and their relationship with the diagnosis, severity, treatment, and prognosis of COPD are still poorly understood.

Quantification of emphysema by visual scores usually uses scales ranging from 1 to 4 or from 1 to 5; the disease being graded according to the proportion of lung involvement (0%, 25%, 50%, 75%, or 100% of the lungs). The relationship between this technique and pathologic examination findings has a correlation coefficient of r = 0.91 in vitro (cadaver lung specimens). However, it should be taken into account that there are natural limitations when quantification of emphysema is analyzed subjectively, whether by radiological imaging or by macroscopic or microscopic pathologic examination.[1-5]

Predictably, comparisons between methods for quantification of emphysema by visual scores with those by automatic quantification using computer graphics have shown a significant difference in favor of automation. The density mask introduced by Müller et al.[9] was one of the most important techniques for the automated assessment of emphysema, being cited in virtually all other such studies. That was the first large-scale study that aimed at diagnosing emphysema on the basis of computer-aided CT assessment. The correlation between density mask findings and pathologic examination findings reaches r = 0.89. However, visual assessment is still used, because of its simplicity, which facilitates its use in clinical practice.

The study published in the current issue of the JBP by Bastos et al.[10] assesses a cohort of patients with emphysema and demonstrates that lower lung predominant pulmonary emphysema is associated with more severe disease than is upper lung predominant pulmonary emphysema. In addition, the authors report that patients with homogeneous emphysema tend to have greater hyperinflation. These findings are important in building a body of knowledge about the influence of the different morphostructural changes of the COPD phenotypes, so that we can arrive at a tailored and more efficient treatment.

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Influence of emphysema distribution on pulmonary function parameters in COPD patients

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Study carried out at the *Serviço de Pneumologia, Centro Hospitalar de São João* EPE, Porto, Portugal.

ABSTRACT

Objective: To evaluate the impact that the distribution of emphysema has on clinical and functional severity in patients with COPD. **Methods:** The distribution of the emphysema was analyzed in COPD patients, who were classified according to a 5-point visual classification system of lung CT findings. We assessed the influence of emphysema distribution type on the clinical and functional presentation of COPD. We also evaluated hypoxemia after the six-minute walk test (6MWT) and determined the six-minute walk distance (6MWD). **Results:** Eighty-six patients were included. The mean age was 65.2 ± 12.2 years, 91.9% were male, and all but one were smokers (mean smoking history, 62.7 ± 38.4 pack-years). The emphysema distribution was categorized as obviously upper lung-predominant (type 1), in 36.0% of the patients; slightly upper lung-predominant (type 2), in 25.6%; homogeneous between the upper and lower lung (type 3), in 16.3%; and slightly lower lung-predominant (type 4), in 22.1%. Type 2 emphysema distribution was associated with lower FEV_1, FVC, FEV_1/FVC ratio, and DLCO. In comparison with the type 1 patients, the type 4 patients were more likely to have an FEV_1 < 65% of the predicted value (OR = 6.91, 95% CI: 1.43-33.45; p = 0.016), a 6MWD < 350 m (OR = 6.36, 95% CI: 1.26-32.18; p = 0.025), and post-6MWT hypoxemia (OR = 32.66, 95% CI: 3.26-326.84; p = 0.003). The type 3 patients had a higher RV/TLC ratio, although the difference was not significant. **Conclusions:** The severity of COPD appears to be greater in type 4 patients, and type 3 patients tend to have greater hyperinflation. The distribution of emphysema could have a major impact on functional parameters and should be considered in the evaluation of COPD patients.

Keywords: Pulmonary disease, chronic obstructive; Pulmonary emphysema; Respiratory function tests; Tomography, X-ray computed.

INTRODUCTION

The lung disease known as COPD is characterized by persistent airflow limitation that is usually progressive, consisting of a combination of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema).[1] There is increasing evidence to suggest that distinguishing different phenotypic profiles of patients with COPD has prognostic and therapeutic implications.[2-4] In fact, COPD patients with confirmed emphysema have more severe lung function impairment, more intense airway inflammation, and possibly more important extrapulmonary disability than do those without emphysema.[2,5,6] The lung hyperinflation caused by the loss of lung elastic recoil has been associated with limitations in the functional capacity of these patients.[7,8] In addition, the destruction of the alveolar-capillary membrane in emphysema is responsible for more profound hypoxemia.[9]

Advances in CT scanning and image processing software have allowed the precise measurement of the extent of low-attenuation areas corresponding to emphysema. In validation studies, the results obtained with these techniques have been found to correlate well with pathologic and functional features.[10-13] This kind of assessment has been mainly used in order to evaluate patients for lung volume reduction procedures and to monitor replacement therapy in alpha-1 antitrypsin-deficient patients.[14-16] However, quantifying emphysema might have broader utility, given that some reports have shown that the heterogeneity of the distribution of parenchymal damage might be associated with different degrees of clinical severity.[13,17-19] Nevertheless, the results are contradictory, which might be attributable to the different methods that have been used in those analyses. The majority of authors have employed computer-assisted measurements, which are expensive and not widely available. In order to promote a definitive widespread use of imaging data in the clinical evaluation of patients with emphysema, we believe that there is also a need to standardize qualitative methods.

The aim of the present study was to evaluate the impact that the distribution of emphysema has on clinical and functional features in COPD patients. In order to test our hypothesis, we used a visual classification system to categorize patients according to the regional distribution of their emphysema.

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METHODS

Study subjects

This was a cross-sectional observational study involving COPD patients with emphysema, recruited between August of 2011 and August of 2012 from the pulmonology outpatient clinic of the *Centro Hospitalar de São João*, a tertiary care medical center located in the city of Porto, Portugal. We included patients with pulmonary emphysema and any degree of airflow limitation who had been clinically stable in the 3 months prior to their inclusion in the study. The inclusion criteria were having a post-bronchodilator FEV_1/FVC < 0.70 and showing evidence of emphysema on visual inspection of CT images, estimated to involve > 25% of the lung parenchyma.[20] Patients with a history of asthma, bronchiectasis, tuberculosis sequelae, lung fibrosis, thoracic surgery, or other confounding diseases were excluded (Figure 1). The study was approved by the local research ethics committee, and all patients gave written informed consent.

Clinical and pulmonary function assessment

We recorded demographic and anthropometric data, namely age, gender, and BMI.[21] Patients also underwent clinical evaluation, which included the completion of the COPD Assessment Test (CAT) and the modified Medical Research Council (mMRC) scale (for the determination of dyspnea severity),[22] as well as the evaluation of smoking status (current smoker, former smoker, or nonsmoker), smoking history (in pack-years), the presence of significant comorbidities, and current medication use. The number of COPD exacerbations in the last year[23,24] was retrospectively obtained by patient recall, and, in most cases, hospital records were used in order to corroborate the information. Each patient was submitted to spirometry (MasterScreen™ Body; Jaeger, Würzburg, Germany), lung volumes and DLCO also being determined, in accordance with international guidelines.[25,26] The six-minute walk test (6MWT) was performed using the methodology described by the American Thoracic Society.[27] Arterial blood gases were measured (RapidLab™ 1265; Siemens, Munich, Germany) after a minimum 30-min rest period in a sitting position. We defined hypoxemia as a PaO_2 < 60 mmHg at an FiO_2 of 0.21.

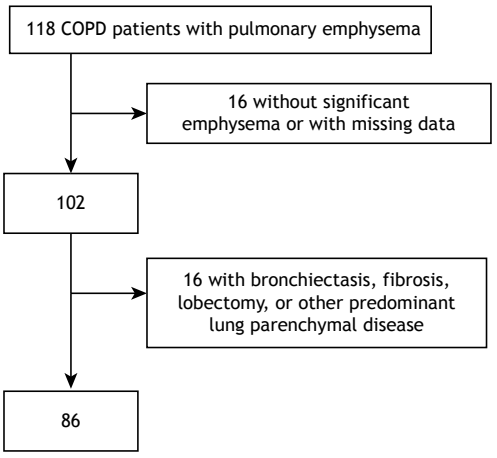

Figure 1. Flowchart for the selection of the participating patients.

CT evaluation

All patients underwent multidetector CT of the chest at suspended full inspiration, from the thoracic inlet to the adrenal glands, using a 64-detector row scanner (Somatom Sensation 64; Siemens Healthcare, Erlangen, Germany). The following imaging parameters were used: tube voltage, 120 kVp; tube current, 40 mAs; rotation time, 0.33 s; pitch, 1.3; detector collimation, 32 × 0.6 mm; and slice acquisition by means of a z-flying focal spot, 64 × 0.6 mm. No contrast media were used. From the raw data, 1 mm-thick sections were obtained using a soft tissue kernel reconstruction (B50f; Siemens Healthcare). For the subjects submitted to multiple CT scans, the one performed the closest to study enrollment was used.

Two thoracic radiologists independently reviewed the CT imaging studies. Both were blinded to the clinical information of the patients. Disagreement between the two radiologists was resolved by consensus. They reviewed CT images on the coronal and sagittal planes to assess the heterogeneity of emphysematous changes in an apical-to-caudal direction. For image interpretation, we used a window level of −700 to −900 HU and a window width of 600-1,600 HU.[28] A five-point visual classification system was applied, as previously described.[18] This qualitative evaluation ranks pulmonary emphysema according to its predominant distribution, as follows: type 1, obviously predominant in the upper lung; type 2, somewhat predominant in the upper lung; type 3, equal extent in the upper and lower lung (homogeneous distribution); type 4, somewhat predominant in the lower lung; and type 5, obviously predominant in the lower lung.

Statistical analysis

Variables with normal distribution are expressed as means and standard deviations, whereas those with non-normal distribution are expressed as median and interquartile range (25th to 75th percentile) and categorical variables are expressed as absolute values and proportion. The Student's t-test for independent samples was used in order to compare variables with normal distribution, and the Mann-Whitney U rank test was used in order to compare variables with non-normal distribution. The Pearson's chi-square test was used for categorical variables. One-way ANOVA was used in order to compare the emphysema distribution groups, together with Tukey's post hoc test to identify significant differences. Odds ratios and the corresponding 95% confidence intervals were calculated using binary logistic regression. Odds ratios were adjusted for age and BMI. Statistical significance was set at $p < 0.05$ (two-tailed), and all statistical analyses were performed with the SPSS Statistics software package, version 19.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

During the study period, 86 COPD patients with pulmonary emphysema were selected, the characteristics of whom are shown in Table 1. Male gender was predominant in this population, all but one of the patients were current or former smokers, and 1 patient presented with homozygous PiZZ alpha-1 antitrypsin deficiency. The CAT scores indicated severe symptoms more often than did the mMRC dyspnea scale scores: 56.1% of the patients had CAT scores ≥ 10, whereas only 40.8% had mMRC scale scores ≥ 2. Only 24.4% of the patients had frequent exacerbations (≥ 2 exacerbations in the last year). Hypoxemia was present in 15 patients (18.8%). The characteristics of the patients demonstrated a wide range of airflow limitation, with an even distribution across the *Global Initiative for Chronic Obstructive Lung Disease* severity classification,[1] which is based on FEV_1—mild, in 27.9%; moderate, in 22.1%; severe, in 29.1%; and very severe, in 20.9%—reflecting the spectrum of the disease encountered in clinical practice. However, there was a clear tendency for hyperinflation to be seen in this group of patients, with a median residual volume/total lung capacity (RV/TLC) ratio of 55.5% and a significant median oxygen desaturation during the 6MWT of 6%.

In most (36.0%) of the patients, the emphysema was obviously predominant in the upper lung (type 1 distribution). The next most common distributions were types 2 and 4 (somewhat predominant in the upper lung and somewhat predominant in the lower lung, seen in 25.6% and 22.1% of the patients, respectively). Type 3 emphysema distribution (homogeneous distribution between the upper and lower lung) was the least common, seen in only 16.3%. None of the patients in our sample were classified as presenting with type 5 emphysema distribution (obviously predominant in the lower lung). The interobserver correlation for emphysema classification scores was good ($r_s = 0.621$, $p < 0.001$).

Figure 2 shows the differences found in the clinical parameters according to CT scan classification of emphysema distribution. The six-minute walk distance (6MWD), post-6MWT oxygen desaturation, FVC, FEV_1, and FEV_1/FVC ratio (in % of the predicted values), as well as DLCO, were found to differ significantly among the groups. Tukey's post hoc test revealed that there were significant differences in all of the abovementioned variables between the patients classified as type 1 than those classified as type 4. In fact, all of those variables appear to get worse in upper-to-lower predominance direction. Patients classified as type 3 showed the highest RV/TLC ratio, although it did not reach statistical significance (p = 0.064).

The logistic regression analysis for different dimensions of the functional status revealed that type 4 patients had a significantly higher risk for having

Table 1. Demographic, clinical, and imaging characteristics of selected patients with emphysema-predominant COPD.[a]

Characteristic	(n = 86)
Age, years	65.2 ± 12.2
Gender	
Male	79 (91.9)
Female	7 (8.1)
BMI, kg/m^2	23.1 ± 4.5
Smoking history, pack-years	54 (38-79)
mMRC dyspnea scale score	1 (0.5-3.0)
mMRC dyspnea scale score ≥ 2	35 (40.8)
CAT score	12 (7.0-22.5)
CAT score ≥ 10	48 (56.1)
Exacerbations in the last year	1 (0-2)
≥ 2 exacerbations in the last year	21 (24.4)
Hypoxemia	15 (18.8)
Post-6MWT desaturation, %	6 (4.0-9.8)
6MWD, m	400 (256.3-463.8)
FVC, % of predicted	86.1 ± 24.8
FEV_1	50.0 (32.0-83.3)
FEV_1/FVC ratio	45.9 (35.0-63.2)
RV	162.0 (125.1-225.0)
TLC	118.3 ± 24.4
RV/TLC ratio	55.5 (43.9-67.1)
DLCO	59.0 (40.0-77.7)
Emphysema distribution	
Type 1 (obvious upper-lung predominance)	31 (36.0)
Type 2 (slight upper-lung predominance)	22 (25.6)
Type 3 (equal upper- and lower-lung extent)	14 (16.3)
Type 4 (slight lower-lung predominance)	19 (22.1)

mMRC: modified Medical Research Council; CAT: COPD Assessment Test; 6MWT: six-minute walk test; and 6MWD: six-minute walk distance. [a]Values are presented as mean ± SD, n (%), or median (interquartile range).

FEV_1 < 65% of the predicted value (adjusted OR = 6.92; 95% CI: 1.43-33.45; p = 0.016), 6MWD < 350 m (adjusted OR = 6.36; 95% CI: 1.26-32.18; p = 0.025), and hypoxemia (adjusted OR = 32.66; 95% CI: 3.26-326.84; p = 0.003; Table 2). However, none of the different types of emphysema distribution were found to be significant predictors of BMI ≤ 21 kg/m^2, ≥ 2 exacerbations in the last year, mMRC dyspnea scale score ≥ 2, or post-6MWT oxygen desaturation ≥ 4%.

DISCUSSION

Although COPD is a highly heterogeneous disease, its phenotyping can be more precise when CT of the lung parenchyma is combined with an evaluation of the clinical and physiological characteristics. Here, we describe the role of using a qualitative analysis of CT findings in order to determine the distribution of pulmonary emphysema and the potential contribution

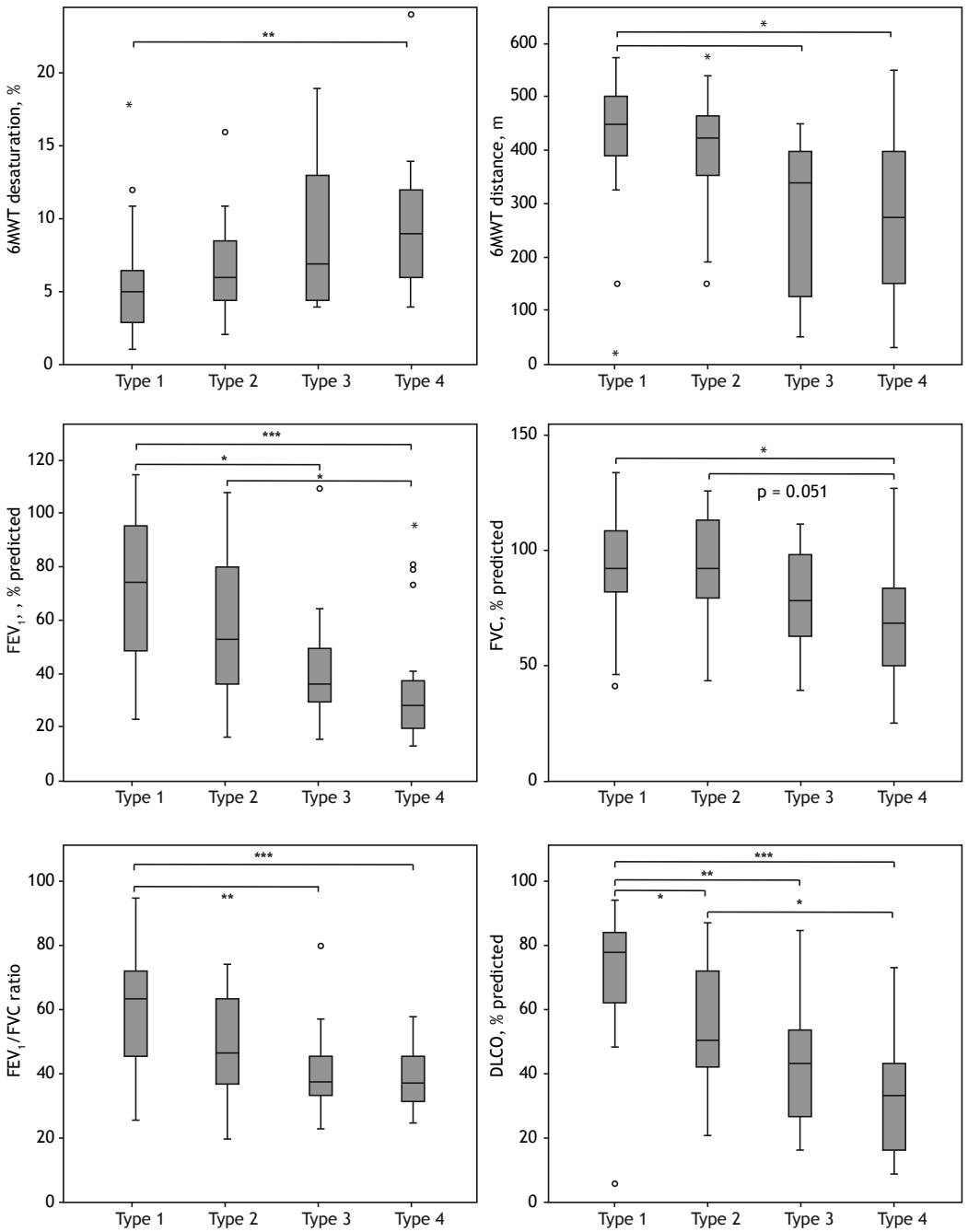

Figure 2. Lung functional characteristics of patients with different emphysema distribution. *Indicates a p value < 0.05. 6MWT: six-minute walk test; type 1: obviously predominant emphysema in upper lung; type 2: somewhat predominant emphysema in upper lung; type 3: equal extent of emphysema in upper and lower lung; and type 4: somewhat predominant emphysema in lower lung.

of that distribution to further characterizing the clinical severity of these patients.

Patients with COPD were classified according to a subjective heterogeneity analysis of upper versus lower lung distribution of pulmonary emphysema, using a visual scoring system first described by Chae et al.[18] In their assessments of the regional heterogeneity of the distribution of emphysema, those authors found a significant correlation between the quantitative assessment (with a computer algorithm) and the visual assessment. They also found that there was a considerable interobserver agreement in the visual assessment. Therefore, visual assessment of the distribution of pulmonary emphysema could be a reliable method, with one major advantage, which is the fact that everyone can use it, especially when CT analysis software is not available.

Our results suggest that, among COPD patients with emphysema, there is greater COPD severity, defined as a higher degree of airflow obstruction and lower alveolar-capillary diffusing capacity, in those with predominantly lower-lung emphysema, whereas functional status is better in those with predominantly upper-lung emphysema. These results can be explained, in part, by the smaller area of the lung affected when emphysema is predominantly in the upper lobes.

Regarding the COPD patients with homogeneous emphysema (type 3), our data indicate a tendency toward higher hyperinflation, with a higher RV/TLC ratio (Figure 2), although the difference did not reach statistical significance. That is probably associated with the broader, more uniform distribution of parenchymal destruction, together with the fact had a median pack-year smoking history was higher among the patients with type 3 emphysema distribution (60 pack-years vs. 40.5 pack-years for those with type 1 emphysema distribution; p = 0.012).

After stratifying the study population according to the cut-off values for the assignment of at least 1 point on the **B**ody mass index, airflow **O**bstruction, **D**yspnea, and **E**xercise capacity (BODE) index,[21] which assesses the risk of death for COPD patients, we observed that type 4 emphysema distribution (slightly predominant in the lower lung) significantly increases the risk of severe airway obstruction (FEV_1 < 65% of predicted) and reduced the 6MWD to < 350 m (Table 2). Hypoxemia was identified as another risk factor for mortality in COPD.[21,29] Our results show that patients with emphysema that is slightly predominant in the lower lung are more likely to be hypoxemic.

Our findings are consistent with those of previous studies showing a strong association between lower-zone emphysema and airflow limitation.[18,19,30] In another study, however, upper-zone predominance of emphysema was associated with a worse total St George's Respiratory Questionnaire score, although it was not significantly associate with FEV_1 (% of predicted).[17] Reports are also inconsistent concerning the relationship between diffusing capacity and regional differences in emphysema distribution. Gurney et al.[31] observed that DLCO is more strongly affected by lower-lung emphysema than by upper-lung emphysema, whereas Parr et al.[32] found DLCO to be relatively preserved in patients with lower-lung emphysema. Those differences might be attributable to the different methods applied for assessing the regional distribution of emphysema.

The present study has a number of limitations. First, the female gender is not well represented in this study group. However, that is representative of the gender distribution of emphysema patients treated at our outpatient clinic. Second, our sample did not include any subjects with clearly lower lung-predominant emphysema (type 5). Because most of the patients were smokers, that type of emphysema distribution (sparing the upper lung) would be expected to be rather rare. We can presume that the clinical-radiological correlations for type 5 emphysema would be similar to those found for type 4. In order to extrapolate our results, a larger study sample, with similar gender proportions and including all types of emphysema distribution, will be needed. Finally, some interobserver

Table 2. Distribution of pulmonary emphysema according to functional status and the respective functional severity.

Variable	Emphysema distribution	Frequency[a] n (%)	Adjusted OR[b] (95% CI)	p
FEV_1 < 65% of predicted[c]	Type 1	14 (45.2%)	1 (reference)	0.045*
	Type 2	13 (61.9%)	1.69 (0.32-8.92)	0.537
	Type 3	12 (85.7%)	5.79 (1.06-31.64)	0.043*
	Type 4	15 (78.9%)	6.92 (1.43-33.45)	0.016*
6MWD < 350 m[c]	Type 1	1 (3.6%)	1 (reference)	0.064
	Type 2	2 (9.5%)	1.63 (0.31-8.70)	0.567
	Type 3	3 (21.4%)	5.58 (1.01-30.84)	0.049*
	Type 4	9 (52.9%)	6.36 (1.26-32.18)	0.025*
Hypoxemia[d]	Type 1	3 (13.0%)	1 (reference)	0.006*
	Type 2	4 (20.0%)	2.85 (0.24-33.89)	0.408
	Type 3	6 (50.0%)	7.60 (0.67-86.19)	0.102
	Type 4	9 (52.9%)	32.66 (3.26-326.84)	0.003*

6MWD: six-minute walk distance; type 1: obvious upper-lung predominance; type 2: slight upper-lung predominance; type 3: equal upper- and lower-lung extent; type 4: slight lower-lung predominance. [a]Corresponds only to patients with the lowest functional status, as defined in the first column. [b]Adjusted for age and body mass index. [c]Cut-off value for the assignment of at least 1 point on the Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity (BODE) index. [d]Defined as a PaO_2 < 60 mmHg with an FiO_2 of 0.21. *p < 0.05.

variability is predictable, as previously noticed.[18,33,34] Such disagreement can be seen primarily for patients with the least severe emphysema and with only partial upper or lower lung predominance. In fact, most discordant cases were related to classification differences between contiguous types.

In the past, direct visual observation and subjective visual grading were considered to have similar precision as the computer-assisted methods of emphysema quantification on CT scans.[35-39] Although we have not provided a direct measure of emphysema severity, the purpose of this study was to present a qualitative (rather than quantitative), simple, affordable alternative method that could be widely used by clinicians to classify the heterogeneity of pulmonary emphysema.

In summary, in this group of COPD patients with pulmonary emphysema, lower lung-dominant distribution, as assessed by a subjective score, was found to have a significant impact on physiologic parameters, including pulmonary function test results and exercise capacity, although not on the clinical presentation of the disease, as assessed by the mMRC dyspnea scale score and the number of exacerbations in the last year. Further studies are warranted in order to confirm the importance of our findings.

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Factors associated with quality of life in patients with severe asthma: the impact of pharmacotherapy

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ABSTRACT

Objective: To identify, characterize, and quantify associations of various factors with quality of life (QoL) in patients with asthma, according to the pharmacotherapy employed. **Methods:** This was a cross-sectional study involving 49 patients (≥ 18 years of age) with severe uncontrolled or refractory asthma treated at a specialized outpatient clinic of the Brazilian Unified Health Care System, regularly using high doses of inhaled corticosteroids (ICs) or other medications, and presenting comorbidities. At a single time point, QoL was assessed with the Asthma Quality of Life Questionnaire (AQLQ). The overall AQLQ score and those of its domains were correlated with demographic variables (gender and age); Asthma Control Questionnaire score; pharmacotherapy (initial IC dose, inhaler devices, and polytherapy); and comorbidities. **Results:** Better AQLQ scores were associated with asthma control—overall (OR = 0.38; 95% CI: 0.004-0.341; p < 0.001), "symptoms" domain (OR = 0.086; 95% CI: 0.016-0.476; p = 0.001), and "emotional function" domain (OR = 0.086; 95% CI: 0.016-0.476; p = 0.001)—and with IC dose ≤ 800 µg—"activity limitation" domain (OR = 0.249; 95% CI: 0.070-0.885; p = 0.029). Worse AQLQ scores were associated with polytherapy—"activity limitation" domain (OR = 3.651; 95% CI: 1.061-12.561; p = 0.036)—and number of comorbidities ≤ 5—"environmental stimuli" domain (OR = 5.042; 95% CI: 1.316-19.317; p = 0.015). **Conclusions:** Our results, the importance of this issue, and the lack of studies taking pharmacotherapy into consideration warrant longitudinal studies to establish a causal relationship between the identified factors and QoL in asthma patients.

Keywords: Asthma; Asthma/drug therapy; Quality of life; Medication therapy management.

INTRODUCTION

Asthma is a chronic inflammatory disease of the lower airways and is among the most common chronic conditions, affecting children and adults. It is characterized by increased airway responsiveness to a variety of stimuli, resulting in airflow obstruction that is typically recurrent and reversible.[1]

Asthma treatment and its duration play a role in the severity of the aforementioned clinical manifestations (i.e., the severity of asthma). The more severe the clinical manifestations of asthma, the greater the difficulty in managing the disease.[2]

The estimated prevalence of asthma in Brazil is 10%. In large Brazilian cities, the mean prevalence of asthma symptoms is 24.3% in children and 19.0% in adolescents. A history of wheezing has been reported in 46.6% of the children living in the city of Salvador, Brazil, as has a trend toward an increase in the rate of physician-diagnosed asthma among children and adolescents in Brazil.[3,4]

In 2003, the *Programa de Controle da Asma e da Rinite Alérgica na Bahia* (ProAR, Bahia State Program for the Control of Asthma and Allergic Rhinitis) was created. The ProAR is a multidisciplinary education, research, and treatment program integrating the *Sistema Único de Saúde* (SUS, Brazilian Unified Health Care System) and the Federal University of Bahia, located in the city of Salvador. The ProAR focuses on preventing and treating asthma and allergic rhinitis; providing free medication regularly; reducing hospitalizations, emergency room visits, and mortality; and improving quality of life (QoL).[5-7]

The information obtained by assessing the QoL of patients treated at a given health care facility can inform decisions regarding the choice of procedures and treatments for achieving optimal patient health.[8] According to La Scala et al., QoL assessment is relevant to clinical practice because treatment planning and progression are focused on the patient rather than on the disease. They also state that a holistic approach is required in order to assess QoL, which should not be seen purely in terms of treatment outcome.[9]

The Asthma Quality of Life Questionnaire (AQLQ) is a disease-specific instrument that was developed in 1992 specifically for use in clinical studies. It is the instrument that is most widely used in asthma studies. The AQLQ comprises domains assessing multiple aspects of the daily life of asthma patients and assesses their physical and emotional status, thus allowing assessment of the subjective experience of asthma. It was validated for use in Brazil in 2007.[10,11]

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The use of inhaler devices in the pharmacotherapy of asthma requires patient education on inhaler technique and handling. Optimal inhaler use increases lung drug deposition and, consequently, treatment efficacy, resulting in asthma control, which is important for a better QoL.[12] The level of patient satisfaction with their inhaler device has been found to have a positive influence on patient-reported outcomes in asthma, resulting in fewer emergency room visits, fewer nocturnal exacerbations, and improved QoL.[13]

Studies have shown a correlation between the level of asthma control and QoL. Questionnaires have been developed in order to assess the level of asthma control, and studies have assessed the correlation between asthma control and QoL.[14,15] The Asthma Control Questionnaire (ACQ) is an instrument that can be used in clinical practice, clinical trials, and cross-sectional studies, ACQ scores correlating well with AQLQ scores.[14,16]

Severe asthma has been associated with numerous comorbidities that are related to poor asthma control, increased use of the health care system, and reduced QoL, the management of which has been reported to have a positive impact on asthma outcomes.[17] Comorbidities are common and include allergic rhinitis, obesity, osteoporosis, gastroesophageal reflux disease, tuberculosis, hypertension, and diabetes.[18]

In addition to presenting with comorbidities, asthma patients are often on polypharmacy. The risk of drug interactions and adverse drug reactions increases exponentially with the number of drugs used. Iatrogenic complications can lead to the addition of other medications, polypharmacy therefore being a public health problem that has a negative impact on patient QoL.[19]

In Bahia, patients with severe asthma have access to a program that provides treatment with inhaled corticosteroids (ICs) and bronchodilators, as well as asthma education and guidance on the use of inhalers. However, given the complexity of the pharmacological treatment of severe asthma and the clinical manifestations of the underlying disease, asthma management involves more than disease control and access to drugs. In the context of pharmaceutical care, few studies have examined the impact of pharmacotherapy on the QoL of patients with severe asthma.

Given the importance of this issue, the objective of the present study was to identify and characterize factors associated with QoL in patients with severe asthma treated at a referral center in the city of Salvador, as well as to determine the association of QoL-related factors with AQLQ scores (overall and individual domain scores).

METHODS

This was a cross-sectional study to assess the QoL of patients with severe asthma. The study was conducted between September and November of 2013. The data were collected from the database of a randomized controlled clinical trial conducted at an SUS asthma outpatient clinic, where the ProAR is headquartered.

The study population consisted of patients 18 years of age or older treated at the ProAR outpatient clinic and presenting with severe asthma, refractory asthma, or uncontrolled asthma (or meeting clinical criteria for severe asthma); receiving drugs regularly from the ProAR pharmacy; using polypharmacy, high-dose ICs, or both; presenting with comorbidities; and having an $FEV_1 \leq 60\%$ of predicted.

At a single time point, QoL was assessed with the AQLQ, which was administered by three previously trained pharmacists. The AQLQ is a disease-specific questionnaire consisting of 32 items grouped into four domains: activity limitation (11 items); symptoms (12 items); emotional function (5 items); and environmental stimuli (4 items). It can be interviewer-administered or self-administered. The overall AQLQ score is the arithmetic mean of all items, the minimum score being 1 (extremely low QoL) and the maximum score being 7 (excellent QoL).[10]

The level of asthma control was assessed with the ACQ, which was administered at the same time point as was the AQLQ. The ACQ consists of seven questions: five questions regarding symptoms; one question regarding the use of short-acting β_2 agonists; and one question regarding FEV_1. All items have the same weight, and the level of asthma control is given by the arithmetic mean of all items, ranging from zero (well-controlled asthma) to six (severely uncontrolled asthma).[20]

The following data were collected from the aforementioned database: sociodemographic data (gender, age, level of education, race, and occupation); clinical data (history of smoking, history of pulmonary tuberculosis, presence of other respiratory diseases, diagnosis of refractory asthma, BMI, presence of comorbidities, percent predicted FEV_1, and ACQ scores); clinical data on pharmacotherapy (starting dose of ICs, types of inhalers, number of inhalers, and number of drugs used); and QoL data (AQLQ scores).

Given that the AQLQ was administered at a single time point, a cut-off score of 4 (moderate QoL) was used as reference. Scores > 4 were considered to indicate moderate-to-excellent QoL, whereas scores ≤ 4 were considered to indicate moderate-to-poor QoL.[21]

For the ACQ, the cut-off score was set at 1.5. Scores ≤ 1.5 were considered to indicate controlled asthma, whereas scores > 1.5 were considered to indicate uncontrolled asthma.[20]

Polytherapy was defined as the use of at least five drugs.[19]

High-dose IC use was defined as the use of more than 800 µg of budesonide or equivalent.[2]

Descriptive statistics were calculated for sociodemographic, clinical, QoL, and pharmacotherapy variables.

The Kolmogorov-Smirnov test was used in order to determine whether quantitative variables were normally

distributed. Variables with normal distribution were summarized as means, whereas those with non-normal distribution were summarized as medians.

For variables with normal distribution, the Student's t-test was used in order to assess significant differences between comparison groups. For variables with non-normal distribution, the Mann-Whitney test was used. The value of p was derived from those two tests, in accordance with the characteristics of the study variables.

The variables of interest were dichotomized as follows: gender (male/female); age (< 60 years/≥ 60 years); number of inhalers used in combination (≤ 2 inhalers/> 2 inhalers); IC dose (≤ 800 µg/> 800 µg); polytherapy (yes/no); level of asthma control (ACQ ≤ 1.5/ACQ > 1.5); number of comorbidities (≤ 5 comorbidities/> 5 comorbidities); overall AQLQ score and individual AQLQ domain scores (≤ 4 /> 4). The odds ratios (ORs) for the associations of the study variables with the overall AQLQ score and those of its domains were thus estimated.

Finally, the factors associated with QoL in the study sample were identified and characterized, and their association with the overall AQLQ score and individual AQLQ domain scores was determined.

Independent variables were associated with better QoL when 0 < OR < 1, being associated with worse QoL when OR > 1. An OR of 1 indicated that there was no association between a given independent variable and QoL. Values of $p < 0.05$ were considered statistically significant.

The present study was approved by the Research Ethics Committee of the Federal University of Bahia Professor Edgard Santos University Hospital (CAAE 128/2008), in the city of Salvador.

Statistical analysis was performed with the Statistical Package for the Social Sciences, version 14.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 50 patients whose data were available in our database, 49 (98%) were evaluated in the present study, 1 (2%) being excluded from the analysis because of missing data.

The sociodemographic and clinical characteristics of the patients studied are presented in Table 1. The data on pharmacotherapy are presented in Table 2.

The AQLQ scores reveal a moderate QoL in our sample (approximately 4), both regarding the overall AQLQ scores and the AQLQ domain scores (Table 3).

Neither the overall AQLQ score nor individual AQLQ domain scores showed significant differences regarding gender, age, or number of inhalers used in combination. Although the overall AQLQ score did not show statistically significant differences regarding IC dose, polytherapy, or number of comorbidities, some of the individual AQLQ domain scores did.

There was a statistically significant difference between the level of asthma control (mean ACQ scores) and the overall AQLQ score ($p < 0.01$).

Regarding the AQLQ domain scores, there were statistically significant differences of polytherapy and IC dose with AQLQ "activity limitation" domain scores.

There was a statistically significant difference between the number of comorbidities and AQLQ "environmental stimuli" domain scores.

Asthma control (ACQ scores) was found to show statistically significant differences with AQLQ "emotional function" and "symptoms" domain scores (Table 4).

The ORs for the associations of the study variables with the overall AQLQ score and those of its domains are shown in Table 4.

DISCUSSION

In the present study, neither the overall AQLQ score nor individual AQLQ domain scores were significantly associated with gender, age, or number of inhalers used in combination.

In contrast, the overall AQLQ score and those of its domains (symptoms, activity limitation, emotional function, and environmental stimuli) were significantly associated with the following variables: polytherapy; IC dose; ACQ score; and number of comorbidities.

Of the study variables, polytherapy and IC dose are directly related to the pharmacological treatment of asthma. In contrast, the ACQ score and the number of comorbidities are indirectly related to the pharmacological treatment of asthma.

The ACQ score is indirectly related to the pharmacological treatment of asthma because the latter is aimed at controlling the disease, reducing airway remodeling, and reducing mortality.[1,15] The number of comorbidities is also related to the pharmacological treatment of asthma, in the form of polytherapy use or untreated conditions. Therefore, the association of those variables with QoL was assessed (with the AQLQ).

Many studies have assessed the QoL of asthma patients, showing that severe asthma has a strong impact on QoL.[9-11,22,23]

Given that the present study was a cross-sectional study in which the AQLQ was administered at a single time point, an AQLQ score of 4 (i.e., moderate QoL) was used as a cut-off point for the association of independent variables with QoL. In another cross-sectional study, the same cut-off point was used in order to assess the QoL of asthma patients at a single time point. The AQLQ is an instrument that is cross-sectionally and longitudinally correlated with clinical measures.[10,24]

The concept of polytherapy remains controversial in the literature. Studies have shown that polytherapy does not improve the QoL of patients, as well as showing drug interaction rates as high as 50% and the possibility of iatrogenic complications from the concomitant use of at least five drugs.[19,25-27]

Table 1. Sociodemographic and clinical characteristics of 49 patients with severe or refractory asthma treated at a Brazilian Unified Health Care System asthma outpatient clinic in the city Salvador, Brazil.[a]

Characteristic	Result
Age, years	53.6 ± 13.4
Gender	
Female	41 (84)
Male	8 (16)
Race	
Black	22 (45)
Mulatto	7 (14)
White	7 (14)
Other	6 (13)
No data	7 (14)
Occupation	
Homemaker	18 (37)
Workers in the commercial sector	3 (6)
Legal assistant	7 (14)
Retired	10 (20)
Seamstress	2 (4)
Housekeeper	2 (4)
Unemployed	1 (2)
Other	6 (14)
Level of education	
Illiterate	2 (4)
9 years of schooling	28 (57)
High school	12 (25)
College	7 (14)
History of smoking	
Yes	19 (38)
No	30 (62)
History of pulmonary tuberculosis	
Yes	12 (25)
No	37 (76)
Refractory asthma	
Yes	10 (20)
No	39 (80)
Obesity	
Yes	14 (29)
No	35 (71)
FEV_1, % of predicted	47.6 ± 15.8

[a]Values expressed as n (%). or as mean ± SD.

Table 2. Descriptive statistics for the independent variables associated with pharmacotherapy in patients with severe asthma treated at an asthma referral center in the city of Salvador, Brazil.[a]

Variable	Result
ACQ score[b]	2.73 ± 1.37
Number of comorbidities[c]	4 (2-8)
Inhaled corticosteroid dose, μg[c]	1,600 (800-1,800)
Combined use of inhaler devices (DPI + MDI)	19 (39)
Aerolizer® used as the primary treatment for asthma	28 (57)
MDI used as an add-on device	30 (61)
Concomitant use of at least 5 drugs	31 (62)

ACQ: Asthma Control Questionnaire; DPI: dry powder inhaler; and MDI: metered dose inhaler. [a]Values expressed as n (%), except where otherwise indicated. [b]Value expressed as mean ± SD. [c]Values expressed as median (range).

Table 3. Overall Asthma Quality of Life Questionnaire score and individual domain scores.[a]

AQLQ score	Result
Overall	3.66 ± 1.41
Symptoms domain	3.69 ± 1.52
Activity limitation domain	3.59 ± 1.45
Emotional function domain	3.60 ± 1.87
Environmental stimuli domain	4 (1-7)

AQLQ: Asthma Quality of Life Questionnaire. [a]Values expressed as mean ± SD or as median (range).

In the present study, polytherapy was significantly associated with AQLQ "activity limitation" domain scores. It can be assumed that the use of polytherapy increased the likelihood of worse QoL outcomes in the "activity limitation" domain. Although mean overall scores were more likely to be negatively influenced by the "activity limitation" domain score (< 4, i.e., moderate-to-poor QoL), there was no significant association between polypharmacy and the overall AQLQ score to confirm this assumption.

The level of asthma control (as measured by the ACQ) was found to be a "protective factor" for the overall AQLQ score and for AQLQ "symptoms" and "emotional function" domain scores. An ACQ score ≤ 1.5 (controlled asthma) increased the likelihood of better overall AQLQ scores (> 4) and better AQLQ "symptoms" and "emotional function" domain scores. Other studies have shown an association between well-controlled asthma and better QoL, patients with well-controlled asthma having higher overall AQLQ scores.[16,28]

In the present study, an association was found between the number of comorbidities and AQLQ "environmental stimuli" domain scores. It is of note that patients with fewer than five comorbidities were more likely to have worse "environmental stimuli" domain scores. Consequently, their overall AQLQ scores were more likely to be negatively influenced by their "environmental stimuli" domain scores, although the association was not statistically significant.

Although the study design does not allow causal interpretations, it is possible that, in our sample, there were patients with other respiratory diseases or with medical conditions influenced by factors associated with environmental stimuli, and that those factors played a role in the lack of asthma control (atopy, difficult-to-control allergic rhinitis, etc.). Therefore, it is possible that patient perception of QoL was negatively influenced by the presence of such comorbidities, regardless of the number of comorbidities.

Allergy might be linked to asthma by genetic or environmental factors.[17] However, allergy was not assessed in the present study.

Table 4. Association of independent variables with the overall Asthma Quality of Life Questionnaire score and those of its individual domains.

Variable	Overall score		Symptoms domain score		Activity limitation domain score		Emotional function domain score		Environmental stimuli domain score	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Gender	2.215 (0.382-11.828)	0.382	0.962 (0.201-4.604)	0.961	4.480 (0.503-39.919)	0.149	1.920 (0.344-10.711)	0.452	0.864 (0.190-3.932)	0.851
Age	1.064 (0.467-5.512)	0.451	1.830 (0.528-6.342)	0.338	2.100 (0.599-7.361)	0.242	0.808 (0.225-2.896)	0.743	3.231 (0.901-11.586)	0.069
Number of inhalers	0.900 (0.285-2.843)	0.858	0.750 (0.234-2.408)	0.628	0.889 (0.274-2.885)	0.845	1.067 (0.334-3.40)	0.913	2.489 (0.787-7.870)	0.121
Polytherapy	1.800 (0.554-5.845)	0.326	2.100 (0.638-6.916)	0.219	3.651 (1.061-12.561)	0.036	1.008 (0.306-3.318)	0.990	1.029 (0.325-3.253)	0.962
ACQ score	0.380 (0.004-0.341)	0.000	0.086 (0.016-0.476)	0.001	0.262 (0.062-1.111)	0.060	0.086 (0.016-0.476)	0.001	0.298 (0.067-1.330)	0.105
Number of comorbidities	0.461 (0.122-1.741)	0.253	0.317 (0.075-1.330)	0.110	0.587 (0.154-2.237)	0.438	0.808 (0.225-2.896)	0.745	5.042 (1.316-19.317)	0.015
IC dose	0.500 (0.148-1.691)	0.266	0.435 (0.127-1.487)	0.184	0.249 (0.070-0.885)	0.029	0.643 (0.189-2.187)	0.483	1.771 (0.522-6.003)	0.362

ACQ: Asthma Control Questionnaire; and IC: inhaled corticosteroid.

The results of the present study differ from those of other studies. According to Heyworth et al., a higher number of chronic conditions translates to a greater negative impact on QoL.[29]

The use of ≤ 800 µg of budesonide or equivalent was found to be associated with better QoL outcomes in the "activity limitation" domain (a score > 4, i.e., moderate-to-excellent QoL) in the present study. Patients using ≤ 800 µg of budesonide or equivalent were more likely to have better AQLQ "activity limitation" domain scores. Therefore, it is possible that the use of ≤ 800 µg of budesonide or equivalent contributed positively to the overall AQLQ score. However, no statistically significant association was found between the use of ≤ 800 µg of budesonide or equivalent and the overall AQLQ score to confirm this assumption.

The results of the present study differ from those of a study of patients with moderate to severe asthma before and after treatment with high-dose fluticasone (equivalent to 1,600 µg of budesonide).[30] The overall AQLQ score was correlated with better QoL, as were individual AQLQ domain scores. However, the aforementioned study was a longitudinal study of 60 patients. Therefore, it is possible that the degree of association in that study was different from that in the present study. In addition, the aforementioned study was not conducted in Brazil, meaning that various patient-related factors might have influenced QoL outcomes.[30]

In the present study, it was impossible to assess other aspects of pharmacotherapy, such as adherence to treatment, adverse reactions to ICs or other drugs, use of medicinal plants/herbal medicines, and stratification by drug class, because the available data were insufficient to do so.

Studies that have a cross-sectional design preclude the establishment of causal relationships between QoL and independent variables. However, the importance of this issue, the results presented herein, and the lack of QoL studies taking pharmacotherapy into consideration warrant longitudinal studies to establish such relationships.

The importance of this issue and the results of the present study indicate the need for studies investigating pharmacotherapy-related factors influencing the QoL of patients with severe asthma treated at an SUS referral outpatient clinic.

With regard to the goals established by the clinical protocols and treatment guidelines for asthma control, improving the QoL of patients with severe asthma is as important as choosing the appropriate pharmaceutical interventions and drug therapies, given that QoL reflects how patients perceive asthma management outcomes and how they live with the disease.

Pharmacists play an extremely important role in the management of severe asthma, recognizing pharmacotherapy-related factors associated with QoL measures and aiding in choosing the appropriate drug therapy for controlling asthma, reducing morbidity, reducing mortality, and enhancing patient well-being.

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Evaluation of quality of life according to asthma control and asthma severity in children and adolescents

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ABSTRACT

Objective: To evaluate quality of life according to the level of asthma control and degree of asthma severity in children and adolescents. **Methods:** We selected children and adolescents with asthma (7-17 years of age) from the Pediatric Pulmonology Outpatient Clinic of the State University of Campinas *Hospital de Clínicas*, located in the city of Campinas, Brazil. Asthma control and asthma severity were assessed by the Asthma Control Test and by the questionnaire based on the Global Initiative for Asthma, respectively. The patients also completed the Paediatric Asthma Quality of Life Questionnaire (PAQLQ), validated for use in Brazil, in order to evaluate their quality of life. **Results:** The mean age of the patients was 11.22 ± 2.91 years, with a median of 11.20 (7.00-17.60) years. We selected 100 patients, of whom 27, 33, and 40 were classified as having controlled asthma (CA), partially controlled asthma (PCA), and uncontrolled asthma (UA), respectively. As for asthma severity, 34, 19, and 47 were classified as having mild asthma (MiA), moderate asthma (MoA), and severe asthma (SA), respectively. The CA and the PCA groups, when compared with the NCA group, showed higher values for the overall PAQLQ score and all PAQLQ domains (activity limitation, symptoms, and emotional function; $p < 0.001$ for all). The MiA group showed higher scores for all of the PAQLQ components than did the MoA and SA groups. **Conclusions:** Quality of life appears to be directly related to asthma control and asthma severity in children and adolescents, being better when asthma is well controlled and asthma severity is lower.

Keywords: Asthma; Quality of life; Child; Adolescent.

INTRODUCTION

Asthma is a heterogeneous chronic inflammatory disease, characterized by recurrent episodes of wheezing, dyspnea, chest tightness, and cough, that is very common in children and adolescents.[1,2] Asthma is considered a global health problem and affects approximately 300 million people worldwide; in Brazil, it affects 24.3% of school-age children and 19.0% of adolescents.[1,3]

Quality of life is defined as the perception that individuals have of their position in life, in the context of the culture and system of values in which they live and in relation to their objectives, expectations, standards, and concerns. Quality of life can change according to the environment and the experiences had up to that point, as well as in response to certain diseases.[4,5]

From that perspective, it becomes important to evaluate quality of life in patients with chronic diseases such as asthma, because they can impair quality of life in its various biopsychosocial domains and can affect the daily lives of the affected population.[6,7] In addition, children and adolescents deserve special attention, because asthma affects not only the individuals with the disease, but also their caregivers, thereby altering the family routine and the quality of life of all involved.[8-10]

Children and adolescents with well-controlled asthma and lower asthma severity, which lead to a reduction in symptoms and medication use, can have a better quality of life.[11-13] The present study is warranted because it is necessary to characterize quality of life in children and adolescents with asthma treated at asthma referral centers. The understanding of the extent to which asthma control status and asthma severity can affect quality of life will help establish therapeutic, environmental, and behavioral strategies, resulting in increased awareness within the health care system as a whole, so that interventions allowing a favorable disease outcome are promoted.

The objective of the present study was to evaluate quality of life according to the level of asthma control and degree of asthma severity in children and adolescents treated at an asthma referral center.

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METHODS

This was an observational, cross-sectional, analytical clinical study conducted at the Pulmonary Physiology Laboratory of the Center for Pediatric Studies of the *Universidade Estadual de Campinas* (Unicamp, State University at Campinas), in the state of São Paulo, Brazil, between November of 2013 and January of 2015.

We included all children and adolescents 7-17 years of age and diagnosed with atopic asthma from the Pediatric Pulmonology Outpatient Clinic of the Unicamp *Hospital de Clínicas*.[1,2] We excluded subjects with cardiac comorbidities resulting in significant hemodynamic changes; those with respiratory diseases resulting in anatomical and structural changes confirmed by ancillary tests; those with cognitive or motor limitations that could compromise their performance in or understanding of the tests; and those who had an exacerbation on the day of testing.

Asthma control was assessed by the Asthma Control Test (ACT), which has been validated for use in Brazil and consists of five questions regarding signs, symptoms, and rescue medication use in the last four weeks.[14-16] In the present study, the following ACT scores were used for defining the level of asthma control: controlled asthma (CA), 25 points; partially controlled asthma (PCA), 20-24 points; and uncontrolled asthma (UA), < 19 points.[1,14-16]

The classification of asthma severity was based on the modified criteria of the Global Initiative for Asthma guidelines, through analysis of the following parameters: symptoms; nocturnal awakenings; rescue medication use; activity limitation; and FEV_1.[1,17,18] As a result, asthma patients were divided into three groups: mild asthma (MiA); moderate asthma (MoA); and severe asthma (SA). This classification always took into account the most severe clinical or functional manifestation.

Quality of life was analyzed by using the Paediatric Asthma Quality of Life Questionnaire (PAQLQ), which has been validated for use in Brazil and consists of 23 questions divided into three domains.[19] The activity limitation domain includes five questions regarding the discomfort that the disease causes during certain activities; the symptoms domain, which consists of ten questions, refers to the discomfort that asthma attacks, cough, dyspnea, wheezing, chest tightness, and nocturnal awakenings cause in children and adolescents; and the emotional function domain, which consists of eight questions, addresses the frequency at which asthma makes patients feel angry, feel afraid because of an asthma attack, feel different from others or excluded, and feel irritated or upset because they cannot keep pace with others.[5,19,20] Responses were made on a 7-point scale, on which 1 indicates the most severe impairment and 7 indicates no impairment at all.[5,19,20] All items have equal weight, and, in addition to the domain scores, the arithmetic means of the responses to the 23 questions is calculated to give an overall score.[5,19,20]

In order to analyze the extent to which asthma control status and asthma severity affected the quality of life of the children and adolescents included in the study, patient quality of life was classified as follows (on the basis of the PAQLQ score): minimal or no impairment (≥ 6.0 points); moderate impairment (3.0-5.9 points); and severe impairment (< 3.0 points).[11]

The data were processed with the Statistical Package for the Social Sciences for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA).

Categorical variables were presented in a descriptive fashion, and differences were analyzed with the Fisher-Freeman-Halton test, bilateral probability being estimated by the Monte Carlo method. Kruskal-Walli. In order to compare the distributions of nonparametric quantitative variables among three groups, we used the Kruskal-Wallis test, using a nonparametric multiple comparison test when significant differences were found. In all cases, the level of significance was set at 5%.

This study was submitted to and approved by the Research Ethics Committee of the Unicamp School of Medical Sciences (Ruling no. 438.481/2013). The parents or legal guardians of all children and adolescents participating in the study gave written informed consent.

RESULTS

We evaluated all patients diagnosed with atopic asthma who were treated at the Pediatric Pulmonology Outpatient Clinic of the Unicamp *Hospital de Clínicas* during the study period. We selected 136 patients on the basis of the inclusion criteria. Of those, 14 were excluded because they had heart disease resulting in significant hemodynamic changes; 18 were excluded because of other respiratory comorbidities, such as bronchiectasis and bronchiolitis obliterans; 2 were excluded because of cognitive limitations; and 2 were excluded because of motor limitations.

The mean age of the 100 patients included in the study was 11.22 ± 2.91 years, with a median of 11.20 (7.00-17.60) years. Of the 100 patients, 55 (55.0%) were male and 45 (45.0%) were female.

Participants were divided into three groups according to the level of asthma control: the CA, PCA, and UA groups, which included 27 patients (27.0%), 33 patients (33.0%), and 40 patients (40.0%), respectively. Of the 27 children and adolescents in the CA group, 21 (77.8%) had MiA, whereas 6 (22.2%) had MoA and none had SA. In the PCA group, 12 (36.9%) had MiA, 12 (36.9%) had MoA, and 9 (27.3%) had SA. In the UA group, only 1 (2.5%) had MiA, 1 (2.5%) had MoA, and 38 (95.0%) had SA. Therefore, the MiA, MoA, and SA groups included 34 patients (34.0%), 19 patients (19.0%), and 47 patients (47.0%), respectively.

We found an association between asthma control and asthma severity ($p < 0.001$); the patients in the SA group were significantly more likely to belong to

the UA group (OR = 107.67; 95% CI: 21.98-527.3; p < 0.001).

We found no association between gender and asthma control or between gender and asthma severity.

When comparing the asthma control groups, we found no significant differences in age, Z-score for height, or BMI (Table 1). As for the asthma severity groups, the MoA group had a significantly higher mean age than did the SA group, but there were no differences among the groups in terms of Z scores for height or BMI (Table 2), which makes them comparable.

The distribution of means and standard deviations of the overall PAQLQ score, as well as of the scores for the activity limitation, symptoms, and emotional function domains of the PAQLQ, is shown in Tables 3 and 4. When analyzing the values in terms of asthma control and asthma severity, we found significant differences in all of the parameters evaluated (p < 0.001).

The CA and the PCA groups showed significantly higher values for the overall PAQLQ score and all PAQLQ domains than did the UA group (p < 0.001 for all; Table 3). The MiA group showed significantly higher values for the overall PAQLQ score and the PAQLQ symptoms and emotional function domains than did the MoA and the SA groups (p < 0.001 for all). In contrast, when we compared the MiA and the MoA groups in terms of the scores for the PAQLQ activity limitation domain, we found no significant difference (Table 4). In both cases, the PAQLQ activity limitation domain was the most affected.

The distribution of the degree of impairment reported by the patients in the PAQLQ components (overall score and domains), by level of asthma control and by asthma severity, is shown in Tables 5 and 6, respectively. Significant differences were found in all components (p < 0.001 for all). In terms of the overall score, 37.0% of the patients had minimal or no impairment; 57.0% had moderate impairment; and 6.0% had severe impairment. These 6 participants who reported severe impairment of their quality of life belonged to the UA and the SA groups (Tables 5 and 6).

In terms of the activity limitation domain, 31% of the study participants had minimal or no impairment, 58% had moderate impairment, and 11% had severe impairment. Of the 31 individuals with minimal or no impairment, 58.1% belonged to the CA group, whereas 64.5% belonged to the MiA group (Tables 5 and 6).

Analysis of the symptoms domain showed that 49% of the children and adolescents had minimal or no impairment, 45% had moderate impairment, and 6% had severe impairment. As was true for the overall score, the 6 subjects with severe impairment belonged to the UA and the SA groups (Tables 5 and 6).

Assessment of the emotional function domain showed that 55% of the subjects had minimal or no impairment, 36% had moderate impairment, and 9% had severe impairment. Of the participants with minimal or no impairment, 23 belonged to the CA group and 30 belonged to the MiA group (Tables 5 and 6).

Table 1. Distribution of age (in years), Z scores for height, and BMI in the children and adolescents in the study, by level of asthma control.

Variable	Group	n	Mean	SD	Minimum	Median	Maximum	p
Age	CA	27	11.26	2.78	7.3	11.2	17.2	0.473
	PCA	33	11.70	3.23	7.2	11.4	17.6	
	UA	40	10.80	2.71	7.0	10.8	17.2	
Height	CA	27	0.05	1.14	−2.19	−0.22	1.96	0.682
	PCA	33	−0.14	0.87	−1.58	−0.26	1.96	
	UA	40	−0.16	1.04	−2.43	−0.10	1.96	
BMI	CA	27	0.23	1.36	−2.61	0.69	2.47	0.491
	PCA	33	0.48	1.50	−2.40	0.39	3.35	
	UA	40	0.71	1.34	−1.74	0.75	1.34	

CA: controlled asthma; PCA: partially controlled asthma; and UA: uncontrolled asthma. Kruskal-Wallis test.

Table 2. Distribution of age (in years), Z scores for height, and BMI in the children and adolescents in the study, by asthma severity.

Variable	Group	n	Mean	SD	Minimum	Median	Maximum	p
Age	MiA	34	11.21	2.79	7.2	11.2	17.2	0.043
	MoA	19	12.47	3.23	7.8	13.6	17.6	
	SA	47	10.62	2.68	7.0	10.8	17.2	
Height	MiA	34	−0.14	1.01	−2.19	−0.30	1.96	0.911
	MoA	19	−0.07	1.01	−1.58	−0.26	1.91	
	SA	47	−0.08	1.03	−2.43	−0.01	1.96	
BMI	MiA	34	0.38	1.49	−2.61	0.61	3.35	0.614
	MoA	19	0.34	1.19	−1.51	0.65	2.43	
	SA	47	0.66	1.42	−2.40	0.71	3.25	

MiA: mild asthma; MoA: moderate asthma; and SA: severe asthma. Kruskal-Wallis test and multiple comparison test (age: MoA > SA).

Table 3. Distribution of the values for the Paediatric Asthma Quality of Life Questionnaire components, by level of asthma control.

Variable	Group	Mean	SD	Minimum	Median	Maximum	p
Overall	CA	6.39	0.88	3.92	6.61	7.00	< 0.001
	PCA	5.83	0.84	3.65	5.20	7.00	
	UA	4.20	1.16	1.50	4.44	6.10	
Activity limitation	CA	6.16	1.17	3.40	7.00	7.00	< 0.001
	PCA	5.51	1.09	2.20	5.40	7.00	
	UA	3.73	1.09	1.60	4.00	6.00	
Symptoms	CA	6.51	0.77	4.20	6.60	7.00	< 0.001
	PCA	6.02	0.77	3.80	6.10	7.00	
	UA	4.33	1.37	1.20	4.40	6.70	
Emotional function	CA	6.49	0.98	2.75	6.87	7.00	< 0.001
	PCA	5.96	1.14	1.63	6.37	7.00	
	UA	4.54	1.54	1.25	4.87	6.63	

CA: controlled asthma; PCA: partially controlled asthma; and UA: uncontrolled asthma. Kruskal-Wallis test and multiple comparison test (CA > UA and PCA > UA for all variables).

Table 4. Distribution of the values for the Paediatric Asthma Quality of Life Questionnaire components, by asthma severity.

Variable	Group	Mean	SD	Minimum	Median	Maximum	p
Overall	MiA	6.37	0.63	4.90	6.50	7.00	< 0.001
	MoA	5.56	1.09	3.65	5.48	7.00	
	SA	4.49	1.31	1.50	4.56	7.00	
Activity limitation	MiA	6.02	1.09	3.60	6.40	7.00	< 0.001
	MoA	5.32	1.37	2.20	5.20	7.00	
	SA	4.09	1.32	1.60	4.10	7.00	
Symptoms	MiA	6.50	0.56	5.20	6.70	7.00	< 0.001
	MoA	5.69	1.04	3.80	5.80	7.00	
	SA	4.66	1.48	1.20	4.70	7.00	
Emotional function	MiA	6.59	0.54	5.00	6.75	7.00	< 0.001
	MoA	5.69	1.22	2.75	6.12	7.00	
	SA	4.71	1.63	1.25	5.06	7.00	

MiA: mild asthma; MoA: moderate asthma; and SA: severe asthma. Kruskal-Wallis test and multiple comparison test: (overall: MiA > MoA; MiA > SA; and MoA > SA); (activity limitation: MiA > SA; MoA > SA); and (symptoms and emotional function: MiA > MoA; MiA > SA).

DISCUSSION

Our data demonstrate that quality of life is directly related to asthma control and asthma severity in children and adolescents from a referral center.

Roncada et al. conducted a systematic review of questionnaires that have been validated and used for evaluating quality of life in children and adolescents with asthma, concluding that the PAQLQ is the most suitable for use in the Brazilian population.[21] Therefore, the data of the present study were compared with those of other studies that used the same questionnaire.

Our results for the overall PAQLQ score corroborate those of the validation study of the PAQLQ for use in Italy, in which the authors found that the questionnaire correlates well with asthma control and asthma severity and that lower values for the overall PAQLQ score are observed in pediatric patients with poorly controlled asthma and greater asthma severity.[6]

Studies have demonstrated that asthma control is directly related to a better quality of life, and, consequently, there is less impairment in social interaction and in the presence of physical and emotional changes in the asthma population.[8,22-26] Al-Gewely et al. evaluated quality of life in children and adolescents with asthma in Egypt by using the PAQLQ and also found higher scores in the group with controlled asthma.[27]

When following children and adolescents with asthma at three hospitals in Spain for five weeks, Tauler et al. evaluated asthma severity, quality of life, diary PEF, the global index of change, and the general health perception scale.[28] The authors found that the patients with mild intermittent or mild persistent asthma showed higher values for the overall score than did those with moderate or severe persistent asthma. In our study, the MiA group also showed higher values than did the MoA and the SA groups.

In contrast, in a validation study of the PAQLQ conducted in Turkey, no differences were found in the overall score between the MiA and the MoA groups, a finding the authors attributed to the fact that they did not include patients with SA, and, therefore, the comparison involved only children and adolescents with MiA or MoA.[29]

The activity limitation domain was the PAQLQ component with the lowest values in the asthma control

Table 5. Distribution of the cases by level of asthma control and by degree of impairment reported in the components of the Paediatric Asthma Quality of Life Questionnaire.

Variable	CA	PCA	UA	Cases	p
	n (%)	n (%)	n (%)	n	
Cases	27 (27.0)	33 (33.0)	40 (40.0)	100	
Overall					
Minimal or no impairment	21 (56.8)	14 (37.8)	2 (5.4)	37	< 0.001
Moderate impairment	6 (10.5)	19 (33.3)	32 (56.1)	57	
Severe impairment	0 (0.0)	0 (0.0)	6 (100.0)	6	
Activity limitation					
Minimal or no impairment	18 (58.1)	12 (38.7)	1 (3.2)	31	< 0.001
Moderate impairment	9 (15.5)	20 (34.5)	29 (50.0)	58	
Severe impairment	0 (0.0)	1 (9.1)	10 (90.9)	11	
Symptoms					
Minimal or no impairment	23 (46.9)	20 (40.8)	6 (12.2)	49	< 0.001
Moderate impairment	4 (8.9)	13 (28.9)	28 (62.2)	45	
Severe impairment	0 (0.0)	0 (0.0)	6 (100.0)	6	
Emotional function					
Minimal or no impairment	23 (41.8)	21 (38.2)	11 (20.0)	55	< 0.001
Moderate impairment	3 (8.3)	11 (30.6)	22 (61.1)	36	
Severe impairment	1 (11.1)	1 (11.1)	7 (77.9)	9	

CA: controlled asthma; PCA: partially controlled asthma; and UA: uncontrolled asthma. Fisher-Freeman-Halton test.

Table 6. Distribution of the cases by asthma severity and by degree of impairment reported in the components of the Paediatric Asthma Quality of Life Questionnaire.

Variable	MiA	MoA	SA	Cases	p
	n (%)	n (%)	n (%)	n	
Cases	34 (34.0)	19 (19.0)	47 (47.0)	100	
Overall					
Minimal or no impairment	24 (70.6)	6 (6.2)	7 (8.9)	37	< 0.001
Moderate impairment	10 (17.5)	13 (22.8)	34 (59.6)	57	
Severe impairment	0 (0.0)	0 (0.0)	6 (100.0)	6	
Activity limitation					
Minimal or no impairment	20 (58.1)	7 (22.6)	4 (12.9)	31	< 0,001
Moderate impairment	14 (24.1)	11 (19.0)	33 (56.9)	58	
Severe impairment	0 (0.0)	1 (9.1)	10 (90.9)	11	
Symptoms					
Minimal or no impairment	28 (57.1)	8 (6.3)	13 (26.5)	49	< 0.001
Moderate impairment	6 (13.3)	11 (24.4)	28 (62.2)	45	
Severe impairment	0 (0.0)	0 (0.0)	6 (100.0)	6	
Emotional functioning					
Minimal or no impairment	30 (54.5)	10 (18.2)	15 (27.3)	55	< 0.001
Moderate impairment	4 (11.1)	8 (22.2)	24 (66.7)	36	
Severe impairment	0 (0.0)	1 (5.3)	8 (88.9)	9	

MiA: mild asthma; MoA: moderate asthma; and SA: severe asthma. Fisher-Freeman-Halton test.

groups and the asthma severity groups, there being 11% of children and adolescents in the study who reported severe impairment of their quality of life. In addition, the lowest values in this domain were found in the UA and the SA groups, i.e., the groups with poorest asthma control and greatest asthma severity.

Basso et al. performed spirometry and the six-minute step test (6MST) in, as well as administering physical activity and quality of life questionnaires to, 19 adolescents with asthma (11-15 years of age) in Brazil.[30] Those authors concluded that the sensation of dyspnea and leg fatigue reported at the end of the 6MST reflected the discomfort that asthma caused during their activities of daily living.

In contrast, Andrade et al. compared physical and cardiorespiratory performance in the six-minute walk test (6MWT) in 40 children with moderate and severe asthma (6-16 years of age) and found that, regarding quality of life assessment, the PAQLQ activity limitation domain had the worst scores and correlated negatively with difference in distance walked.[31] The authors concluded that the performance of the asthma patients

in the 6MWT, as evaluated on the basis of distance walked, was significantly lower than the predicted values for healthy individuals of the same age group.[31]

Therefore, those authors demonstrated that asthma causes discomfort in the daily lives of asthma patients, and that this discomfort will consequently result in greater limitation of activities of daily living in patients with poorly controlled asthma and greater asthma severity.[30,31]

Ricci et al. also found lower scores in the PAQLQ activity limitation domain, which was the most affected, together with the symptoms domain; the authors explained that the children and adolescents in that study seemed to be quite worried about asthma attacks and about the limitations that symptoms could impose on their daily lives.[6]

The highest means of the CA and the PCA groups are those for the PAQLQ symptoms domain. In the study conducted in Egypt, the symptoms domain was the most affected, a finding that was explained by the medical care limitations in the country or by poor patient adherence to treatment.[27]

In a study of children and adolescences with asthma conducted in Portugal, the PAQLQ symptoms domain also was the most affected, which resulted in poor health-related quality-of-life outcomes in the asthma patients.[32]

Ayuk et al. evaluated 90 children and adolescents with asthma in Nigeria and also found lower values for the PAQLQ symptoms domain in the adolescents 14-17 years of age; they concluded that older age was a strong predictor of poor quality of life in their study population.[33]

Emotional function was the PAQLQ domain with the highest values in the asthma severity groups, 55% and 9% of the participants of the present study reporting minimal/no impairment and severe impairment, respectively. Our findings corroborate those of the study conducted in Turkey, whose authors found higher values in the MiA group than in the MoA group, as well as those of the study conducted in Nigeria, which also found the emotional function domain to be the least affected.[29,33]

Cvejoska-Cholakovska et al. followed children and adolescents with asthma in Macedonia for three months; they assessed quality of life and clinical stability to determine the level of asthma control.[34] By the end of the three-month follow-up period, the authors found higher values for the PAQLQ, which indicates improvement in asthma control, the patients with well-controlled asthma having higher scores on the questionnaire.[34] Regarding asthma severity, only the emotional function domain showed differences among the groups.[34]

In terms of the extent to which asthma control status and asthma severity affect the quality of life of children and adolescents with asthma, our results are consistent with those reported in the literature, because differences were found in the overall PAQLQ score and the PAQLQ domains among the groups, the scores being higher in the patients with CA and lower asthma severity.[6,22-34]

In the present study, as well as in the study by Ricci et al.,[6] the PAQLQ activity limitation domain was the most affected. In contrast, other studies found the symptoms domain to be the most affected[27,32,33]; this difference between findings can be explained by lack of reporting about the exclusion of patients experiencing asthma attacks or about the presence of any asthma attack-related symptoms, which can change the perception of quality of life in this population.[27,32,33]

Quality of life appears to be directly related to asthma control and asthma severity in children and adolescents, being better when asthma is well controlled and asthma severity is lower.

Asthma control and asthma severity can affect the quality of life of asthma patients and their family members. Therefore, we emphasize the importance of appropriate follow-up care for this population, with an emphasis on factors that lead to an unfavorable disease outcome, such as nonadherence to treatment, contact with asthma attack-triggering factors, improper use of inhalers, and lack of access to medications and medical care.

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Variation in lung function is associated with worse clinical outcomes in cystic fibrosis

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Study carried out at the Centro Infant, Instituto de Pesquisas Biomédicas, Pontifícia Universidade Católica do Rio Grande do Sul, and at the Ambulatório de Fibrose Cística, Hospital São Lucas, Porto Alegre (RS) Brasil.

ABSTRACT

Objective: To determine whether the variation in lung function over one year is associated with worse clinical outcomes, as well as with a decline in lung function in the following years, in patients with cystic fibrosis (CF). **Methods:** This was a retrospective study involving CF patients (4-19 years of age), evaluated over a three-year period. We evaluated demographic characteristics, chronic *Pseudomonas aeruginosa* infection, antibiotic use, hospitalization, six-minute walk distance (6MWD), and lung function. The inclusion criterion was having undergone pulmonary function testing at least three times in the first year and at least once in each of the next two years. **Results:** We evaluated 35 CF patients. The variation in FEV_1 in the first year (ΔFEV_1) was greater among those who, in the third year, showed reduced FEV_1, had a below-average 6MWD, or were hospitalized than among those with normal FEV_1, normal 6MWD, or no hospital admissions, in that same year ($p < 0.05$), although no such difference was found for antibiotic use in the third year. Subjects showing a $\Delta FEV_1 \geq 10\%$ also showed a greater decline in FEV_1 over the two subsequent years ($p = 0.04$). The ΔFEV_1 also showed an inverse correlation with absolute FEV_1 in the third year ($r = -0.340$, $p = 0.04$) and with the rate of FEV_1 decline ($r = -0.52$, $p = 0.001$). Linear regression identified ΔFEV_1 as a predictor of FEV_1 decline (coefficient of determination, 0.27). **Conclusions:** Significant variation in lung function over one year seems to be associated with a higher subsequent rate of FEV_1 decline and worse clinical outcomes in CF patients. Short-term ΔFEV_1 might prove useful as a predictor of CF progression in clinical practice.

Keywords: Cystic fibrosis; Respiratory function tests; Disease progression; Hospitalization; Forced expiratory volume.

INTRODUCTION

Cystic fibrosis (CF) is a genetic disease, with a chronic evolution, that compromises the normal function of various organs and systems. It is characterized by changes in the secretions of the respiratory and gastrointestinal tract.[1] It is most common (at 1/3,500 live births) in the White population.[2,3] It is a progressive condition in which lung disease is the major determinant of morbidity and mortality.[4]

Due to advances in the treatment and understanding of CF, there has been a significant increase in life expectancy of individuals suffering from the disease. In Europe, CF survival has reached a mean age of approximately 35 years.[3,5] Estimates showed that subjects born after 2000 will have a life expectancy of over 50 years of age.[2,5] However, the progressive decline in lung function over time appears to be an inevitable characteristic of the disease in nearly all cases.[4] Therefore, impaired lung function, as quantified by measuring FEV_1, expressed as a percentage of the predicted value, is one of the main markers affecting clinical decision making about changing or intensifying the treatment regimens employed in CF patients.[6,7]

In recent decades, the FEV_1 of subjects with CF has been studied in order to gain a better understanding of the progression of the associated lung disease and to identify risk groups in which more aggressive therapy is indicated.[7-9] A decline in FEV_1 has been reported to be a marker of greater risk of hospitalization and death in subjects with chronic obstructive pulmonary diseases,[6,10] as well as being considered the best single indication for lung transplantation. Previous findings have shown that 80% of CF-related deaths are directly or indirectly associated with reduced lung function.[11]

The risk factors most commonly associated with a progressive decline in FEV_1 among CF patients include advanced age, female gender, a ΔF508 mutation in the CF transmembrane conductance regulator, the presence of modifier genes, pancreatic insufficiency, low nutritional status, diabetes mellitus, and colonization of the respiratory tract by *Pseudomonas aeruginosa* or *Burkholderia cepacia*. In addition, daily production of sputum, wheezing, and the number of lung exacerbations treated with intravenous

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antibiotics also seem to be related to a decline in lung function among CF patients.[7,12,13] The significance and magnitude of the effects of these factors seem to depend on patient age.[13] Furthermore, recent findings suggest that a reduction in the six-minute walk distance (6MWD) is associated with greater severity of lung disease.[14] Although studies have demonstrated that acute exacerbations in CF patients do not modify the coefficient of variation for lung function measured over the course of the same day,[15] other studies have shown that such exacerbations do significantly reduce spirometric values if measured over the course of a year.[16] However, there is still little information on how the variation in lung function over one year can influence the pulmonary and functional decline associated with the disease in subsequent years.

It would be useful to identify additional factors that might help predict lung function decline in the early stages of CF, given that, in many cases, FEV_1 becomes abnormal only in the advanced stages of the disease. Therefore, the objective of the present study was to determine whether variation in lung function over the course of one year is associated with worse clinical outcomes and lung function decline in subsequent years.

METHODS

This was a retrospective cohort study, conducted by reviewing a secondary database. We included subjects with a diagnosis of CF, as confirmed by sweat chloride or genetic testing, who were 4-19 years of age and had been treated at the Cystic Fibrosis Outpatient Center of the São Lucas Hospital of the *Pontifícia Universidade Católica do Rio Grande do Sul* (PUCRS, Pontifical Catholic University of [the state of] Rio Grande do Sul), located in the city of Porto Alegre, Brazil. During the period under study, approximately 80 CF patients were being followed at the Cystic Fibrosis Outpatient Center. Once every three months, each patient underwent clinical evaluation and pulmonary function testing, at which time samples (oropharyngeal swab or sputum samples) were collected for culture. The principal criterion for inclusion was having undergone pulmonary function testing (spirometry) at least three times in the first year (each set of tests having been performed at least three months apart) and at least once in each of the two following years. In addition, we included only individuals for whom the spirometric values were acceptable and reproducible according to international guidelines, including those established for preschool-age children.[17] The variation in FEV_1 (ΔFEV_1) in the first year was calculated by the following formula:

$$\Delta FEV_1 = (hiFEV_1 - loFEV_1) / hiFEV_1$$

where *hiFEV1* is the highest FEV_1 (% of predicted) and *loFEV1* is the lowest FEV_1 (% of predicted). If a subject underwent pulmonary function testing more than once in the second or third year, we selected the best spirometric result obtained, meaning the highest FEV_1 (in percentage of the predicted value), in each year evaluated. We excluded subjects for whom the database contained incomplete data. The study was approved by the PUCRS Research Ethics Committee (Protocol no. 08/04102).

For each subject, we collected demographic data (age, gender, and race) and anthropometric data, as well as information related to chronic infection with *P. aeruginosa*, number of days using antibiotics (oral, intravenous, or both), and hospitalization. Chronic *P. aeruginosa* infection was defined as persistent *P. aeruginosa* infection for at least six consecutive months (three consecutive tests), as determined by culture of oropharyngeal swab or sputum samples (depending on age or clinical status). To facilitate further analysis, antibiotic use and hospitalization were evaluated as dichotomous variables (antibiotic use, yes/no; hospitalization, yes/no). In addition, we collected data on pulmonary function test (spirometry) results and 6MWD. Furthermore, we determined the rate of FEV_1 decline by subtracting the best third-year FEV_1 from the best first-year FEV_1. The final results are expressed as percentages of the predicted values. The data were entered into a database, stratified by year (first, second, and third year).

Pulmonary function tests were performed with a Koko spirometer (PDS Instrumentation, Inc., Louisville, CO, USA). The spirometric parameters evaluated included FVC, FEV_1, and $FEF_{25-75\%}$. All procedures were performed in accordance with the criteria established by the American Thoracic Society.[17] Spirometric data are presented as percentages of the predicted values.[18] A normal FEV_1 was defined as a value ≥ 80% of that predicted.

The six-minute walk test (6MWT) was performed in accordance with the American Thoracic Society guidelines.[19] The parameters evaluated in the test included heart rate; SpO_2, measured with a pulse oximeter (PalmSAT 2500; Nonin Medical, Plymouth, MN, USA); blood pressure, measured with a sphygmomanometer (Tycos CE0050; Welch Allyn, Skaneateles Falls, NY, USA); respiratory rate, counted as chest wall excursions per minute; and the modified Borg scale score, to quantify the perceived intensity of dyspnea. Subjects were instructed to walk as quickly as possible for six minutes in a 30-m corridor. The 6MWD was calculated by counting the total number of turns made during the test and is expressed in meters. We normalized the 6MWD using a reference equation.[20] Like FEV_1, the 6MWD was considered normal if ≥ 80% of the predicted value.

Sample size was estimated based on the behavior of the main variables of interest (FEV_1 and 6MWD). Adopting a level of significance of $p = 0.05$, a power of 80% and a minimum correlation of 0.40, we estimated the minimum sample size to be approximately 32 subjects.

Data normality was tested with the Kolmogorov-Smirnov test. Data with normal distribution are expressed as means and standard deviations. The ΔFEV_1 in the first year was calculated as described

above. Because ΔFEV_1 in the first year had a skewed distribution, we applied square root transformation of the data. Categorical variables are presented as absolute and relative frequencies. In order to analyze differences in the ΔFEV_1 in the first year in relation to the main clinical outcomes assessed in the two subsequent years (rate of FEV_1 decline, hospitalization, 6MWD, absolute FEV_1, and antibiotic use), we used the Student's t-test for independent samples. Correlations between variables were assessed using the Pearson correlation test. We also used a stepwise multiple linear regression model to assess the influence that potential predictor variables (age, gender, body mass index, chronic infection with *P. aeruginosa*, absolute FEV_1 at baseline, and ΔFEV_1 in the first year) had on the rate of FEV_1 decline. Data were processed and analyzed with the IBM SPSS Statistics software package, version 18.0 (IBM Corporation, Armonk, NY, USA). In all tests, values of $p < 0.05$ were considered statistically significant.

RESULTS

A total of 38 CF patients were selected for inclusion. For three patients, the data in the database were incomplete, and those patients were therefore excluded. Consequently, the final study sample comprised 35 subjects, of whom 19 (54.2%) were male. The mean age was 11.3 ± 3.8 years. The majority of patients presented anthropometric values within the normal ranges. In general, the sample presented with mild impairment of lung function. The demographic, anthropometric, and clinical characteristics of the sample are shown in Table 1.

In the sample as a whole, the mean ΔFEV_1 in the first year was 0.39 ± 0.13%. As can be seen in Figure 1A, that variation was significantly greater among patients who required hospitalization in the third year than among those who did not ($p = 0.03$). Figure 1B shows that the mean ΔFEV_1 in the first year was also significantly greater among patients in whom the 6MWD in the third year was below normal than among those in whom it was normal ($p = 0.02$). In addition, the mean ΔFEV_1 in the first year was significantly greater among the patients who showed lower FEV_1 values in the third year ($p = 0.03$; Figure 1C). However, regarding the use of antibiotic therapy (Figure 1D), the mean ΔFEV_1 in the first year did not differ significantly between the patients who were treated with antibiotics in the third year and those who were not ($p = 0.44$).

Among the patients who showed a ≥ 10% ΔFEV_1 in the first year, the rate of FEV_1 decline over the two following years was significantly greater than among those who did not ($p = 0.04$; Figure 2). In addition, we identified a significant negative correlation between ΔFEV_1 in the first year and absolute FEV_1 (% of predicted) in the third year ($r = -0.340$, $p = 0.04$), demonstrating that greater variation in lung function in the first year translated to lower FEV_1 in the third year (Figure 3A). Likewise, there was a significant negative correlation between the ΔFEV_1 in the first year and the rate of FEV_1 decline over the two following years ($r = -0.52$, $p = 0.001$; Figure 3B).

The stepwise multiple linear regression model, which included age, gender, body mass index, chronic infection with *P. aeruginosa*, FEV_1 (% of predicted) at baseline, and ΔFEV_1 in the first year (Table 2), revealed that ΔFEV_1 in the first year was the only significant predictor of the rate of FEV_1 decline over the two following years ($p = 0.001$). The model showed that ΔFEV_1 in the first year explained 27% of the subsequent rate of FEV_1 decline.

DISCUSSION

The results of the present study suggest that, in children and adolescents with CF, a greater ΔFEV_1 over a one-year period is associated with a more pronounced decline in lung function and worse clinical outcomes over the subsequent years. In addition, although the subjects evaluated here showed only mild impairment of lung function and preserved nutritional status, the ΔFEV_1 was found to be a predictor of progressive pulmonary decline, indicating that, even in the early stages of CF progression, quantification of this parameter can facilitate clinical detection of the disorder.

Reduced lung function, as identified by the measurement of FEV_1, seems to be associated with higher mortality in CF.[12,21] However, in many cases, lung function decreases only in the advanced stages of the

Table 1. Characteristics of the study sample at baseline.[a]

Characteristic	(N = 35)
Age (years)	11.3 ± 3.8 (4.74-19.7)
Male, n (%)	19 (54.2)
White, n (%)	31 (88.5)
Weight (kg)	39.3 ± 13.4 (19.4-63.7)
Height (cm)	142.2 ± 19.3 (104.0-178.5)
BMI (kg/m^2)	
Absolute	18.9 ± 2.6 (15.0-24.6)
Percentile	57.5 ± 31.5 (9.0-99.0)
Lung function	
FEV_1 (L)	1.9 ± 0.8 (0.72-4.28)
FEV_1 (% of predicted)	84.7 ± 22.1 (40.6-121.0)
FVC (L)	2.4 ± 1.0 (0.99-4.47)
FVC (% of predicted)	93.4 ± 17.7 (55.0-125.6)
$FEF_{25-75\%}$ (L)	1.8 ± 1.0 (0.33-5.80)
$FEF_{25-75\%}$ (% of predicted)	70.7 ± 35.2 (14.8-150.2)
Chronic bacterial infection	
Pseudomonas aeruginosa, n (%)	12 (34.2)
Burkholderia cepacia, n (%)	2 (5.7)
Staphylococcus aureus, n (%)	17 (48.5)
Genotype with at least one ΔF508 allele, n (%)	13 (81.2)[b]
Pancreatic insufficiency, n (%)	30 (85.7)

BMI: body mass index. [a]Results presented as mean ± standard deviation (range), except where otherwise indicated. [b]Genotype data available for only 16 subjects.

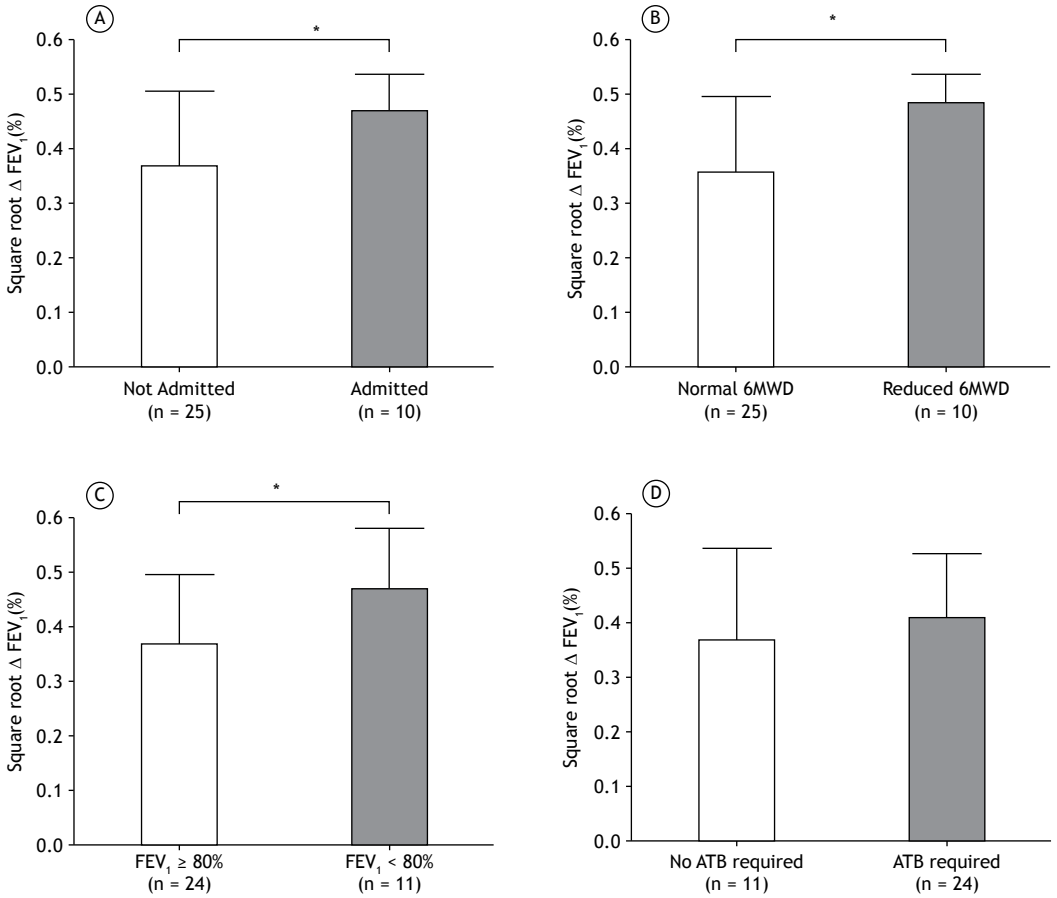

Figure 1. Variation in FEV_1 (ΔFEV_1) in the first year, in relation to the following variables in the third year: hospital admission (A); six-minute walk distance (B); FEV_1, as a percentage of the predicted value (C); and antibiotic use (D). 6MWD: six-minute walk distance; and ATB: antibiotic. *p < 0.05.

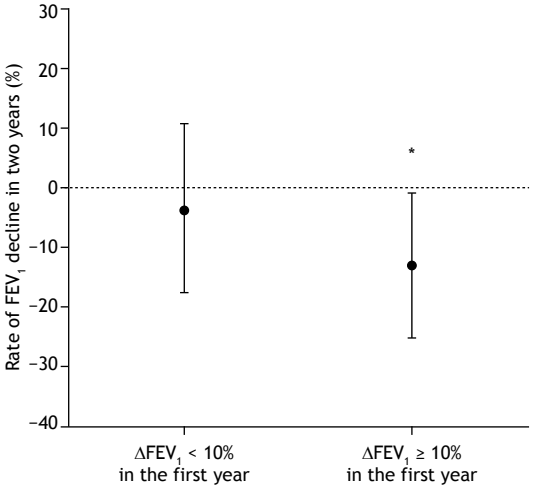

Figure 2. Comparison of the rate of FEV_1 decline between subjects with low and high variation in FEV_1 (ΔFEV_1) in the first year. *p = 0.04.

disease. The findings of the present study demonstrate that subjects who showed greater variation in FEV_1 over a one-year period had a greater decline in lung function over the next two years of monitoring. However, the correlation was not strong, which might be explained by the fact that the study sample was composed of young subjects with preserved nutritional status and mild pulmonary impairment. In addition, our findings show that there was a moderate correlation between the ΔFEV_1 in the first year and the rate of FEV_1 decline over the two following years, indicating that greater variation in lung function over a one-year period translates to a higher rate of decline in lung function in subsequent years. In a previous study,[8] FEV_1 variations ≥ 13% were found to be predictive of more rapid clinical progression of lung impairment in CF, and lesser changes were attributed to normal fluctuations in the test. However, other studies have suggested that better lung function is associated with greater variability on the test.[22]

Subjects for whom the ΔFEV_1 in the first year was greater showed a reduction in lung function over the next two years of monitoring. That finding demonstrates that, although the determination of FEV_1 is considered a useful tool for monitoring the progression of pulmonary impairment in patients with CF, calculating the ΔFEV_1 could be a complementary monitoring tool, given that

it could be used earlier than can the measurement of FEV_1 at a single time point, because, in many cases, the latter is associated with increased mortality only in the advanced stages of the disease.[12,21] In the present study, the subjects who showed a ≥ 10% ΔFEV_1 in the first year presented a more pronounced decline in FEV_1 over the two following years.

As previously mentioned, the multiple linear regression model showed that 27% of the rate of FEV_1 decline over the next two years of monitoring could be explained by the ΔFEV_1 during the first year. This result highlights the importance of assessing the variation in lung function over a relatively short period of time, given the observed decrease in lung function thereafter. Therefore, we believe that such assessment can represent an additional, useful tool for monitoring disease progression in CF, because an isolated reduction in FEV_1 is often seen only in the advanced stages of the disease. Nevertheless, when analyzing the data on variability, we found that approximately 46% of our subjects had a low baseline FEV_1, with a consequent increase in FEV_1 over the first year, showing that this parameter indicates the variability in lung function in general, rather than specifically indicating the progressive decline expected in CF.

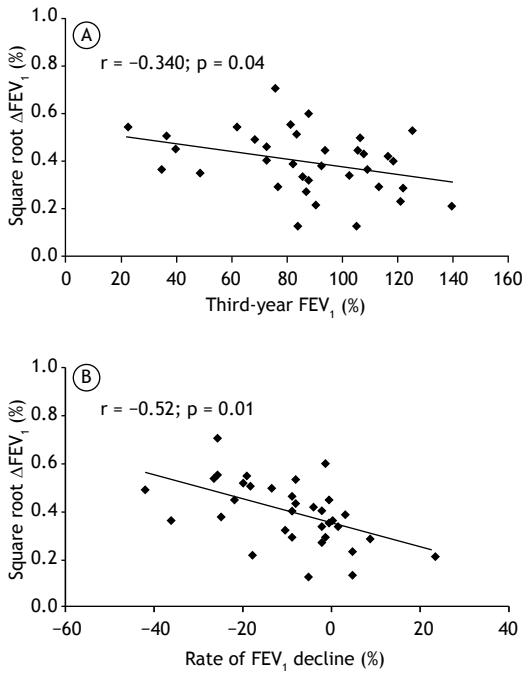

Figure 3. Variation in FEV_1 (ΔFEV_1) in the first year, correlated with FEV_1 (% of predicted) in the third year (A) and with the rate of FEV_1 decline (B).

On the basis of a recent review of the literature, we believe that this is the first study to show that short-term variation in lung function is associated with worse clinical outcomes over time in CF patients. Our findings demonstrate that subjects who showed greater ΔFEV_1 in the first year were more likely to require hospitalization in the third year. These findings corroborate those of previous studies showing that pulmonary exacerbations cause a decline in lung function over time and that a decline in FEV_1 is associated with the severity of pulmonary exacerbations, requiring hospitalization and intravenous administration of antibiotics.[7,23,24] In addition, a decrease in FEV_1 seems to be a predictor of hospitalization and mortality in CF,[6,13] and we found that ΔFEV_1 over a one-year period had a similar relationship with CF outcomes in the present study.

Previous studies have found an association between the use of antibiotics and a decline in lung function in patients with CF.[7,24] In the present study, we found no statistically significant correlation between ΔFEV_1 in the first year and antibiotic use. That might be attributable to the small size of our sample and the short study period. Other authors have shown that the use of intravenous antibiotics to treat pulmonary exacerbations is a risk factor for the decline in lung function over time in CF patients.[23,25] In addition, it has been suggested that consecutive exacerbations over a short period of time contribute to the progression of lung disease. Furthermore, one previous study demonstrated that the occurrence of three pulmonary exacerbations per year increases the risk of a decline in FEV_1 by approximately 5%.[26]

The 6MWT is featured as an important tool for the functional assessment of individual responses to exercise, providing a comprehensive analysis of the cardiovascular and pulmonary function, in the general population as well as in individuals with CF.[19,27] Impaired lung function, malnutrition, and muscle weakness have been described as playing major roles in determining the physical performance of CF patients. In addition, a higher respiratory rate, with reduced tidal volume ventilation and hypoxemia, also seems to limit physical activity.[27,28] Recent studies have shown that there is a significant correlation between the 6MWD and other important clinical outcomes, such as FEV_1, FVC, and disease severity, in CF patients.[14,29,30] In our study, subjects who showed a greater ΔFEV_1 in the first year also presented a below-normal 6MWD in the third

Table 2. Multiple linear regression of the rate of FEV_1 decline over the course of two years (the second and third years of the study period).

Parameter	B	Standard error of B	95% CI		p	R^2
			Minimum	Maximum		
Constant	12.014	6.415	−1.036	25.065		
Variation in FEV_1 in the first year (%)	−53.494	15.323	−84.668	−22.319	0.001	0.27

B: unstandardized coefficient; and R^2: coefficient of determination.

year, indicating that the calculation of ΔFEV_1 can be an important tool for predicting functional worsening in CF patients. Although two equations have been devised for standardizing 6MWD values in Brazil,[31,32] we chose to use international reference values,[20] because the latter include the entire age range represented in our sample and were generated from White individuals, which is relevant given that the majority of the patients in our sample were White.

Our study has certain limitations, primarily those that are inherent to the use of a retrospective design and data collection based on searches of secondary databases. In addition, our sample was quite homogeneous in terms of lung function and nutritional status.

In summary, our findings suggest that variation in lung function over a one-year period is associated with a higher rate of FEV_1 decline and worse clinical outcomes in subsequent years. Assessing the ΔFEV_1 over a relatively short period of time could, in conjunction with routine monitoring of FEV_1, contribute to the prediction of disease progression. Therefore, the calculation of this parameter might become an additional tool for more careful monitoring of the clinical progression of lung disease in patients with CF.

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ORIGINAL ARTICLE

Sport-specific influences on respiratory patterns in elite athletes

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ABSTRACT

Objective: To examine differences in lung function among sports that are of a similar nature and to determine which anthropometric/demographic characteristics correlate with lung volumes and flows. **Methods:** This was a cross-sectional study involving elite male athletes (N = 150; mean age, 21 ± 4 years) engaging in one of four different sports, classified according to the type and intensity of exercise involved. All athletes underwent full anthropometric assessment and pulmonary function testing (spirometry). **Results:** Across all age groups and sport types, the elite athletes showed spirometric values that were significantly higher than the reference values. We found that the values for FVC, FEV_1, vital capacity, and maximal voluntary ventilation were higher in water polo players than in players of the other sports evaluated ($p < 0.001$). In addition, PEF was significantly higher in basketball players than in handball players ($p < 0.001$). Most anthropometric/demographic parameters correlated significantly with the spirometric parameters evaluated. We found that BMI correlated positively with all of the spirometric parameters evaluated ($p < 0.001$), the strongest of those correlations being between BMI and maximal voluntary ventilation ($r = 0.46$; $p < 0.001$). Conversely, the percentage of body fat correlated negatively with all of the spirometric parameters evaluated, correlating most significantly with FEV_1 ($r = -0.386$; $p < 0.001$). **Conclusions:** Our results suggest that the type of sport played has a significant impact on the physiological adaptation of the respiratory system. That knowledge is particularly important when athletes present with respiratory symptoms such as dyspnea, cough, and wheezing. Because sports medicine physicians use predicted (reference) values for spirometric parameters, the risk that the severity of restrictive disease or airway obstruction will be underestimated might be greater for athletes.

Keywords: Athletes; Sports; Spirometry; Respiratory function tests.

INTRODUCTION

Spirometry is a gold standard pulmonary function test that measures how an individual inhales or exhales volumes of air as a function of time. It is the most important and most frequently performed pulmonary function testing procedure, having become indispensible for the prevention, diagnosis, and evaluation of various respiratory impairments.[1]

In Europe, spirometric results are currently interpreted in accordance with the guidelines established by the European Coal and Steel Community (ECSC), which provide the normal-range reference values for the general population.[2] Among the known determinants of lung function, the duration, type, and intensity of exercise have been shown to affect lung development and volumes.[3-5] In addition, athletes can be distinguished from members of the general population in that, in general, the former show better cardiovascular function, larger stroke volume, and greater maximal cardiac output.[4,5] Bearing all of this in mind, we can assume that athletes would present with higher spirometric values in comparison with the general population. However, there have been only a few studies addressing the effect of physical activity on pulmonary function test results and investigating the association between body composition and respiratory parameters in athletes.[6-8] This takes on greater importance when we consider the fact that there is also a lack of studies dealing with spirometric measures specific to athletes, which could lead to the misclassification or misdiagnosis of certain respiratory dysfunctions. Furthermore, it is possible that highly trained athletes develop maladaptive changes in the respiratory system—such as intrathoracic and extrathoracic obstruction; expiratory flow limitation; respiratory muscle fatigue; and exercise-induced hypoxemia—that can influence their performance.[9] Moreover, some studies have reported positive adaptive changes in lung function in comparison with sedentary individuals,[7,10] whereas other studies have reported no such changes.[11] From a theoretical point of view, the differences among the various types of sports could explain this lack of uniformity across studies. Nevertheless, whether regular physical activity increases lung function in elite athletes remains an open question.

The objective of this study was twofold. One aim was to examine differences in lung function among sports that are of a similar nature, according to the type and

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intensity of exercise performed. An additional aim was to investigate which anthropometric/demographic characteristics correlate with lung volumes and flows.[12]

METHODS

This was a cross-sectional study involving 150 male athletes (mean age, 20.9 ± 3.5 years) from four different sports (basketball, handball, soccer, and water polo). The inclusion criteria were playing a sport at the national or international level and engaging in that sport for ≥ 15 h per week. The inclusion criteria were playing a sport at the national or international level and engaging in that sport for ≥ 15 h per week. The exclusion criteria were being a smoker or former smoker, using any medication at the time of testing, and having any disease. The results of the pre-enrollment medical examination indicated that all of the subjects were in good health. Within the last three weeks, none of the subjects had taken any medications on a regular basis; had undergone surgery for cardiac, respiratory, allergic, eye, or ear problems; had had a respiratory infection; had had uncontrolled blood pressure; or had undergone thoracic surgery. In addition, none had a history of pulmonary embolism, active hemoptysis, or unstable angina. We grouped the sports according to the type and intensity of exercise involved, classifying each as involving either static (isometric) or dynamic (isotonic) exercise,[12] and all of the sports evaluated belonged to the highly dynamic group. All participants were informed of the possible risks of participating in the study, and all gave written informed consent. All procedures were approved by the Research Ethics Committee of the University of Belgrade School of Medicine, in the city of Belgrade, Serbia, and were conducted in accordance with the World Medical Association Declaration of Helsinki for medical research involving human subjects.

Anthropometric parameters

Athletes reported to the laboratory after fasting and refraining from exercise for at least 3 h. Without shoes and wearing minimal clothing, each athlete underwent anthropometric assessments, including the determination of weight and percentage of body fat (BF%), which were measured, respectively, with a scale (to the nearest 0.01 kg) and with a segmental body composition analyzer (BC-418; Tanita, Arlington Heights, IL, USA). Height was measured to the nearest 0.1 cm with a portable stadiometer (Seca 214; Seca Corporation, Hanover, MD, USA), according to standardized procedures described elsewhere.[13] The BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Spirometry

Spirometry was performed following the recommendations of the American Thoracic Society/European Respiratory Society Task Force.[10,14] Predicted (reference) values for gender, age, and height were in accordance with the ECSC standards. Subjects were instructed not to smoke, exercise, consume alcohol, drink caffeinated beverages, take theophylline, or use β-agonist inhalers prior to the spirometry tests. The testing took place in a laboratory setting, and all tests were performed at the same time of day (between 8:00 and 9:30 a.m.), with the same instruments and techniques. Measurements were carried out under standard environmental conditions: at a comfortable temperature (18-22°C); at an atmospheric pressure of 760 mmHg; and at a relative humidity of 30-60%. The temperature, humidity, and atmospheric pressure in the laboratory were continuously monitored.

Spirometry was performed using a Pony FX spirometer (Cosmed, Rome, Italy). At least three acceptable maneuvers were required for each subject, and the best of the three values was recorded. The highest values for FVC and FEV_1 were taken independently from the three curves.

Statistical analysis

Continuous data are expressed as mean ± standard deviation. Categorical data are expressed as frequencies. To assess differences between athletes according to the type of sport in which they engaged, we used ANOVA, with multiple post hoc Bonferroni tests. Pearson's correlation coefficient was used in order to test the relationships between anthropometric/demographic and spirometric characteristics. Statistical analysis was performed using the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA). All tests were two-tailed, and p values < 0.05 were considered statistically significant.

RESULTS

The demographic and anthropometric characteristics of the athletes are shown in Table 1. All investigated parameters differed among the four sports. In comparison with the other athletes, basketball players had significantly higher heights and weights ($p < 0.001$), although they also showed the lowest BF%. Water polo players had the highest BMI, whereas handball players had the highest BF% ($p < 0.001$ for both). The difference in BF% was statistically significant in the comparison between handball players and water polo players ($p < 0.001$).

The measured spirometric values for the athletes in all four groups are shown in Table 2. The FVC, FEV_1, vital capacity (VC), and maximal voluntary ventilation (MVV) values were higher for water polo players than for athletes in the other groups ($p < 0.001$ for all). In addition, PEF values were significantly higher in basketball players than in handball players ($p < 0.001$). The differences among the sports in relation to the measured values were not significant for any of the other spirometric parameters evaluated ($p > 0.05$).

The percentages of predicted values for the spirometric parameters evaluated are shown in Table 3. The FVC, VC, and MVV percentage of predicted values were higher for water polo players than for athletes in the other groups ($p < 0.001$ for all). In addition, the

percentage of predicted FEV_1 was significantly higher in water polo players than in basketball players ($p < 0.001$). The differences among the sports in relation to the percentage of predicted values were not significant for any of the other spirometric parameters evaluated ($p > 0.05$ for all).

Figure 1 shows the mean values of the residuals (observed minus predicted values) for age-predicted respiratory parameters in all four groups. Not only were the measured values of VC, FVC, FEV_1, and MVV significantly higher for water polo players than for athletes in the other groups, but the residuals for those parameters were also significantly different among the various sports ($p < 0.001$). The residuals for MVV and VC were highest in water polo players, whereas they were lowest in basketball and soccer players, respectively. In addition, there was a statistically significant difference between the highest and lowest residuals for FEV_1, which were observed in water polo players and basketball players, respectively ($p < 0.001$).

The results of the collective (overall) correlation analysis of anthropometric/demographic and spirometric parameters are presented in Table 4. Most of the anthropometric/demographic parameters correlated significantly with the spirometric parameters evaluated. We found that FVC correlated positively with weight, height, and BMI, the strongest of those correlations being between FVC and weight ($r = 0.741$; $p < 0.001$). We also found that FEV_1 correlated positively with all anthropometric/demographic parameters except age and BF%, although none of those positive correlations were statistically significant ($p > 0.05$ for all). In addition, BMI correlated positively with all spirometric parameters ($p < 0.001$), the strongest positive correlation being between BMI and MVV ($r = 0.46$; $p < 0.001$). In contrast, BF% correlated negatively with all spirometric parameters, the strongest negative correlation being between BF% and FEV_1 ($r = -0.386$; $p < 0.001$).

When we looked at within-group correlations, we found that they were similar to those observed in the overall analysis shown in Table 4, except for the water polo group, in which only MVV correlated significantly with weight and BMI ($r = 0.503$ and $r = 0.424$, respectively; $p < 0.05$ for both). In the basketball group, most of the anthropometric/demographic parameters correlated with all of the spirometric parameters, the most significant positive correlations being between age and FVC ($r = 0.618$; $p < 0.001$) and between height and VC (r =

Table 1. Demographic and anthropometric characteristics of the elite athletes evaluated, by sport played.[a]

Variable	Basketball (n = 48)	Handball (n = 42)	Soccer (n = 35)	Water polo (n = 25)
Age, years	20 ± 2	22 ± 4	23 ± 4	19 ± 1
Height, cm	200.1 ± 7.1*,†	180.7 ± 9.4*	183.5 ± 7.1‡,*	191.0 ± 4.3
Weight, kg	91.7 ± 10.1†	76.1 ± 12.3*	78.7 ± 7.6‡,*	90.0 ± 9.8
BMI, kg/m^2	22.75 ± 1.86*	23.15 ± 1.88*	23.31 ± 1.27	24.67 ± 2.65
BF%	8.3 ± 1.0*,†	13.9 ± 3.5*	9.5 ± 2.0†	11.5 ± 2.9

BF%: percentage of body fat. [a]Data are expressed as mean ± SD. *p < 0.01 vs. water polo. p < 0.01 vs. handball. ‡p < 0.01 vs. basketball.

Table 2. Measured spirometric values for the elite athletes evaluated, by sport played.[a]

Variable	Basketball (n = 48)	Handball (n = 42)	Soccer (n = 35)	Water polo (n = 25)
FVC (L)	5.7 ± 0.9*,†,‡	6.5 ± 1.3†,‡	4.9 ± 1.04‡	6.7 ± 0.8
FEV_1 (L)	4.9 ± 0.8*,‡	4.4 ± 0.9†	4.4 ± 0.8‡	5.5 ± 0.7
PEF (L)	10.3 ± 2.5	11.1 ± 2.3†	9.4 ± 2.3	10.4 ± 0.8
VC (L)	5.8 ± 0.9*,‡	6.4 ± 1.1†	5.2 ± 1.0‡	6.8 ± 0.8
FEV_1/FVC	84.9 ± 8.3	85.2 ± 8.0	84.6 ± 7.2	82.0 ± 7.5
MVV (L)	172.5 ± 42.7	177.7 ± 44.5	161.7 ± 38.6‡	200.7 ± 34.6

VC: vital capacity; and MVV: maximal voluntary ventilation. [a]Data are expressed as mean ± SD. *p < 0.01 vs. basketball. †p < 0.01 vs. handball. ‡p < 0.01 vs. water polo.

Table 3. Percentage of predicted spirometric values for the elite athletes evaluated, by sport played.[a]

Variable	Basketball (n = 48)	Handball (n = 42)	Soccer (n = 35)	Water polo (n = 25)
FVC (%)	102.4 ± 11.7*	98.2 ± 20.0*	100.9 ± 11.2*	111.8 ± 16.4
FEV_1 (%)	104.1 ± 14.4	98.1 ± 18.4*	103.7 ± 11.5	113.4 ± 15.9
PEF (%)	101.1 ± 22.7	106.2 ± 21.0	104.8 ± 16.4	104.5 ± 21.0
VC (%)	99.5 ± 11.5*	94.7 ± 14.8*	102.6 ± 11.2*	114.8 ± 16.5
FEV_1/FVC	101.5 ± 9.5	101.3 ± 9.8	100.4 ± 7.9	97.8 ± 8.9
MVV(%)	108.3 ± 26.7*	104.5 ± 31.7*	111.6 ± 17.6*	143.0 ± 17.4

VC: vital capacity; and MVV: maximal voluntary ventilation. [a]Data are expressed as mean ± SD. * p < 0.01 vs. water polo.

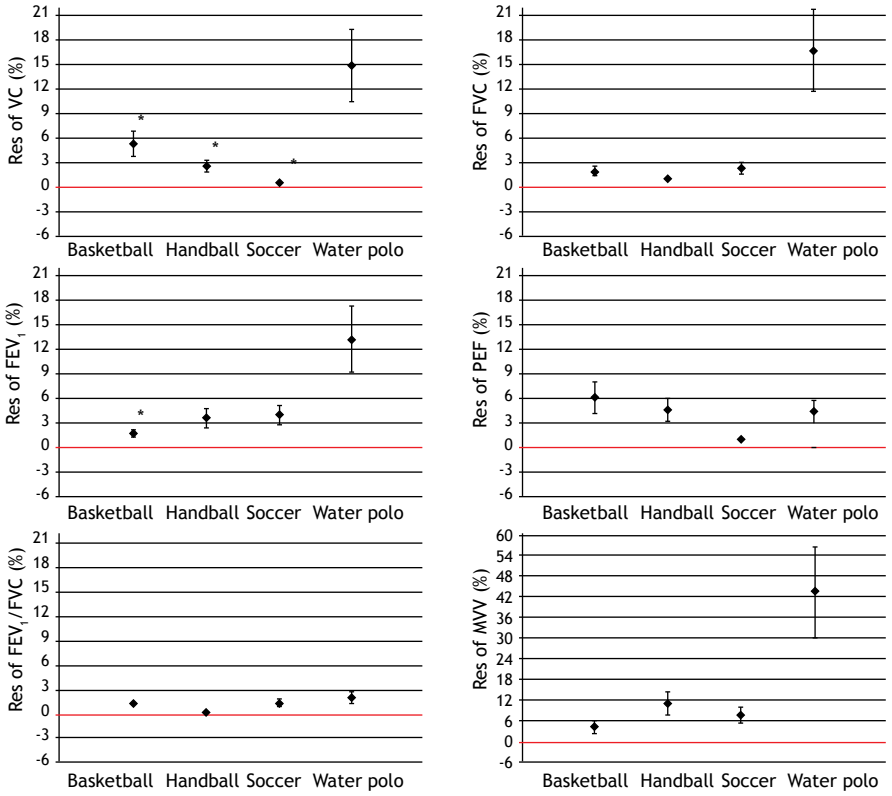

Figure 1. Mean ± SD of the residuals (observed minus predicted values) for age-predicted respiratory parameters in the elite athletes evaluated, by sport played. Res: residual; VC: vital capacity; and MVV: maximal voluntary ventilation. *p < 0.05 vs. water polo.

0.649; p < 0.001). In the soccer group, height, weight, and BMI all correlated positively with FVC and VC (p < 0.001 for all), the strongest such correlation being between weight and VC (r = 0.76; p < 0.001). We found that BF% did not correlate significantly with any of spirometric parameters evaluated (p > 0.05 for all). In the handball group, the most significant correlations were those that FVC and VC presented with all of the anthropometric/demographic parameters evaluated (p < 0.001 for all).

As can be seen in Figure 2, all of the abovementioned correlations were positive, except for those that BF% presented with all of the spirometric parameters evaluated. As in the overall correlation analysis, the most significant negative correlation was that between BF% and FEV_1 (r = −0.326; p < 0.001).

DISCUSSION

It is generally accepted that elite athletes and physically active individuals tend to have higher cardiorespiratory fitness levels. In the present study, the measured values were significantly higher than the predicted values for most of the spirometric parameters in all four groups of athletes. This finding could be of great importance in the diagnosis of respiratory disorders, especially in cases of airway obstruction.[1]

Our results are in agreement with those reported in other studies.[15,16] In a cross-sectional study conducted by Myrianthefs et al., which included 276 athletes engaged in various sports, the results were similar to those obtained in our study.[1] Those authors reported not only that the measured values for spirometric parameters were higher in the athletes than in the general population but also that those values were highest among the athletes who engaged in water-based sports. That leads us to one of the most striking results of our study—the fact that the values for spirometric parameters were highest among the athletes who engaged in water polo, which is a representative water-based sport, than among those who engaged in other sports involving the same type and intensity of exercise. Another major finding of the present study was that, in addition to the fact that the values for spirometric parameters were higher among the athletes who engaged in water polo than among those who engaged in land-based sports, the ECSC prediction equations underestimated certain spirometric values in the elite athletes, as has previously been reported.[17,18] This finding is in accordance with those of other studies showing that water polo players present statistically higher values for the major spirometric parameters (FVC, FEV_1, VC, and MVV), suggesting that swimming on a regular basis improves lung function.[7,19]

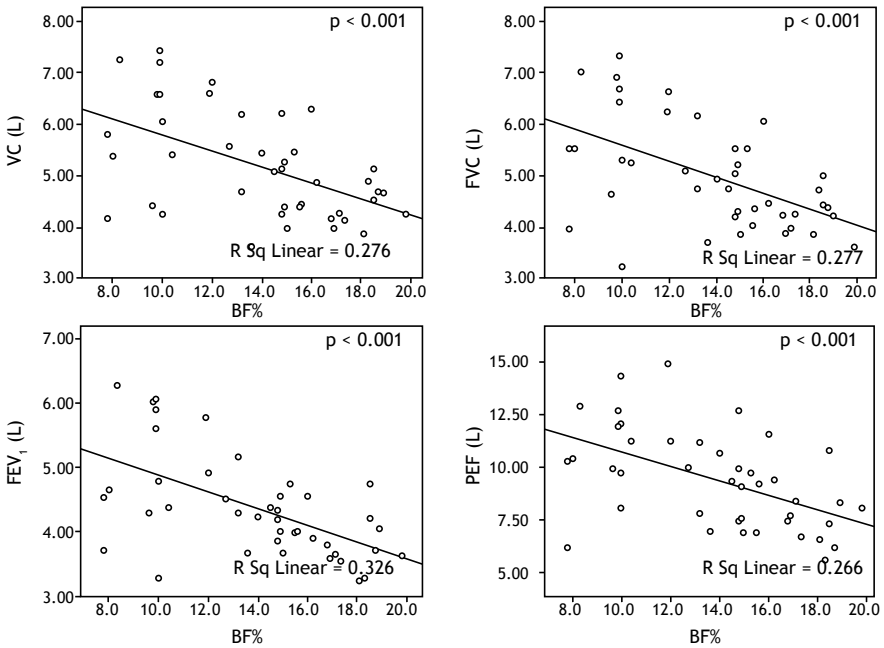

Figure 2. Correlations between percentage of body fat (BF%) and spirometric parameters, in handball players. VC: vital capacity.

Table 4. Overall correlation analysis for the sample of elite athletes, as a whole (N = 150).

	FVC (L)	FEV_1 (L)	PEF (L)	VC (L)	FEV_1/FVC	MVV (L)
Age (years)	0.019	−0.540	0.114	0.020	−0.156	0.100
Height (cm)	0.652†	0.619†	0.456†	0.657†	−0.127	0.275†
Weight (kg)	0.741†	0.675†	0.548†	0.765†	−0.235†	0.496†
BMI (kg/m²)	0.396†	0.307†	0.313†	0.428†	−0.263†	0.460†
BF%	−0.372†	−0.386†	−0.274†	−0.344†	−0.061	−0.176*

BF%: percentage of body fat; VC: vital capacity; and MVV: maximal voluntary ventilation. *Correlation is significant at the 0.05 level (two-tailed). †Correlation is significant at the 0.01 level (two-tailed).

In the present study, the athletes who engaged in land-based sports showed relatively "normal" spirometric values in relation to age- and height-predicted values, whereas water polo players showed FEV_1 values approximately 16% higher than the predicted values. Although this is well known, the question remains: is the superior lung volume in athletes who engage in water-based sports a consequence of their training, or is it (to some extent or completely) due to natural endowment? In addition, although we found the values of FEV_1 and FVC to be higher in the water polo players than in the other athletes, the FEV_1/FVC ratio was lower in the former group. This suggests that lung efficiency was higher in the other athletes, or that the water polo players had more residual capacity.[13] There are various explanations for why water polo players and athletes who engage in other water-based sports generally have higher lung volumes than do athletes who engage in land-based sports. Swimmers not only tend to have characteristic skeletal features at an early age but also tend to be tall and thin, as well having a high biacromial diameter for their age. Furthermore, some studies have shown that swimming on a regular basis alters the elasticity of the lungs and of the chest wall, which leads to further improvement in the lung function of swimmers and of athletes who engage in other water-based sports.[7,20] Moreover, the fundamental nature of the exercise engaged in by water polo players is, in some aspects, diametrically different from that of the exercise engaged in by athletes who play land-based sports. During immersion, the water pressure increases the load on the chest wall, thus elevating airway resistance. The ventilatory restriction that occurs momentarily in every respiratory cycle leads to intermittent hypoxia, which triggers an increase in the respiratory rate.[1] Overall, athletes who engage in water-based sports tend to have functionally better respiratory muscles as a result of the greater pressure they are subjected to during immersion in the water.[7,20,21] Last but not least, it has been demonstrated that genetic factors make a substantial contribution to the enhanced lung function in swimmers.[22]

In addition to the significant differences between athletes who play water-based sports and those who play land-based sports, in terms of the spirometric values observed and confirmed in this study, another noteworthy aspect of our results is the obvious distinction

among the three land-based sports evaluated. To our knowledge, there have been no studies investigating such differences, which makes our study even more important. One possible explanation is that every sport differs in terms of the type and intensity of the exercise involved, which varies by season, as well as that there are sport-specific adaptations of body composition, a phenomenon known as "sport-specific morphological optimization".[23]

The results of our overall correlation analysis showed that almost all of the anthropometric/demographic parameters correlated significantly with the spirometric parameters evaluated. We found that FVC correlated positively with weight, height, and BMI, correlating most strongly with weight. In addition, BMI correlated positively with all spirometric parameters, the strongest positive correlation being between BMI and MVV. However, BF% correlated negatively with all spirometric parameters, correlating most strongly with FEV_1. In our analysis of within-group differences, we found that the correlations were similar to those observed in the overall analysis, except for the water polo players, among whom MVV correlated significantly with weight and BMI. Our results showed that some anthropometric parameters, especially BF%, correlated negatively with the spirometric parameters evaluated, thereby demonstrating, as in other studies, that an increase in body fat can induce a decrease in lung function.[16,24] This finding is in accordance with those of other studies in the literature and can be explained by a reduction in expiratory reserve volume and functional residual capacity as a result of decreased lung compliance, decreased chest wall volume, and increased airway resistance. [24] Our results are in agreement with those of a study involving obese individuals, which demonstrated that lung function, expressed as DLCO, correlates positively with lean body mass,[25] which is the opposite of BF%. In addition, some authors have reported that DLCO correlates positively with BMI,[26] although not with BF%.[27] It is well known that in normal individuals (those engaged in regular physical activity), DLCO can double in proportion to the increased cardiac output,[28] thus potentially explaining the fact that BF% has no influence on the variability of DLCO in elite athletes.

According to the literature, higher levels of fat mass and obesity in general, even in athletes, are significantly associated with less low-frequency heart rate variability, which mainly reflects sympathetic activity. In addition, recent studies have shown that in some pulmonary disorders, even mild disorders, cardiac autonomic modulation is increased when there is sympathetic dominance of the autonomic balance. This is also associated with decreased DLCO, which could explain the negative correlations observed in our study.[29]

Perhaps the most important finding of the present study is that water polo players showed higher spirometric values than did the athletes in the other groups, indicating that the lung volumes and capacities of water polo players are mostly affected by the fact that they engage in a water-based sport. However, what is responsible for the high prevalence of asthma among swimmers remains an open question. Nevertheless, although the unique anthropometric characteristics of athletes engaged in water-based sports have, as previously mentioned, been shown to be mostly attributable to genetic endowment, it remains unclear whether the superior lung function found in such athletes is due to genetic influences or to the specific pattern of exercise.[22]

We found that measured spirometric values were significantly higher in elite athletes than in the general population, regardless of age or the type of sport played. These results are particularly relevant for cases in which an athlete seeks treatment for respiratory symptoms such as dyspnea, cough, and wheezing. Because sports medicine physicians use predicted (reference) values for spirometric parameters, the risk that the severity of restrictive disease or airway obstruction will be underestimated might be greater for athletes. Nevertheless, although our study included only athletes engaged in sports that were similar in terms of the type and intensity of exercise involved, water polo players stood out for their relatively high spirometric values. Our results suggest that the type of sport has a significant impact on respiratory adaptation. Because of these sport-specific differences, there is a need for further investigations examining specific exercise patterns; the influence of the duration, severity, and intensity of exercise; the early years of training; respiratory muscle strength; and specific genetic influences.

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The impact of anti-smoking laws on high school students in Ankara, Turkey

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ABSTRACT

Objective: To determine the factors affecting the smoking habits of high school students, their thoughts about changes resulting from anti-smoking laws, and how they are affected by those laws. **Methods:** In this cross-sectional study, 11th-grade students at eight high schools in Ankara, Turkey, were invited to complete a questionnaire. **Results:** A total of 1,199 students completed the questionnaire satisfactorily. The mean age of the respondents was 17.0 ± 0.6 years; 56.1% were female, of whom 15.3% were smokers; and 43.9% were male, of whom 43.7% were smokers ($p < 0.001$). The independent risk factors for smoking were male gender, attending a vocational school, having a sibling who smokes, having a friend who smokes, and poor academic performance. Of the respondents, 74.7% were aware of the content of anti-smoking laws; 81.8% approved of the restrictions and fines; and 8.1% had quit smoking because of those laws. According to the respondents, the interventions that were most effective were the (television) broadcast of films about the hazards of smoking and the ban on cigarette sales to minors. The prevalence of smoking was highest (31.5%) among students attending vocational high schools but lowest (7.5%) among those attending medical vocational high schools. Although 57.1% of the smokers were aware of the existence of a smoking cessation helpline, only 3.7% had called, none of whom had made any attempt to quit smoking. **Conclusions:** Although most of the students evaluated were aware of the harmful effects of smoking and approved of the anti-smoking laws, only a minority of those who smoked sought professional help to quit.

Keywords: Smoking/prevention & control; Smoking/trends; Smoking/psychology; Students/statistics & numerical data; Adolescent; Young Adult.

INTRODUCTION

Smoking is a major health problem threatening the lives of people of all ages. Worldwide, there are 1.3 billion smokers, 84% of whom live in developing countries.[1] Every year, 5.4 million people die from tobacco-related diseases, and this number is expected to exceed 8 million by 2030.[2] Smoking-related diseases and deaths are preventable. This knowledge has increased the importance of smoking control and cessation programs, and many countries have therefore implemented such programs.

In Turkey, the comprehensive fight against cigarette smoking began on November 26, 1996. In 2008, the list of smoke-free areas was expanded to include the corridors of public buildings; the outdoor areas of schools and training centers; shopping malls; hotels; and taxis. On July 19, 2009, a ban on smoking in the enclosed spaces of businesses within the catering sector, such as restaurants and coffeehouses, went into effect.[3] Businesses that allow smoking in the workplace or sell cigarettes to minors (individuals < 18 years of age) are fined. Businesses that continue to do so after the first two infractions are not only fined but are also subject to closure. In the first four years after the enactment of the anti-smoking laws (2008-2012), 2.2 million people quit smoking.[3] Although smoking in the home was not banned, the number of smokers smoking in their own homes decreased. In addition, the prevalence of smoking in the segment of the population comprising individuals over 15 years of age declined from 33.4% to 27.1% between 2006 and 2012.[3] On the basis of the criteria established by the World Health Organization,[2,4] Turkey now ranks sixth in the world and fourth among European countries in terms of the measures taken to control smoking.

Many studies have demonstrated that people usually start smoking before the age of 18.[2,5] One of the main ways in which tobacco control programs attempt to reduce smoking among the adult population is smoking prevention. Another focus of such programs is smoking cessation. Recent studies conducted in Turkey have examined the effects of tobacco control programs on university students and public employees.[6,7] However, there has been only one such study involving high school students and that was limited to examining the deterrent effects of the pictures appearing on cigarette packs.[8]

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In this study, we attempted to determine the factors affecting the smoking habits of high school students in Turkey, their level of knowledge about the smoking control measures taken in the country, and how they are affected by anti-smoking regulations.

METHODS

Subjects and procedures

This was a cross-sectional study involving students attending high schools in Keçiören, one of the districts of Ankara, the capital of Turkey. The Regional Ethics Board and the Provincial Directorate of National Education approved the study. In the Keçiören district, there are twenty-nine high schools, with a collective total of 16,175 11th-grade students. The study sample was drawn from among 11th-grade students at eight high schools that were randomly selected from among those twenty-nine. Each of the selected high schools was either a (regular) public high school, a non-medical vocational high school, a medical vocational high school, a public Anatolian[1] high school, or a private Anatolian high school.

Using a 30-item questionnaire prepared for the purposes of this study, we obtained data related to various aspects of the lives of the students evaluated: demographic characteristics; personal smoking habits; social environment; and knowledge of/thoughts about anti-smoking laws and regulations. These students completed the questionnaires anonymously, under the supervision of their teachers. The questionnaires were subsequently divided into three groups on the basis of the smoking status of the respondents: current smokers, defined as individuals who have smoked at least 100 cigarettes in their lifetime and still smoked on a regular basis, daily or otherwise, or had quit smoking recently (within the last 12 months); former smokers, defined as individuals who had quit smoking at least 12 months ago; and never smokers, defined as individuals who had never smoked or had smoked fewer than 100 cigarettes in their lifetime.[9]

Via the questionnaires, students provided data regarding their gender; the smoking status of their first-degree relatives and friends; the type of school they attended; and their level of academic success. Schools were broadly categorized as belonging to one of three groups: public high schools; Anatolian high schools (public or private); and vocational high schools (medical or other).

Statistical analysis

We compared continuous variables analysis using t-tests or the Mann-Whitney U test. The chi-square test was used in order to compare categorical variables. We identified the risk factors for smoking by comparing the smoking students with the nonsmoking students. We then performed multivariate analysis using a variable-dependent forward stepwise logistic regression model. The level of statistical significance was defined as $p < 0.05$.

RESULTS

Collectively, there were 1,308 11th-grade students enrolled in the eight high schools selected. However, on the day the questionnaires were administered, 42 students were absent. Consequently, the questionnaires were distributed to 1,266 students, 22 of whom were excluded from the study because they did not complete the survey. Therefore, the study sample comprised 1,244 students. The mean age of the respondents was 17.1 ± 0.6 years (range, 15-20 years). Of the 1,244 respondents, 697 (56%) were female. The demographic characteristics of the respondents are shown in Table 1. There were 45 students who did not complete the questionnaire satisfactorily. Therefore, the final sample comprised 1,199 students, Of those students, 238 (19.8%) were classified as smokers, 97 (8.1%) were classified as former smokers, and 864 (72.1%) were classified as never smokers. All of the students classified as former smokers stated that they had quit smoking because of the anti-smoking laws. Of the 238 students classified as smokers, 173 (72.6%) were male. Male gender was found to correlate significantly with smoking ($p < 0.001$).

Among the various types of schools, the prevalence of smoking was highest (31.5%) at the vocational high schools, although students enrolled in non-medical vocational high schools accounted for 24% of that prevalence, whereas those enrolled in medical vocational high schools accounted for only 7.5%. The students classified as current or former smokers (n = 335 collectively) had started smoking at a mean age of 14.1 ± 2.0 years (range, 9-17 years), 107 (32%) having started at 15 years of age and 67 (20%) having started at 16 years of age. Of the current smokers, 30% reported smoking 11-15 cigarettes/day, 24% reported smoking 16-20 cigarettes/day, and 5% reported smoking > 20 cigarettes/day. The most common reason given for starting smoking was to find a source of comfort following a stressful event, which was the answer given by 19% of the current smokers, followed by envying a friend, reported by 16%; seeking pleasure, reported by 15%; peer pressure, reported by 9%; curiosity, reported by 7%; and as a weight loss strategy, reported by 4%. In addition, 6% of the current smokers reported that, when they started smoking, they were unaware of its harmful effects.

The prevalence of smoking was significantly lower among the students whose academic performance was classified as successful than among those in whom it was classified as poor ($p < 0.001$), whereas it was significantly higher among the students who had a sibling or friend who smoked than among those who did not ($p < 0.001$ for both). The prevalence of smoking among the people close to the respondents was highest (50.4%) for their fathers, followed by 32.9% for their friends, 27.1% for their siblings, and 21.9% for their mothers.

When the students were asked who the first person they remember smoking around them was, 38.8%

Table 1. Sociodemographic profile of the high school students evaluated.

Characteristic	(N = 1,244)
Gender, n (%)	
Male	547 (43.9)
Female	697 (56.1)
Type of high school, n (%)	
Regular	251 (20.2)
Non-medical vocational	682 (54.8)
Medical vocational	67 (5.4)
Public Anatolian[a]	184 (14.8)
Private Anatolian[a]	60 (4.8)
Maternal level of education, n (%)	
Illiterate	34 (2.7)
Literate	591 (47.5)
Secondary school graduate	259 (20.8)
High school graduate	226 (18.2)
University graduate	108 (8.7)
No response	26 (2.1)
Paternal level of education, n (%)	
Illiterate	6 (0.5)
Literate	327 (26.3)
Secondary school graduate	293 (23.5)
High school graduate	344 (27.6)
University graduate	259 (20.8)
No response	15 (1.3)
Occupation of parents, n (%)	
Educator	58 (4.7)
Health care worker	21 (1.7)
Other	1,165 (93.6)
Monthly income of parents, n (%)	
≤ 250 USD	74 (5.9)
251-500 USD	454 (36.5)
501-1,000 USD	420 (33.8)
> 1,000 USD	226 (18.2)
No response	70 (5.6)
Academic performance, n (%)	
Excellent	176 (14.1)
Good	335 (27.0)
Mediocre	344 (27.6)
Poor	364 (29.2)
No response	25 (2.1)

[a]Refers to high schools in Turkey that admit only students with high scores on the nationwide standardized test known as the Transition from Primary to Secondary Education exam.

first listed one or both of their parents. The difference between parents and the other groups was statistically significant ($p < 0.001$). We found that the smoking habits of the students did not correlate with their level of mathematical or verbal education, nor with level of education or income of their parents.

Using logistic regression analysis to evaluate the smokers and former smokers collectively (Table 2), we determined that the independent risk factors for smoking were male gender ($p < 0.001$), attending a non-medical vocational high school ($p = 0.002$), having a sibling who smokes ($p < 0.001$), having a friend who smokes ($p < 0.001$), and poor academic performance ($p = 0.0013$). We found that 58.7% of the students classified as current smokers had tried to quit smoking at least once in their lives, with varying rates of success—53.6% had quit for less than a week, 18.4% had quit for 1-4 weeks, and 28.0% had quit for 5-12 weeks. When asked "Are you thinking about quitting smoking?", 54.9% of the smokers answered in the affirmative. Of the quitters (former smokers plus smokers who had quit and subsequently started smoking again), only 8.1% had quit smoking simply because they wanted to, the other reasons for quitting including "for my own health", cited by 42.9%, and "to set a good example for others", cited by 18.5%. Of the students classified as current smokers, 29.1% reported that they were not thinking about quitting. Although there was no predominant reason given for taking that position, 23.6% of those students stated that they loved smoking. We also found that 91.4% of never smokers, 55% of current smokers, and 78% of former smokers thought that cigarettes were harmful. When asked to name the most common smoking-related diseases, 492 students (42.4%) answered "lung cancer", whereas 472 (40.7%) answered "cardiovascular diseases".

In our assessment of student awareness of smoking cessation resources, we found that 61.6% of the students were aware of the existence of the smoking cessation helpline. Of the 238 students classified as current smokers, 136 (57.1%) were aware of the smoking cessation helpline. Of those 136 smokers, 5 (3.7%) had called the helpline but had not made any attempt to quit smoking. The majority of students (74.7%) were aware of the legislation pertaining to the tobacco control program. That rate was 77.0% among the never smokers, 69.9% among the smokers, and 66.7% among the former smokers.

We found that 81.8% of the students agreed with the restrictions and punishments imposed by the anti-smoking laws. The rate of approval among smokers was 69.9%. The comparison between smokers, never smokers, and former smokers is shown in Table 3. In the opinion of the respondents, the legislation-related interventions that were most effective in reducing the prevalence of smoking were the ban on sales of cigarettes to individuals under 18 years of age ($p = 0.003$) and the (television) broadcast of short films about the hazards of smoking ($p < 0.001$).

DISCUSSION

In this study, we evaluated high school students in terms of their smoking status, as well as their knowledge of and agreement with anti-smoking laws. We found that approximately 20% of the high school students smoked, current and former smokers collectively accounting for approximately 30% of the study sample. On average, the students had started smoking at approximately 14 years of age. The primary risk factors for smoking

Table 2 - Independent and dependent variables affecting student smoking.

Variable[a]	n	Smoking[b] %	OR (95% CI)	Adjusted OR (95% CI)
Gender (N = 1,199)				
Female	666	15.3	1	1
Male	533	43.7	4.29 (3.27-5.63)**	2.79 (2.02-3.85)**
Type of high school (N = 1,199)				
Regular	239	20.9	1	1
Anatolian[c]	234	23.9	2.07 (1.17-3.66)*	1.19 (0.77-1.83)
Vocational	726	31.5	1.92 (1.25-2.93)*	1.74 (1.23-2.47)*
Academic performance (N = 1,177)				
Good	496	16.9	1	1
Poor	681	36.1	2.77 (2.09-3.68)**	1.85 (1.28-2.68)*
Maternal smoking (N = 1,179)				
No	858	25.3	1	1
Yes	321	34.6	1.56 (1.18-2.06)	1.27 (0.89-1.79)
Paternal smoking (N = 1,171)				
No	438	25.1	1	1
Yes	733	29.6	1.25 (0.96-1.63)	0.97 (0.70-1.35)
Has a sibling who smokes (N = 1,199)				
No	868	21.4	1	1
Yes	331	45.0	3.00 (2.29-3-93)**	2.61 (1.88-3.62)**
Has a friend who smokes (N = 1,199)				
No	769	13.9	1	1
Yes	430	53.7	7.42 (5.61-9.82)**	5.08 (3.72-6.92)**

[a]The N differs among the variables, because some students did not answer all of the questions. [b]Current and former smokers were evaluated collectively. [c]Refers to high schools in Turkey that admit only students with high scores on the nationwide standardized test known as the Transition from Primary to Secondary Education exam. *p < 0.01. **p < 0.001.

Table 3. The opinions of high school students regarding the changes associated with anti-smoking laws in Turkey.

Opinion	Smoking status			p[a]	p[b]
	Never (%)	Current (%)	Former (%)		
I know the anti-smoking laws.	66.2	57.1	64.6	0.012	0.268
The restrictions and the punishments imposed by the laws are just.	75.9	69.9	78.3	< 0.001	0.004
Cigarette should not be sold to minors (individuals under the age of 18).	77.8	35.2	53.1	< 0.001	0.003
Cautionary photographs on cigarette packages are effective.	66.2	73.8	66.3	0.026	0.179
The television broadcast of videos about the harms of smoking is effective.	71.2	43.7	67.4	< 0.001	< 0.001
Recommendations on the subject are more effective if made by a nonsmoking role model.	71.1	49.6	60.6	< 0.001	0.086
Courses teaching the harmful effects of smoking should be implemented in schools.	76.9	50.9	58.7	< 0.001	0.217

[a]Never-smokers vs. current smokers. [b]Current smokers vs. former smokers.

were male gender, attending a non-medical vocational high school, and poor academic performance, as well as having a sibling or friend who smoked. Our findings also indicate that, although the majority of students who smoked thought that smoking was harmful and were aware of the resources provided via the tobacco control program, only a small proportion (8%) had made an effort to quit.

Various studies conducted in Turkey before the implementation of the tobacco control program showed that the prevalence of smoking among secondary and high school students ranged from 13.3% to 29.0%, and that the mean age at which those students started smoking was 13.2 ± 2.7 years.[10,11] In a study conducted in the United States, researchers found that the prevalence of smoking among middle and high school students

declined from 65.5% to 40.5% within the first nine years after the implementation of a tobacco control program.[12] In Turkey, the prevalence of smoking among adults decreased from 31.2% to 27.0% within the first four years after the implementation of the tobacco control program.[13] However, to date, there have been no studies evaluating the impact of the program on adolescents. Although our study was conducted after the implementation of the tobacco control program, we found the prevalence of smoking among adolescents to be similar to that reported before the control program was implemented. Possible explanations for this finding include the fact that individual adolescents have inaccurate perceptions of smoking-related health problems or ignore those future problems due to the immediate pleasure derived from smoking. Therefore, we believe that using understandable language and accessible media to explain the harmful effects of smoking on human health to the students, in their schools and homes, reduces the rate of the initiation of the smoking habit.

In the present study, we identified the following independent risk factors for smoking: male gender, attending a non-medical vocational high school, having a sibling who smokes, having a friend who smokes, and poor academic performance. Similar to what has been reported in other studies, the prevalence of smoking was higher in males than females (male/female ratio, 3.3:1).[14,15] This higher rate might be due to the fact that smoking among males is seen as a symbol or confirmation of masculinity. Peer pressure is a common cause of the initiation of smoking in adolescents. The likelihood that adolescents will start smoking increases 3 to 4 times when they have peers who smoke.[16] In the present study, most of the siblings who smoked were older and were likely perceived as role models. The implementation of anti-smoking laws in recreational areas where adolescents spend time with their friends, such as cafes, playing fields, and cinemas, can be an effective deterrent to the initiation of the smoking habit.

Poor academic performance and attending a low-tier school were identified as risk factors for smoking in our study and in the study conducted by Morin et al.[17] In addition, we found that the prevalence of smoking was lowest in medical vocational high schools. This demonstrates that increasing awareness about the adverse effects of smoking is an important deterrent. It seems that giving space to health-related courses in the education system beginning in the lower grades is an effective means of increasing awareness and raising a smoke-free generation.

To our knowledge, there have been no previous studies comparing students attending medical vocational high schools with those attending other types of high schools, in terms of the prevalence of smoking. However, there have been studies showing that the prevalence of smoking is lower among college students in the medical field than among those in any other field.[7,18]

Researchers have suggested that teacher attitudes toward smoking affect those of their adolescent students.[19] In the present study, approximately 70% of the students stated that recommendations from nonsmoking teachers and doctors could be effective. In addition, the students were in favor of school courses on the harmful effects of smoking. Furthermore, various studies conducted in schools have shown that anti-smoking campaigns have positive effects on students.[13,20]

In previous studies, researchers showed that adolescents might start smoking due to envy[21] or curiosity, and that many adolescents are unaware of the harmful effects of smoking.[22] In our study population, the most common reason given for starting smoking was as a source of comfort following a stressful event.

Studies conducted in the years prior to the implementation of the tobacco control program in Turkey showed that 42% of high school students had the desire to quit smoking, 3.1% having already achieved that goal.[23] In a study conducted in the United States, it was reported that although 67% of high school seniors wanted to quit smoking, only 3% had done so,[24] compared with 8.1% in the present study. In addition, we observed that none of those who wanted to quit smoking sought help from a professional. We found that the majority of the students classified as current smokers were aware of the smoking cessation helpline. However, only a few of those students had called the helpline and received information, and none of those had made any attempt to quit smoking. Therefore, we concluded that those young people had not yet reached the ideal level of awareness. Nevertheless, it can be said that tobacco control programs have increased the smoking cessation rate among adolescents, as has been reported for the adult population.[13] Another study conducted in Turkey examined the effects of anti-smoking laws on university students.[25] To our knowledge, ours is the first study examining the effects of such laws on high school students in Turkey.

In the present study, we found that 74.7% of the high school students evaluated knew the content of the anti-smoking laws and that approximately 81.8% considered the penalties to be appropriate. Approximately 60% of the students stated that the informative short films about the harms of smoking, broadcast on television, were impressive and approved of the blurring of depictions of smoking in movies and television series. The students classified as former smokers or never smokers approved of the limitations imposed by the anti-smoking laws in greater proportions than did those classified as current smokers. We found that, in the opinion of the students evaluated, the interventions that were most effective in reducing the prevalence of smoking were the ban on cigarette sales to persons under 18 years old and the (television) broadcast of short informative films about the harms of smoking. Lazuras et al.[26] and Chaaya et al.[14] reported similar results in studies of secondary school students in Greece and university students in Lebanon, respectively. The

increased awareness brought about by the anti-smoking laws is a highly positive development.

The authors of another study conducted in Turkey found that 22.5% of high school students who quit smoking were influenced by the warnings about the harms of smoking on cigarette packages.[27] Prior to the enactment of anti-smoking legislation in Turkey, the proportion of people who found warnings on cigarette packages effective was approximately 20%.[28] After the enactment of the legislation, that proportion increased to 80%.[29] In our study, we found a similar proportion (approximately 70%). Anti-smoking campaigns employing visual media have been shown to be effective in reducing the number of people who start smoking, reducing the number of cigarettes smoked, and increasing the smoking cessation rate.[30]

One of the limitations of our study is that it focused on a single district and our findings therefore might not accurately represent the thinking of all high school students in Turkey. Another limitation was that, because of the large number of participants, the questionnaires were administered under the supervision of each classroom teacher, rather than in individual, face-to-face interviews. Nevertheless, we believe that our findings are relevant and indicative of general trends in the country.

In conclusion, we can state that smoking is quite common among high school students in Turkey. Although the rate of the seeking professional help is low, we found that such adolescents are aware of the anti-smoking laws. Significant measures to increase awareness about the hazards of smoking among students in Turkey include more decisive implementation of the anti-smoking laws, implementation of better quality educational programs in schools, improving academic performance, and providing comprehensive information on the harmful effects of smoking. We believe that establishing health centers for students to receive guidance and professional help in schools might also be useful in order to assist students who want to quit smoking rather than waiting for those students to seek help at health care facilities. Family support and professional help will help decrease the prevalence of smoking and increase the rate of smoking cessation among adolescents. We also believe that, in order to be successful, anti-smoking campaigns should take into consideration the opinions of the adolescent population before outlining action plans for tobacco control.

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The rapid shallow breathing index as a predictor of successful mechanical ventilation weaning: clinical utility when calculated from ventilator data

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ABSTRACT

Objective: The use of the rapid shallow breathing index (RSBI) is recommended in ICUs, where it is used as a predictor of mechanical ventilation (MV) weaning success. The aim of this study was to compare the performance of the RSBI calculated by the traditional method (described in 1991) with that of the RSBI calculated directly from MV parameters. **Methods:** This was a prospective observational study involving patients who had been on MV for more than 24 h and were candidates for weaning. The RSBI was obtained by the same examiner using the two different methods (employing a spirometer and the parameters from the ventilator display) at random. In comparing the values obtained with the two methods, we used the Mann-Whitney test, Pearson's linear correlation test, and Bland-Altman plots. The performance of the methods was compared by evaluation of the areas under the ROC curves. **Results:** Of the 109 selected patients (60 males; mean age, 62 ± 20 years), 65 were successfully weaned, and 36 died. There were statistically significant differences between the two methods for respiratory rate, tidal volume, and RSBI ($p < 0.001$ for all). However, when the two methods were compared, the concordance and the intra-observer variation coefficient were 0.94 (0.92-0.96) and 11.16%, respectively. The area under the ROC curve was similar for both methods (0.81 ± 0.04 vs. 0.82 ± 0.04; $p = 0.935$), which is relevant in the context of this study. **Conclusions:** The satisfactory performance of the RSBI as a predictor of weaning success, regardless of the method employed, demonstrates the utility of the method using the mechanical ventilator.

Keywords: Respiration, artificial; Ventilator weaning; Spirometry.

INTRODUCTION

The use of indices predicting weaning outcomes can reduce the risk of weaning failure and complications posing potential morbidity, such as reintubation.[1,2] Weaning indices are used in order to evaluate lung mechanics and can provide information regarding the causes of mechanical ventilation (MV) dependence.[3,4] It is currently recommended that weaning indices be used only in cases in which it is difficult to make a decision; the decision to perform a spontaneous breathing trial (SBT) should not be based on any one weaning index.[5,6]

The rapid shallow breathing index (RSBI), which is also referred to as the ratio of respiratory rate to tidal volume (f/V_T), is the most widely used predictor of weaning success because it is easy to use and interpret.[1,4,7-13] The 2007 international consensus guidelines for weaning from MV, the 2007 Brazilian consensus guidelines for weaning from MV, and the 2013 Brazilian guidelines for MV underscore the clinical utility of the RSBI and recommend its use.[5,8,9]

First described by Yang & Tobin in 1991,[3] the RSBI allows assessment of respiratory mechanics by f/V_T. The RSBI was designed to be measured during spontaneous breathing for 60 s with a spirometer connected to the artificial airway before an SBT. An RSBI of less than 105 breaths/L predicts successful weaning from MV.[3,11,14]

It has been proposed that the RSBI be calculated directly from ventilator data during spontaneous ventilation; however, because of the study design, the small number of patients enrolled, and the limitations of the statistical tests used, the results were inconclusive.[14-17]

The major limitations of the RSBI appear to be related to neurological and neuromuscular diseases, as well as to prolonged ventilation. In such cases, the performance of the RSBI is far worse than that of other predictors, such as the Glasgow Coma Scale score and the recently described timed inspiratory effort (TIE) index.[4,12,13,18,19]

The primary hypothesis of the present study was that the RSBI calculated directly from ventilator data is comparable with the RSBI calculated by the traditional method in terms of their accuracy in predicting successful weaning from MV.

METHODS

The present study evaluated data from a database developed for a previous study of predictors of weaning

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success and was approved by the Research Ethics Committee of the Fluminense Federal University (Protocol no. 259/09). At the time, patients (or their legal guardians) gave written informed consent.

The inclusion criteria were as follows: being over 18 years of age; having been on MV for more than 24 h; and being a candidate for weaning from MV. The study participants also met the following criteria: resolution of the acute phase of the disease that led to their being placed on MV; a preserved cough reflex or absence of excessive tracheobronchial secretion; cardiovascular stability (heart rate ≤ 120 bpm and systolic blood pressure = 90-160 mmHg, with minimal or no use of vasopressors); stable metabolic state; adequate oxygenation (SaO_2 > 90% with an FiO_2 ≤ 0.4 or PaO_2/FiO_2 ≥ 200 mmHg with a positive end-expiratory pressure ≤ 8 cmH_2O); adequate respiratory rate (≤ 35 breaths/min); pressure support ≤ 20 cmH_2O; absence of significant respiratory acidosis (pH > 7.30); and, for endotracheally intubated patients, adequate mental status (a Glasgow Coma Scale score > 10).

The exclusion criteria were as follows: tracheal stenosis; intracranial pressure > 20 mmHg; sedation; severe heart failure or hemodynamic instability; and signs of systemic infection/reinfection during the weaning process.

The following mechanical ventilators were used: eXtend (Air Liquide, Paris, France), Servo-s (Maquet, Rastatt, Germany), and Puritan Bennett™ 840 (Covidien Nellcor, Boulder, CO, USA). Before measurement of MV parameters on the ventilator display, all mechanical ventilators and their circuits were calibrated in order to prevent measurement bias.

Procedures

The RSBI was calculated after the aforementioned weaning criteria were met and before an SBT was performed. For all study participants, the RSBI was calculated by the traditional method (i.e., employing a spirometer) and directly from MV parameters (i.e., employing the parameters from the ventilator display). The choice of which method should be used first was made by random sampling. All patients were on pressure support ventilation (PSV) at 12-20 cmH_2O, without sedation, and with the head of the bed at 45°, having been preoxygenated with an FiO_2 of 1.0 for 2 min and their airways having previously been aspirated.[20,21] After the RSBI was calculated by the two different methods, patients underwent an SBT with a T-piece and an FiO_2 of 0.4 for 30 min, without the influence of previous test results. All patients were continuously monitored by pulse oximetry and electrocardiography, under the supervision of a respiratory physiotherapist.[20,21]

In order to calculate the RSBI by the traditional method, the spirometer (Wright MK20; Ferraris Medical Ltd., Hertford, England) was connected to the artificial airway and left in place for 1 min. Spontaneous V_T was calculated by dividing minute ventilation by respiratory rate, and the RSBI was calculated by dividing respiratory rate by V_T in liters.[3,4]

In order to calculate the RSBI directly from ventilator data, respiratory rate and minute ventilation were obtained from the parameters from the ventilator display, with patients on PSV at 5 cmH_2O and continuous positive airway pressure of 5 cmH_2O. The RSBI was calculated after 5 min of ventilation as described above, and V_T was calculated by dividing minute ventilation by respiratory rate.

The decision to place patients on MV again was made by a respiratory physiotherapist, the attending physician, or both (who were blinded to the RSBIs obtained), being based on signs of poor tolerance (described below). Weaning from MV was considered successful if patients were able to breathe spontaneously after the SBT.[2,4,8,9,16,22,23]

In order to be extubated, patients had to pass the SBT and meet the following criteria: an adequate level of consciousness; an effective cough; and a patent airway. Extubation was considered successful if patients were not reintubated within 48 h after extubation. In tracheostomized patients, extubation was considered successful if, after passing the SBT, patients were able to breathe spontaneously after ventilator disconnection, without the need for reconnection within 48 h after disconnection.[5]

The SBT was interrupted if patients met at least one of the following criteria: SaO_2 < 90%; respiratory rate > 35 breaths/min; heart rate > 140 bpm, a sustained increase in heart rate, or a reduction in heart rate of more than 20%; mean arterial pressure > 130 mmHg or < 70 mmHg; or the presence of agitation, excessive sweating, disorientation, or depressed mental status. Patients who showed any of the aforementioned signs during the SBT or within 48 h after discontinuation of MV were considered to be cases of weaning failure, extubation failure, or both and were again placed on ventilatory support.[2,4,5,8,9,16,22,23]

Statistical analysis

Variables with normal distribution were expressed as means and standard deviations, whereas variables with non-normal distribution were expressed as medians and interquartile ranges. Categorical data were expressed as absolute and relative frequencies. The nonparametric Mann-Whitney test was used, and values of $p < 0.05$ were considered significant.

The performance of the RSBI calculated by the traditional method and that of the RSBI calculated directly from ventilator data in predicting weaning outcomes were evaluated by the following quality indicators: sensitivity; specificity; positive predictive value (PPV); negative predictive value (NPV); positive likelihood ratio (PLR); and negative likelihood ratio (NLR). They were also evaluated by calculating the area under the ROC curve (AUC). The AUCs were compared by the method proposed by Hanley & McNeil, and the cut-off points were calculated by the Youden index.[23]

All statistical analyses were performed with MedCalc, version 11.4.2.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Of the 109 patients who participated in the study, 60 were male, and the mean age was 62 ± 20 years (Table 1). Sixty-five (59.6%) were successfully weaned from MV, and 36 (33%) died, 8 of whom had been successfully weaned from MV. The reintubation rate was 10.7%.

Table 2 shows the medians and interquartile ranges of the parameters used in order to calculate the RSBI, together with a comparison between the two different methods used in order to calculate f/V_T. All variables showed statistically significant differences, with values of $p < 0.001$, the exception being minute ventilation ($p = 0.132$).

Quality indicators (sensitivity, specificity, PPV, NPV, PLR, and NLR) and the cut-off points for the RSBIs calculated by the two different methods are shown in Table 3.

Table 1. General characteristics of the patients studied (N = 109).[a]

Variable	Result
Male gender	60 (55)
Non-White	53 (49)
Intubated patients	62 (57)
Tracheostomized patients	47 (43)
Age, years	62 ± 20
Mechanical ventilation, days	14.2 ± 12.9
APACHE II score	17.9 ± 5.6
Conditions leading to ICU admission	
Sepsis	23 (21.1)
Pulmonary sepsis	22 (20.3)
Stroke	21 (19.3)
COPD	18 (16.5)
Acute myopathy	10 (9.2)
Abdominal surgery	8 (7.3)
Heart failure	5 (4.6)
Acute respiratory distress syndrome	2 (1.8)

APACHE II: Acute Physiology and Chronic Health Evaluation II. [a]Values expressed as n (%) or as mean ± SD.

Table 2. Medians and interquartile ranges of the study parameters.

Variable	Rapid shallow breathing index calculated with the use of		p*
	A spirometer	Pressure support ventilation	
f	29 (26-33)	27.0 (23.7-31.3)	< 0.001
V_E	9.6 (8.3-11.3)	9.6 (8.3-11.4)	0.132
V_T	0.34 (0.30-0.40)	0.36 (0.31-0.42)	< 0.001
f/V_T	86.3 (68.1-106.1)	75.9 (58.2-98.3)	< 0.001

f: respiratory rate; V_E: minute volume; and V_T: tidal volume. *Mann-Whitney test.

As can be seen in Figure 1, there were no statistically significant differences between the AUCs for the RSBIs calculated by the two different methods (0.81 ± 0.04 vs. 0.82 ± 0.04; p = 0.947). As can be seen in Figure 2, Pearson's linear correlation between the two methods was 0.94 (0.92-0.96). As can be seen in Figure 3, the intra-observer variation coefficient was 11.16%.

DISCUSSION

The use of the RSBI as a predictor of weaning success has been widely studied in the intensive care setting.[24] The performance of the RSBI has been shown to range from moderate to good (AUC, 0.72-0.89).[3,4,11,25,26] This variation might be due to the heterogeneity of the study samples, given that the proportions of patients with neurological disease, neuromuscular disease, or prolonged ventilation vary across studies.[4,11-13] The use of different study designs, weaning protocols, measurements, and cut-off points also contributes to this variation.[4,6,15,26-29]

The RSBI and maximal inspiratory pressure (MIP) have historically been recommended by the *American Thoracic Society/European Respiratory Society* and are among the most widely used predictors of weaning outcome in clinical practice.[5,8] The superiority of f/V_T and MIP over other predictors has been reported in two different studies, in which the AUCs for f/V_T and MIP were 0.89[3] and 0.80,[20] respectively. Promising new weaning indices include the integrative weaning index, the AUC for which was found to be 0.96 in a study from which neurological patients were excluded,[11] and the TIE index, the AUC for which was found to be 0.90 for a mixed population of intubated patients and 0.96 for patients with neurological or neuromuscular disease.[4,13]

In our sample of 109 patients, weaning failure occurred in approximately 40%, a proportion that is larger than that reported in the literature (i.e., 30%).[8] This can be explained by advanced age (mean age, 62 ± 20 years), a high prevalence of patients with prolonged ventilation (mean duration of MV, 14.2 days), a high proportion of tracheostomized patients (43%), and high Acute Physiology and Chronic Health Evaluation II scores.[9,17]

The performance of the RSBI calculated by the traditional method and that of the RSBI calculated directly from ventilator data were comparable with the RSBI performance reported in other studies.[4,11,20] It is of note that, regardless of how it was calculated, the RSBI was found to have low accuracy in identifying positive/negative cases (of patients who pass the SBT but cannot be weaned), as evidenced by its relatively low specificity, NPV, and NLR.

Technological advances in patient monitoring and ventilation have made it easy to obtain real-time data that allow determination of the clinical status of patients on ventilatory support. This led to studies comparing the RSBI calculated by the traditional method with the RSBI calculated directly from ventilator data, significant

Table 3. Indicators of the accuracy of the rapid shallow breathing index (calculated with the use of a spirometer and directly from ventilator data) in predicting weaning outcomes.

Index	CP	Sensitivity	Specificity	PPV	NPV	PLR	NLR
f/V_T (spirometer)	88.5	0.82	0.62	78.3	70.6	3.91	0.25
f/V_T (PSV)	80.1	0.80	0.65	76.9	71.2	4.40	0.24

CP: cut-off point for weaning outcome (as determined by the ROC curve); PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio; f/V_T: ratio of respiratory rate to tidal volume (the rapid shallow breathing index); and PSV: pressure support ventilation.

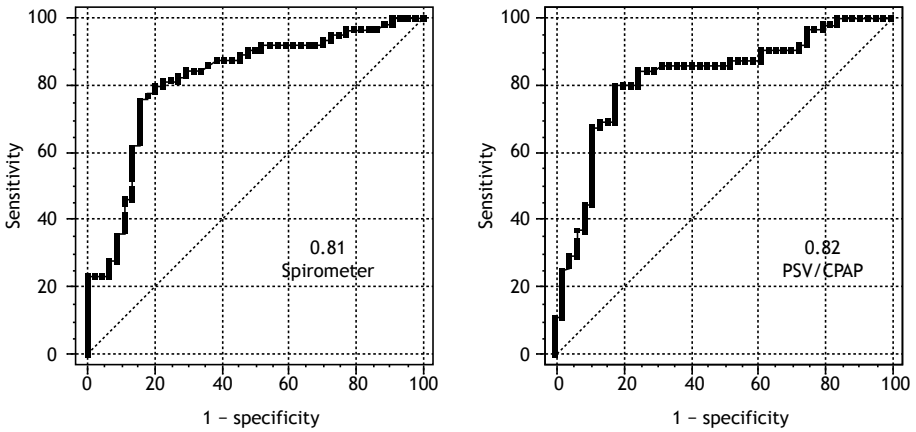

Figure 1. Areas under the ROC curves for the rapid shallow breathing index (f/V_T) calculated with the use of a spirometer and directly from ventilator data, showing no significant difference between the two in terms of their accuracy in predicting successful weaning from mechanical ventilation (p = 0.935; Hanley & McNeil test for pairwise comparisons). PSV: pressure support ventilation; and CPAP: continuous positive airway pressure.

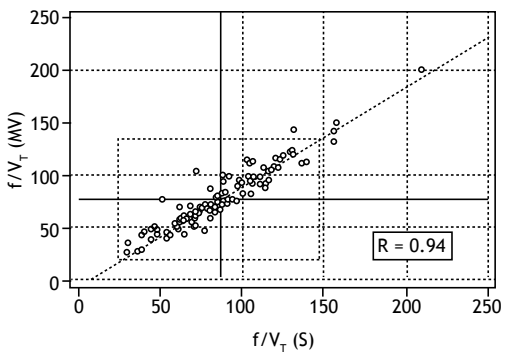

Figure 2. Pearson's linear correlation between f/V_T calculated with the use of a spirometer (S) and f/V_T calculated from the parameters from the mechanical ventilator (MV) display. f: respiratory rate; and V_T: tidal volume.

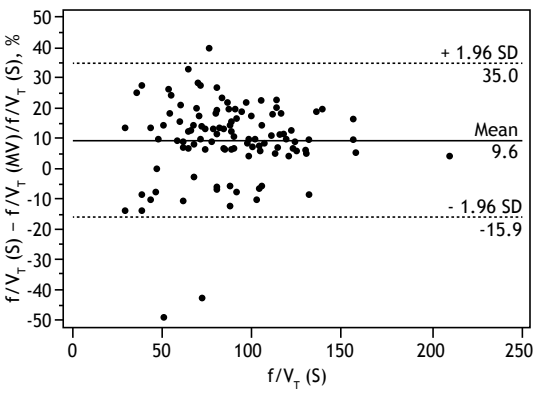

Figure 3. Bland-Altman plots. Intra-observer variation coefficient (11.16%) for f/V_T calculated with the use of a spirometer (S) and f/V_T calculated from the parameters from the mechanical ventilator (MV) display. f: respiratory rate; and V_T: tidal volume.

differences being found between the two.[14,17,22,28-30] However, none of the aforementioned studies evaluated the performance of the RSBI (as calculated by each method) in predicting weaning success.

Unlike the aforementioned studies, the present study was aimed at comparing the RSBI calculated by the traditional method with the RSBI calculated directly from ventilator data in terms of their accuracy in predicting weaning outcome. As in previous studies, the two methods for calculating the RSBI were found to be significantly different in terms of median respiratory rate, V_T, and f/V_T. However, our most important finding was that the performance of the RSBI calculated by the traditional method was statistically similar to that of the RSBI calculated directly from ventilator data, as evaluated by the AUCs (0.81 vs. 0.82; p = 0.19). In addition, the concordance—0.94 (0.92-0.96)—and the intra-observer variation coefficient (11.16%) were all within the recommended range for tests that are reproducible and reliable.

In the present study, the cut-off point for the RSBI calculated with the use of a spirometer was 88.5 breaths/L (as determined by the ROC curve), whereas in the original study it was 105 breaths/L.[3] The cut-off point for the RSBI calculated directly from ventilator data in the present study was even lower (i.e., 80.1 breaths/L). Although we cannot offer a definitive

explanation for these differences, they might be partly due to the characteristics of the study samples.

It is of note that the accuracy of the SBT, which is considered the gold standard for determining the success of weaning from MV and extubation, is approximately 85%.[2,23,25,31] Therefore, the use of predictors such as f/V_T, MIP, the integrative weaning index, and the recently described TIE index can make the outcome of weaning from MV safer, especially in difficult-to-wean patients.[4,11,13,24]

One limitation of the present study is that we did not determine interobserver reproducibility or f/V_T after the SBT. However, the primary objective of the present study was to compare AUCs in terms of their accuracy in predicting weaning success. Therefore, we believe that the aforementioned limitation had little impact on the final result.

In conclusion, the RSBI calculated directly from ventilator data can be easily incorporated into clinical practice, having no negative impact on the RSBI accuracy in predicting weaning outcome. However, our study shows that the cut-off point for the RSBI calculated directly from ventilator data should be approximately 80 breaths/L, which is lower than that for the RSBI calculated by the traditional method.

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Cost analysis of nucleic acid amplification for diagnosing pulmonary tuberculosis, within the context of the Brazilian Unified Health Care System

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ABSTRACT

We estimated the costs of a molecular test for *Mycobacterium tuberculosis* and resistance to rifampin (Xpert MTB/RIF) and of smear microscopy, within the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System). In SUS laboratories in the cities of Rio de Janeiro and Manaus, we performed activity-based costing and micro-costing. The mean unit costs for Xpert MTB/RIF and smear microscopy were R$35.57 and R$14.16, respectively. The major cost drivers for Xpert MTB/RIF and smear microscopy were consumables/reagents and staff, respectively. These results might facilitate future cost-effectiveness studies and inform the decision-making process regarding the expansion of Xpert MTB/RIF use in Brazil.

Keywords: Costs and cost analysis; Tuberculosis; Nucleic acid amplification techniques.

Brazil is among the 22 countries with the highest tuberculosis burden.[1] One of the major obstacles to controlling the disease is the delay in diagnosis. Smear microscopy is a routine test within the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System); however, it has low sensitivity.[2] Xpert® MTB/RIF (Cepheid; Sunnyvale, CA, USA), which is performed in the GeneXpert® system (Cepheid), is a rapid molecular test for detecting *Mycobacterium tuberculosis* and its rifampin-resistant mutants.[3] In 2010, Xpert® MTB/RIF was recommended by the World Health Organization for initial diagnosis in patients with tuberculosis and suspected multidrug resistance or HIV infection.[4] The accuracy of the test is high,[5] and studies have demonstrated that it is cost-effective[6-8] in other scenarios. In Brazil, Xpert® MTB/RIF was approved by the National Committee for Health Technology Incorporation in September of 2013 for use within the SUS.[9]

The objective of the present study was to estimate the unit cost of Xpert® MTB/RIF, since it does not yet have a reference value on the SUS Sigtap unified pricing list of the System for the Management of the Pricing List of Procedures, Drugs, and OPM (orthoses, prostheses, and materials). In addition, we intended to contribute information to support other economic evaluations in this field.

This was a descriptive study, which conducted a partial economic evaluation to estimate the cost of performing Xpert® MTB/RIF and smear microscopy (Ziehl-Neelsen method) within the SUS, performed in parallel with a pilot study of implementation of GeneXpert® use for the diagnosis of pulmonary tuberculosis in two cities in Brazil.[10] We selected two laboratories in the city of Rio de Janeiro, both of which are affiliated with the *Secretaria Municipal de Saúde e Defesa Civil do Rio de Janeiro* (SMSDC/RJ, Rio de Janeiro Municipal Department of Health and Civil Defense), and one laboratory in the city of Manaus, which is affiliated with the *Secretaria de Estado de Saúde do Amazonas* (SES/AM, Amazonas State Department of Health). This selection was based on the organization of the health care facility network, the level of decentralization, and the production output. In Rio de Janeiro, "laboratory 1" is a polyclinic with a medium production output, and "laboratory 2" is a family clinic with a small production output. In Manaus, the selected laboratory ("laboratory 3") is responsible for 71% of all smear microscopy examinations conducted in the city, it being considered to have a large production output.

We performed activity-based costing and micro-costing, on the basis of standard operating procedures for smear microscopy[2] and for Xpert® MTB/RIF.[11] The selected cost items were as follows: administrative costs (electricity, water, cleaning, and safety); staff costs, which included training (only for Xpert® MTB/RIF); laboratory consumable costs; and equipment costs. The Xpert® MTB/RIF cartridge cost R$20.46 (US$9.98),[12] and the GeneXpert® system

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cost R$34,850.00 (US$17,000)—purchase prices for the study of implementation.[10] The Brazilian National Ministry of Health is exempt from the costs of taxes and nationalization regarding the cartridges and GeneXpert®.

Staff costs for Xpert® MTB/RIF use were calculated by a time and motion study undertaken at two separate time points in order to assess the learning curve of professionals: the first was fifteen days after GeneXpert® was installed in the laboratory, which is the time required for professionals to adapt to it; and the second was three months after the equipment was installed, at which point tests were routinely performed. This time was taken into account in the calculation of staff costs. Data collection for estimating the cost of smear microcopy occurred in a single step, because smear microscopy is a well-established procedure within the SUS. The administrative costs refer to the mean quarterly expenditures of the health care facilities where the laboratories are located and were apportioned according to floor space and production. Depreciation was applied when necessary, according to the useful life of the equipment.[13] Costs of calibration and preventive/corrective maintenance on GeneXpert® were taken into account.[3]

The prices of the consumables were obtained from official sources, namely *Comprasnet*, *Banco de Preços em Saúde*, SMSDC/RJ, and SES/AM, and from the manufacturer (Cepheid). The mean cost of the tests is expressed in 2012 Brazilian reals. The costs of the cartridges and of GeneXpert® were converted from Brazilian reals to US dollars at a rate of R$2.05 = US$1.00.

The study was approved by the Brazilian National Research Ethics Committee (Protocol no. 493/2011), by the SMSDC/RJ Research Ethics Committee (Protocol no. 445A/11), and by the Research Ethics Committee of the *Fundação de Medicina Tropical de Manaus Dr. Heitor Vieira Dourado* (Dr. Heitor Vieira Dourado Tropical Medicine Foundation of Manaus) in November of 2011.

We observed the production process of 230 smear microscopy examinations and 463 tests with Xpert® MTB/RIF. There was a 30% reduction in mean completion time for Xpert® MTB/RIF between the first and second observations (9.87 min vs. 7.57 min). The largest reductions were observed in laboratories 2 (54%) and 3 (35%). In the second observation, the mean completion time was 6.20 min (range, 4.87-7.53 min) in laboratories 1 and 2 and 4.30 min (range, 3.53-5.07 min) in laboratory 3.

The mean cost of Xpert® MTB/RIF use was R$35.57 (range, R$33.70-R$39.40), and the mean cost of smear microscopy was R$14.16 (range, R$11.30-R$ 21.00). The major cost drivers for Xpert MTB/RIF were consumables and reagents (62%), especially the cartridges, whereas the major cost driver for smear microscopy was staff (58%). There was great variability in staff costs between the two cities (Table 1). Therefore, the cost of two smear microscopy examinations, which are recommended by the Brazilian National Tuberculosis Control Program and required to achieve a sensitivity of 70%,[2] represents 80% of the cost of an Xpert® MTB/RIF test, which has a sensitivity of 88%.[5]

During the data collection process, the production of Xpert® MTB/RIF tests increased relative to that of smears of the first sample, especially in RJ. The work hours of professionals remained unchanged, which suggests that the introduction of Xpert® MTB/RIF represented a technical efficiency gain in the routine of the laboratories (Table 2).

Xpert® MTB/RIF is considered a promising technology for tuberculosis control because it provides fast, accurate, and cost-effective results.[5-8] The present study conducted a partial economic evaluation, which describes exclusively the costs of performing the two technologies for the diagnosis of tuberculosis. Although we did not conduct a complete economic evaluation, the results detailed herein, together with comparative effectiveness data for the tests performed under routine conditions in the same cities where the pilot study was conducted,[10] served as the basis for the estimates of cost-effectiveness ratios.[14] We concluded that the cost of two smear microscopy examinations, which are usually required when tuberculosis is suspected, is close to (i.e., 80% of) the cost of an Xpert® MTB/RIF test.

One of the advantages of the present study was that it was carried out in parallel with the Xpert® MTB/RIF implementation study,[10] which allowed us to observe the incorporation of the new technology into the use of resources and into the learning process of health professionals within the SUS. One study also estimated the cost of the test during a study of implementation, with results ranging from R$46.40 to R$56.48 (US$22.63 to US$27.55), much higher than ours.[8] However, the price of the cartridge was higher than that used in the present study (R$39.77-US$19.40). The value added by

Table 1. Unit costs for Xpert® MTB/RIF and smear microscopy in the laboratories studied, Rio de Janeiro and Manaus (in Brazilian Reals, 2012).[a]

Cost item	Smear microscopy			Xpert® MTB/RIF		
	Lab 1	Lab 2	Lab 3	Lab 1	Lab 2	Lab 3
Staff costs	5.18	3.76	15.87	3.71	3.01	13.27
Consumable and reagent costs	2.35	2.35	2.35	22.01	22.01	22.01
Equipment costs	1.34	0.85	0.97	4.07	3.96	2.42
Administrative costs	2.51	2.81	2.14	4.18	4.03	2.04
Unit cost	11.38	9.77	21.33	33.97	33.01	39.74

Lab: laboratory. [a]Conversion rate used for the cartridge and GeneXpert®: US$1.00 = R$2.05 (2012).

Table 2. Mean daily number of Xpert® MTB/RIF tests and smears of the first sample, produced in the laboratories studied, Rio de Janeiro and Manaus.

Unit	Smear microscopy	Xpert® MTB/RIF	% increase
Laboratory 1	10	13	30
Laboratory 2	7	9	29
Laboratory 3	31	34	10

the other cost items was similar. Other studies reported costs ranging from R$30.61 (US$14.93) to R$54.41 (US$26.54).[15,16] It is of note that all those studies were conducted in countries with different structures from that of the SUS, which limits the comparison.

The advantage of activity-based costing is the possibility of observing a significant number of tests, which makes it possible to identify a standard completion time and to perform a detailed inventory of the cost items. However, the method limits the possibilities of generalization, because of the organizational characteristics and the functioning of the laboratories studied.

The reduction in test completion time between the two observations was lower in laboratory 1, since, during the second data collection time point, the trained technician was replaced with a less experienced one. In order to minimize the effects of this event, we observed a larger number of tests. It is believed that, with the incorporation of Xpert® MTB/RIF into the routine of the laboratories, test completion time will decrease and production will increase. Therefore, it will be possible to increase technical efficiency and reduce the unit cost.

Among the limitations of the present study is the mean salary value, which does not reflect the Brazilian reality given the diversity of contractual arrangements in operation in the country. In order to minimize this diversity, we adopted the salaries of professionals affiliated with the state of AM and with the city of Rio de Janeiro, on the basis of different salary ranges. A second limitation relates to laboratory floor space, used for estimating cost per square meter. The physical structure varies among the facilities in terms of size and location; therefore, we included three laboratories with extremely different configurations, located in two Brazilian states.

The results of the present study might facilitate future cost-effectiveness studies and contribute to the establishment of a reference value on the Sigtap pricing list. However, since the adoption and use of technologies are dynamic and the results of the present study refer to the initial stage of the incorporation of Xpert® MTB/RIF, it is important to observe whether there will be changes in its use.

In conclusion, the present study aimed to provide subsidies so that health care managers can identify the major cost drivers for Xpert® MTB/RIF as well as possible gains in efficiency and effectiveness from its adoption. In this regard, our results might facilitate both programming and planning measures targeted at tuberculosis control in Brazilian cities.

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REVIEW ARTICLE

Sleep in the intensive care unit

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ABSTRACT

Poor sleep quality is a consistently reported by patients in the ICU. In such a potentially hostile environment, sleep is extremely fragmented and sleep architecture is unconventional, with a predominance of superficial sleep stages and a limited amount of time spent in the restorative stages. Among the causes of sleep disruption in the ICU are factors intrinsic to the patients and the acute nature of their condition, as well as factors related to the ICU environment and the treatments administered, such as mechanical ventilation and drug therapy. Although the consequences of poor sleep quality for the recovery of ICU patients remain unknown, it seems to influence the immune, metabolic, cardiovascular, respiratory, and neurological systems. There is evidence that multifaceted interventions focused on minimizing nocturnal sleep disruptions improve sleep quality in ICU patients. In this article, we review the literature regarding normal sleep and sleep in the ICU. We also analyze sleep assessment methods; the causes of poor sleep quality and its potential implications for the recovery process of critically ill patients; and strategies for sleep promotion.

Keywords: Sleep; Sleep deprivation; Intensive care units.

INTRODUCTION

The ICU is a highly complex environment, the operation of which is traditionally based on constant monitoring and observation. As a result, physical and technical aspects of patient care are given priority, whereas some humanizing aspects of care can be overlooked. The sleep of critically ill patients is a subject of increasing interest in the literature, and there is evidence that sleep in the ICU is poor in quality.[1-3] Although there are gaps in the knowledge of this subject, acute sleep deprivation can be negatively associated with the recovery of ICU patients.[1-3]

This article provides a review of the literature regarding the main physiological aspects of normal sleep and the current knowledge of sleep in critically ill patients.

NORMAL SLEEP

Sleep can be defined as a periodic, reversible state of disengagement from the environment.[4] It consists of an active process that involves multiple, complex physiological and behavioral mechanisms of the central nervous system (CNS). Sleep is essential for rest, for repair, and for the survival of the individual.[2]

Normal sleep is divided into two states: rapid eye movement (REM) and non-rapid eye movement (NREM).[5] Accounting for approximately 25% of total sleep time (TST), REM sleep is characterized by rapid, low-amplitude brain activity; episodes of rapid eye movement; irregular respiratory and heart rates; and atonia or hypotonia of major muscle groups. REM sleep is a restorative stage with a variable arousal threshold. It is during this stage that dreams occur.[4,5]

NREM sleep is divided into three stages (1, 2, and 3).[4] Transition from stage 1 to stage 3 refers to a progressive increase in slow waves on electroencephalography (EEG), an increase in sleep depth, and a progressive increase in the arousal threshold. Therefore, stage 3 is known to be the deepest, most restful sleep stage and to have the highest arousal threshold, as well as playing an important role in restorative processes, such as memory consolidation. In contrast, an increase in the amount of stage 1 sleep usually suggests sleep fragmentation caused by sleep disturbance.[4]

In a normal individual, NREM and REM sleep alternate cyclically throughout the night. The NREM-REM cycle repeats itself every 90-110 min, 5-6 times per night. Typically, NREM sleep predominates in the first part of the night, and REM sleep predominates in the second.[4] However, the distribution of sleep stages across the night can be affected by several factors, including age, circadian rhythm, ambient temperature, drugs, and certain diseases.

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Sleep is regulated by circadian and homeostatic mechanisms. The circadian rhythm, an approximately 24-h cycle upon which the life cycle of almost all living beings is based, is regulated by a biological clock located in the suprachiasmatic nucleus of the hypothalamus and helps set the sleep-wake cycle. The sleep-wake cycle tends to be synchronized with the 24-h cycle through environmental stimuli and, predominantly, by exposure to light. The sleep-wake cycle can easily be disrupted in an environment where there is no light/dark cycle. The secretion of melatonin, a hormone involved in the regulation of the sleep-wake cycle, is regulated by the circadian cycle. In order to promote nighttime sleep, the secretion of melatonin is maximal at night, when there is no light. Homeostatic mechanisms also affect the sleep-wake cycle, and their functioning is similar to that of the thirst mechanism: longer periods of sleeplessness translate to greater sleepiness. This underscores the need for sleep, regardless of environmental stimuli.[6]

SLEEP ASSESSMENT METHODS

Overnight in-laboratory polysomnography (PSG) is the gold standard method for diagnosing sleep disorders.[7] The method allows the polygraphic recording of EEG, electrooculogram (EOG), chin and limb electromyogram, oronasal airflow, thoracoabdominal movement, electrocardiogram, and pulse oximetry. Additional channels are available to record other parameters, such as body position, esophageal pressure, snoring, and additional EEG derivations.

Staging of sleep is based on brain wave patterns, chin muscle activity, and EOG. These variables are analyzed in 30-s time segments, known as "epochs".

Portable systems encompass a range of sleep-assessment devices with different levels of complexity. These systems require less technical skill and result in lower costs than does traditional PSG, thus facilitating the diffusion of sleep assessment. They are mainly used in the diagnosis and monitoring of obstructive sleep apnea syndrome (OSAS).[8]

The American Academy of Sleep Medicine divides sleep assessment methods into four categories, on the basis of their respective level of resolution.[8]

Type 1—standard PSG: recording using a minimum of seven channels, including EEG, EOG, submental electromyogram, electrocardiogram, oronasal airflow, respiratory movement, and oxyhemoglobin saturation. It is performed in an attended laboratory setting.

Type 2—portable PSG: recording using a minimum of seven physiological channels, as in standard PSG. It is usually performed in an unattended home setting.

Type 3—modified portable OSAS testing: recording of at least four channels. Because only cardiorespiratory variables are evaluated, it is not possible to analyze sleep parameters.

Type 4—portable, single-channel recording with oximetry, with or without heart rate monitoring. Sleep parameters are not analyzed.

SLEEP ASSESSMENT METHODS IN THE ICU

Although PSG is considered the gold standard method for evaluating sleep,[7] the cost of performing PSG, as well as the practical difficulties in performing it, has led researchers to adopt other sleep assessment methods in critically ill patients.[1,9]

In the setting of critically ill patients, surrogate methods, such as actigraphy (with an activity monitor) and calculation of the bispectral index, have been used.

An activity monitor is an accelerometer-based sensor that is similar to a wristwatch and measures the level of physical activity. This sensor distinguishes between periods of sleep and wakefulness, on the basis of body movement. Although a high level of agreement has been reported between actigraphy and PSG in evaluating sleep in healthy individuals,[10] the only study comparing the use of actigraphy with that of PSG in critically ill patients showed disappointing results.[11] There were no significant correlations between the two methods in terms of TST, sleep efficiency, or the number of arousals. The explanation given by the authors for the low sensitivity and specificity of actigraphy was that the level of immobility was high in that population, who remained in bed throughout the recording period, with few changes in body position.[11]

The bispectral index is a neurophysiological measure that is primarily used to monitor the level of sedation during anesthetic procedures. The bispectral index is used in order to analyze EEG patterns continuously, providing a numerical value on a scale of 0 to 100. Higher values indicate higher levels of consciousness. Unlike actigraphy, the monitoring of the bispectral index makes it possible to assess sleep depth (although an overlap of values for a given stage can lead to an inaccurate characterization of sleep architecture).[9] Reported difficulties in its use include electrode detachment and motion artifacts.[9] Although the bispectral index could prove to be a promising tool in evaluating sleep in critically ill patients, its benefits in this setting have yet to be established.[2,9]

Subjective instruments have been used in order to evaluate sleep in critically ill patients. In comparison with studies using PSG, those using subjective sleep assessment methods have evaluated larger numbers of patients and interventions, over longer periods. In practice, subjective methods are the only possible means of measuring the efficacy of interventions.[9]

Among the existing subjective sleep assessment methods, the most widely used[2] is the Richards-Campbell Sleep Questionnaire (RCSQ).[12] The RCSQ was validated against PSG in a study of 70 ICU patients, and a moderate correlation was found.[12] The RCSQ evaluates sleep in terms of five dimensions: sleep depth; sleep latency; sleep fragmentation; time to resumption of sleep; and sleep quality. Responses are recorded on a 100-mm visual analog scale, and higher scores indicate better sleep quality. The use of the RCSQ in the ICU can be limited by the presence of sedated patients or patients with delirium, which

can reduce the patient sample by up to 50%.[13] In an attempt to increase the applicability of the RCSQ, a study evaluating agreement between nurse-completed RCSQs and patient-completed RCSQs obtained a correlation that was only mild to moderate, with nurses tending to overestimate patient-perceived quality of sleep.[14]

The Sleep in the Intensive Care Unit Questionnaire[15] is a 27-item instrument that evaluates sleep in terms of four dimensions: sleep quality; disruptive factors produced by the health care team; environmental disruptive factors; and daytime sleepiness. Its usefulness lies in the fact that it allows individual scoring of the role of a number of sleep disruptions resulting from ICU environmental factors or from care routines. Therefore, it has been used in studies implementing protocols for sleep promotion.[16-18]

SLEEP IN THE ICU

Poor sleep quality is consistently reported by patients in the ICU.[1-3,15,19-22] In a study employing 24-h PSG to evaluate 57 ICU patients, sleep architecture was reported to be highly altered. Those patients spent 90% of their TST in superficial sleep (NREM stages 1 and 2), thus being mostly deprived of deep and restorative sleep (NREM stage 3 and REM sleep, respectively).[21] In that population, TST was 5 h, and 41% of TST occurred during the day,[21] which indicates impairment of the circadian rhythm of sleep. In addition, unusual sleep stage transitions, as well as a high frequency of nighttime arousals (mean, 27 events/h), were noted. Similarly, another study demonstrated that critically ill patients experienced 41 ± 28 sleep periods in 24 h, with sleep periods lasting approximately 15 ± 9 min, which means that the process was highly fragmented.[23]

Subjective assessments of sleep in critically ill patients have yielded similar results. One study reported that sleep in critically ill patients was light and was often disrupted by arousals, and that, once awake, patients had difficulty resuming sleep.[24] In another study, most of the patients evaluated rated their sleep quality as poor, the mean RCSQ score being 57.50 points (range, 32.00-70.00).[21]

Patients who are eventually discharged from the ICU (ICU survivors) report that inability to sleep was among the major sources of stress[25] or bad memories during their ICU stay.[26] In one study, 60 patients were interviewed by at 6-12 months after their discharge from the ICU, and 50% reported sleep disturbances during their ICU stay, such disturbances persisting after discharge in approximately 30%.[27]

Such findings demonstrate that there has been no improvement in sleep patterns since similar studies were published more than 10 years ago.[15,19,20] For instance, in 1985, sleep assessment in 9 patients in the postoperative period of non-cardiac surgery revealed that all of those patients had severe or complete suppression of REM sleep and NREM stage 3 sleep.[19] In 1999, it was demonstrated that sleep quality in the ICU was perceived as significantly poorer than sleep at home by all patients interviewed ($p < 0.0001$).[15]

In summary, studies have revealed qualitative and quantitative sleep deficiencies in critically ill patients. The presence of extreme sleep fragmentation and unconventional sleep architecture is indisputable, as are the predominance of light stages and the lack of restorative stages.[1-3,22,28]

Causes of sleep disorders in the ICU

Several factors are related to sleep deprivation in critically ill patients. These factors include environmental factors, such as noise, light, and care activities; factors intrinsic to the patients and the acute nature of their condition; and factors related to the treatments administered, such as ventilatory support and drug therapy.[1,2,22,28] Despite the identification of these factors, the exact role played by each of them in sleep in critically ill patients remains unknown.

Noise

Environmental noise has been reported as the major sleep-disturbing factor,[21,29] the principal sources of such noise being talking by the staff, monitor alarms, infusion pump alarms, telephones, and television.[15,30]

Noise levels in the ICU are estimated to range from 50 to 75 dB, with peaks of 85 dB,[31] whereas the U.S. Environmental Protection Agency recommends that hospital noise levels do not exceed 45 dB during the day and 35 dB during the night.[32] The estimated ICU noise levels are comparable to those reported for factories (80 dB) and busy offices (70 dB).[31] Only 10-30% of arousals can be attributed to environmental noise,[23,29] which belies the traditional hypothesis that noise is one of the major sleep-disrupting factors in the ICU. One study reported that although noise peaks occur frequently in the ICU, only 12% of those peaks result in an arousal.[29]

Light

One ICU study recorded activity occurring while lights were turned on during the night. The activity associated with the greatest amount of light exposure was that related to obtaining samples for laboratory tests, followed by "no activity", suggesting a lack of vigilance on the part of the health care provider team in reducing unnecessary light exposure.[33] However, patients have reported that light is less disturbing to their sleep than are care activities or environmental noise.[15,30]

Given that light plays a vital role in the synchronization of the circadian rhythm, one study evaluated nighttime secretion of melatonin in ICU patients. That study found that, regardless of the levels of light, melatonin secretion was suppressed or erratic, suggesting that factors other than the light/dark cycle affect the circadian rhythm in ICU populations.[34]

Patient care activities

One study found that nursing care activities, such as oral and ocular hygiene, bathing, changing of bed linen,

and catheter management, were usually performed between midnight and 5:00 a.m.,[35] resulting in a mean of 51 interventions per patient per night.[35] In addition, a study evaluating nursing care on the night shift reported that only 9 uninterrupted periods (2-3 h each) were available for sleep on 6% of the 147 nights studied.[36] However, another study demonstrated that only 20% of patient care activities resulted in arousals, which accounted for approximately 7% of the sleep disruption in that patient population.[29] Therefore, although frequent, care activities do not seem to be the major source of sleep disturbances in ICU patients.[1]

Factors intrinsic to the patients

Patients admitted to ICUs can have a preexisting disease that contributes to poor sleep quality. Obstructive pulmonary diseases, such as asthma and COPD, are common comorbidities and can be associated with sleep fragmentation and poor sleep efficiency, as well as with changes in sleep architecture.[2] Patients with neurological disturbances or severe systolic heart failure often exhibit nocturnal Cheyne-Stokes respiration, which can cause sleep fragmentation, excessive daytime sleepiness, paroxysmal nocturnal dyspnea, and insomnia.[2] Sleep-disordered breathing conditions, such as obstructive sleep apnea and obesity hypoventilation syndrome, can lead to serious consequences if not properly treated.[2] In addition, the acute injury responsible for the ICU admission can itself be a sleep-disrupting factor. In the immediate postoperative period after major surgery, deep sleep (NREM stage 3 and REM sleep) is reduced or absent. This finding is characteristically followed by a REM sleep rebound.[19] However, this rebound can be absent in patients taking REM-sleep-suppressing drugs, such as analgesics and benzodiazepines. Furthermore, studies investigating the profiles of patients admitted to ICUs have demonstrated that changes in melatonin secretion are more marked in ICU patients than in their healthy counterparts, a finding that suggests poorer sleep quality in the former group.[37,38]

Patient-related conditions can contribute to poor sleep quality. Pain is a common complaint of patients and can be associated with poor sleep quality.[25] Stress and anxiety due to unfamiliarity with the ICU environment, inability to speak or move, or acute illness are other factors that should be taken into account.

Mechanical ventilation

Studies have shown that mechanical ventilation (MV) is associated with sleep disorders.[20,23] Aspects of MV that contribute to sleep fragmentation include increased work of breathing, gas exchange abnormalities, and patient-ventilator asynchrony.[1,2] Therefore, patients on MV have greater sleep fragmentation and lower sleep efficiency than do their non-ventilated counterparts.[20] Other related factors, such as discomfort from the endotracheal tube, aspiration, frequent repositioning, and ventilator alarms, are also likely to contribute to poor sleep quality, although such associations have yet to be studied.[2,31] It should be borne in mind that, in patients on MV, disease severity is a potential confounding factor, as are the use of sedatives and analgesics.[31]

There is evidence that the mode of ventilation also affects sleep quality.[39,40] One study reported that sleep fragmentation was greater during pressure support ventilation (PSV) than during assist-control ventilation: 79 vs. 54 arousals and microarousals/h.[39] Another study demonstrated that patients receiving neurally adjusted ventilatory assist had a higher proportion of REM sleep than did those receiving PSV—16.5% (range, 13-29%) vs. 4.5% (range, 3-11%; $p = 0.001$)—as well as less sleep fragmentation—16 ± 9 vs. 40 ± 20 arousals and microarousals/h; $p = 0.001$).[40] However, a study comparing the impact of three modes of ventilation (assist-control, PSV, and SmartCare™) on sleep quality in conscious, unsedated patients reported conflicting results. There were no differences among the three modes in terms of sleep architecture, sleep fragmentation, or sleep duration.[41]

Medications

A significant number of medications that are commonly used in the ICU can cause changes in the amount and quality of sleep. These medications can affect the CNS either directly, by penetrating the blood-brain barrier, or indirectly, by interfering with a medical or psychiatric condition, which results in altered sleep. In addition, they can have an equally disturbing effect when withdrawn abruptly.[42] Although it is difficult to study the exact interaction between these medications and sleep in critically ill patients, their effects in healthy individuals are well documented.[42,43]

Sedatives

Benzodiazepines improve sleep efficiency because they decrease sleep latency and the number of arousals, thus increasing TST. However, the chronic use of benzodiazepines is associated with superficial sleep, because it reduces deep sleep and REM sleep. The abrupt withdrawal of benzodiazepines is associated with rebound insomnia.[42] Propofol, which is used primarily for deep sedation, suppresses REM sleep and is associated with poor sleep quality in ICU populations.[1,2] The use of propofol (even at low doses) is associated with delirium in critically ill patients, as is that of benzodiazepines.[42] Dexmedetomidine, a new α_2 agonist, has sedative, anxiolytic, and analgesic effects, with minimal respiratory depression. Similarities between natural sleep and dexmedetomidine-induced sedation have been reported.[1] However, further studies are needed in order to determine the specific effects of dexmedetomidine on sleep in critically ill patients.

Antipsychotic drugs

Antipsychotic drugs are now the pharmacological mainstay of the management of agitation and delirium in the ICU. Haloperidol, the most widely used atypical antipsychotic drug, when administered as a single dose to healthy volunteers, tends to increase sleep

efficiency, especially that of NREM stage 2 sleep, with little effect on slow-wave sleep.[44] Olanzapine and risperidone seem to increase sleep efficiency and TST, as well as increasing deep sleep.[44]

Analgesics

Opioids are the mainstay of the treatment of pain and discomfort in critically ill patients. Opioids are associated with suppression of REM and slow-wave sleep, as well as with sleep fragmentation, and can induce central apnea or even delirium.[1,2] Even nonsteroidal anti-inflammatory drugs can negatively affect sleep, increasing nighttime arousals and decreasing sleep efficiency.[1] However, analgesic medications play a significant role in patient comfort, and a balanced administration of these medications should be sought.

Cardiovascular medications

Beta blockers can have variable effects on sleep, depending on their ability to cross the blood-brain barrier. The use of Beta blockers that are highly lipid soluble is associated with increased sleep disruption, potentially causing nightmares, insomnia, and suppression of REM sleep.[1] Amiodarone has neurological effects, including insomnia and nightmares, in 20-40% of patients.[1] Angiotensin-converting enzyme inhibitors do not seem to affect sleep. Other antihypertensive agents, such as calcium antagonists, hydralazine, diuretics, and α_1 antagonists, have not been evaluated for their effects on sleep.[42] Norepinephrine, epinephrine, and dopamine are associated with insomnia, as well as with suppression of deep sleep and REM sleep.[42]

Respiratory medications

Agitation and insomnia caused by stimulation of the CNS are well-known adverse effects of beta-agonists.[42] However, their effects can ultimately be positive if there is a reduction in the respiratory symptoms that are related to sleep fragmentation.[1,2]

Miscellaneous

Corticosteroids are often associated with insomnia; however, there have not been enough conclusive results.[43] Nevertheless, the use of corticosteroids, depending on the type and dosage, can be associated with suppression of REM sleep and with nighttime arousals.[42,43]

Although tricyclic antidepressants can suppress REM sleep, they increase TST and in general can improve subjective sleep quality. Selective serotonin reuptake inhibitors reduce REM sleep less sharply. However, they decrease TST and can be associated with insomnia, as well as with daytime sleepiness.[42,43]

POTENTIAL CONSEQUENCES OF SLEEP DISTURBANCES IN THE ICU

Cardiovascular consequences

It is well known that chronic sleep deprivation is associated with increased cardiovascular morbidity and mortality. A cohort study conducted in Germany revealed that, among individuals who slept less than 6 h per night, the relative risk (RR) of cardiovascular disease and coronary artery disease was, respectively, 1.11 (95% CI: 0.97-1.27) and 1.19 (95% CI: 1.00-1.40). The risk of those conditions was found to be more than 60% higher among such individuals than among those who slept more than 6 h per night.[45] A systematic review with a collective sample of 474,684 participants revealed that individuals who are chronically sleep deprived are at an increased risk of developing and dying from coronary artery disease (RR = 1.48; 95% CI: 1.22-1.80; $p < 0.0001$) and stroke (RR = 1.15; 95% CI: 1.00-1.31; $p = 0.047$).[46] Despite this evidence, whether sleep deprivation in the ICU contributes to cardiovascular mortality has yet to be established.

Respiratory consequences

Studies conducted outside the ICU setting have demonstrated that even short periods of sleep deprivation can cause respiratory changes. After a sleepless night, healthy individuals show a slight but significant decline in FVC and maximal voluntary ventilation.[47] One study of patients with stable COPD reported similar changes.[48]

Although it used to be believed that sleep deprivation could reduce the ventilatory response to hypercapnia,[47,49] leading to hypoventilation, it has been demonstrated that sleep deprivation does not change respiratory control in healthy individuals.[50] No such studies have been conducted in critically ill patients.

Metabolic consequences

Evidence that sleep has a modulatory effect on the metabolic system has been reported in recent decades. In particular, glucose tolerance, the 24-h pattern of insulin release, and the secretion of counterregulatory hormones (such as growth hormone and cortisol), as well as of those involved in the regulation of appetite (such as leptin and ghrelin), are, at least in part, dependent on sleep duration and quality.[51,52] Such findings, however, are primarily based on epidemiological cohort studies evaluating chronic sleep deprivation or on models of sleep fragmentation in individuals with OSAS, which does not allow extrapolation of the findings to the acute setting of critically ill patients.[51,52]

Consequences for the immune system

It is common sense that sleep deprivation increases the risk of an individual having an infection or disease, and that, conversely, sleep is vital to the recovery of health.[2] A murine model designed to explore the effects of sleep loss on host immunity and defense demonstrated that chronic sleep deprivation led to wasting and death from septicemia, resulting from opportunistic bacterial infections, within 27 days.[53]

Studies of healthy individuals have demonstrated that sleep deprivation leads to changes in the immune functions of lymphocytes, polymorphonuclear cells,

and natural killer cells.[2,28,31] In addition, inflammatory cytokines (such as IL-1, IL-6, and TNF), which are known to cause endothelial dysfunction and increased insulin resistance, are also increased in sleep deprivation,[2,28,31] potentially expanding the physiological impact of sepsis.

Delirium

Delirium is an acute confusional state that is common in critically ill patients, affecting up to 80% of patients receiving MV.[54] Delirium is associated with higher mortality, longer hospital stays and increased hospitalization costs, and cognitive worsening.[2,54] Given that both delirium and sleep deprivation are common findings that often coexist in critically ill patients, it has been hypothesized that the two are related.[2,55,56] However, whether this is a cause-and-effect relationship or simply an association resulting from shared mechanisms remains a matter to be determined. An analysis of 223 critically ill patients demonstrated no association between daily perceived sleep quality and transition to delirium. However, in those patients undergoing MV, the use of sedatives (benzodiazepines or opioids) was strongly associated with a transition to delirium within 24 h.[56]

MEASURES FOR SLEEP PROMOTION IN THE ICU

The mechanisms associated with sleep disorders and abnormal sleep architecture in the ICU have yet to be fully understood. Although factors such as noise and care activities have classically been considered the main causes of sleep disruption in critically ill patients, these factors have been found to account for only 37% of arousals in the ICU.[29] Therefore, addressing these factors individually should not significantly affect sleep deprivation in the ICU.[28]

There is evidence that sleep promotion in the ICU can be achieved through multifaceted interventions focused on multifactorial minimization of nighttime sleep disruptions and maintenance of sleep-wake cycles.[1,3,22,28] Therefore, chief among major approaches are the following: reduction in nighttime light and noise levels; improvement of patient comfort; and organization of care activities to allow uninterrupted periods of sleep.[1,2,28,31] A reduction in noise levels can be achieved by adjusting monitor and ventilator alarms, turning down the telephone ringer volume, closing doors, minimizing staff conversation, and providing earplugs.[16-18,57-60] Light levels can be reduced by dimming the lights in the rooms and surroundings and by providing sleeping masks.[16-18,57-60] Improvement of patient comfort includes ventilator adjustment, optimizing patient-ventilator synchrony[39,40]; adequate pain relief[17,18,57,58]; relaxation techniques, such as massage, music therapy, and playing recordings of ocean sounds[1,2,60]; and administration of drugs, such as zolpidem, haloperidol,[18] or melatonin,[1,22,59] when necessary. Care activities, such as exams and blood collection, hygiene care, and administration of medications, should be planned to prevent unnecessary sleep disruptions.[16-18,57,58]

Studies have been carried out to assess the impact that such multifaceted interventions have on sleep promotion. A protocol was developed to limit nighttime nursing care activities and thereby reduce patient sleep disruptions. There was no significant improvement in the intervention group. However, patients in that group were older and reported more frequent use of sleeping medication than did those in the control group.[58] A similar study implemented a protocol to reduce nighttime light and noise levels, in addition to changing patient care routines. That study demonstrated that mean noise levels were significantly reduced, as was the noise perceived by the patient. There was also a reduction in sleep disruption from environmental factors in the intervention group, as well as improvement in global sleep quality and in sleep efficiency.[16] In contrast, by implementing measures to promote sleep, another group of authors achieved a reduction in nighttime light and noise levels. Consequently, the sleep efficiency index was better in the intervention group than in the control group and the number of arousals associated with the health care team was lower in the intervention group. The incidence of delirium was also lower in the intervention group.[17] A randomized clinical trial that implemented measures to reduce environmental disruptions, as well as the use of music therapy,[60] achieved significant improvements in sleep, as assessed by the different domains of the RCSQ, in the intervention group. However, there were no differences between the intervention and control groups in terms of urinary cortisol or melatonin.

A study that, in addition to the conventional protocol, implemented pharmacological measures to promote sleep achieved significant improvements in perceived nighttime noise and incidence of delirium. There was no difference in perceived sleep quality.[18] A randomized trial that also used pharmacological measures (melatonin)[59] could not adequately compare PSG findings between the two groups, because more than half of the recordings were unscorable (i.e., showed sleep patterns that could not be interpreted).

FINAL CONSIDERATIONS

Sleep in critically ill patients is characterized by frequent disruptions, changes in the circadian rhythm, and poor quality, along with a reduction in the deep, restorative stages.

Such sleep disturbances seem to be due to factors related to the ICU itself, such as care routines and environmental stimuli; factors intrinsic to the patients and the acute nature of their condition; and factors related to the treatments administered, such as MV. However, understanding of the pathogenesis of sleep disturbances in ICU populations remains incomplete, and there is no knowledge of the relative contribution of potential sources of sleep disruption. In addition, although poor sleep quality can affect a number of

metabolic and regulatory processes in the body, the impact of sleep deprivation on certain outcomes, such as weaning from MV, length of ICU stay, and in-hospital morbidity and mortality, remains unknown.

Finally, although protocols for sleep promotion in the ICU have recently been implemented and studied, the degree to which sleep can be improved in ICU patients, as well as the best strategies for sleep promotion, has yet to be defined. While all such questions remain unanswered, it seems appropriate to provide patients with the necessary conditions for restorative sleep if the goal can be achieved safely.

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Lung transplantation: overall approach regarding its major aspects

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ABSTRACT

Lung transplantation is a well-established treatment for patients with advanced lung disease. The evaluation of a candidate for transplantation is a complex task and involves a multidisciplinary team that follows the patient beyond the postoperative period. Currently, the mean time on the waiting list for lung transplantation in the state of São Paulo, Brazil, is approximately 18 months. For Brazil as a whole, data from the Brazilian Organ Transplant Association show that, in 2014, there were 67 lung transplants and 204 patients on the waiting list for lung transplantation. Lung transplantation is most often indicated in cases of COPD, cystic fibrosis, interstitial lung disease, non-cystic fibrosis bronchiectasis, and pulmonary hypertension. This comprehensive review aimed to address the major aspects of lung transplantation: indications, contraindications, evaluation of transplant candidates, evaluation of donor candidates, management of transplant recipients, and major complications. To that end, we based our research on the International Society for Heart and Lung Transplantation guidelines and on the protocols used by our Lung Transplant Group in the city of São Paulo, Brazil.

Keywords: Lung transplantation; Pulmonary disease, chronic obstructive; Cystic fibrosis; Respiratory tract infections; Pulmonary fibrosis; Hypertension, pulmonary.

INTRODUCTION

Lung transplantation is a treatment option for patients with advanced lung disease.

The evaluation of a lung transplant candidate is a task that involves a multidisciplinary team including pulmonologists, thoracic surgeons, infectious disease specialists, nurses, nutritionists, physiotherapists, psychologists, and social workers. When referring patients for an initial evaluation, pulmonologists should inform patients that lung transplantation is a treatment option that will be carefully analyzed by the lung transplant team, who will weigh the risks and benefits of the procedure.

In the state of São Paulo, Brazil, the mean time on the waiting list for lung transplantation is approximately 18 months. Although a donor lung is allocated to a given recipient primarily on the basis of ABO blood compatibility, lung size compatibility is also important. Brazilian law does not provide prioritization criteria for patients on the waiting list for lung transplantation, the exception being acute graft failure within 30 days after the procedure.

Procedures include single lung transplantation (Figure 1) and bilateral lung transplantation, the latter being mandatory in cases of suppurative lung disease. Bilateral lung transplantation is the procedure of choice for patients with pulmonary hypertension because they are at an increased risk of primary graft dysfunction. Patients with severe right ventricular dysfunction, left ventricular dysfunction, or a combination of the two are candidates for heart-lung transplantation. However, procedures involving transplantation of a lung and another solid organ are not currently performed in Brazil.

Brain-dead donor organs are used in all of the aforementioned procedures. In exceptional cases (i.e., for pediatric recipients), living lobar lung transplantation can be performed, in which case there are two donors, each donating one lobe to the recipient.

For Brazil as a whole, data from the Brazilian Organ Transplant Association show that, in 2014, there were 67 lung transplants and 204 patients on the waiting list for lung transplantation.[1]

Lung transplantation is a well-established treatment that improves survival and quality of life in patients with advanced chronic lung disease. The present study is a comprehensive review of the major aspects of lung transplantation, including indications, contraindications, evaluation of transplant candidates, evaluation of donor candidates, management of transplant recipients, and major complications.

In 2014, the International Society for Heart and Lung Transplantation (ISHLT) met in order to update consensus guidelines on indications and contraindications for lung transplantation, as well as on candidate and donor selection.[2] The criteria described below are based on the 2014 ISHLT guidelines and on the protocols used by our Lung Transplant Group at the University of São Paulo School of Medicine *Hospital das Clínicas* Heart Institute, in the city of São Paulo, Brazil.

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Referring patients for lung transplant evaluation is an onerous task, and many patients are referred too late for evaluation.

Although several factors should be taken into consideration when evaluating patients for lung transplantation, patients in whom short- and long-term post-transplant survival rates are estimated to be higher than 80% constitute ideal candidates. The number of donor lungs available for transplantation is not enough to meet the demand, waiting list mortality being approximately 22%. The entire lung transplantation process (from the initial evaluation to postoperative follow-up, from which recipients are never discharged) is complex and costly; therefore, candidates should be carefully evaluated so that financial resources are not unnecessarily spent on cases in which lung transplantation is likely to fail and donor lungs are allocated to patients whose chances of survival are known to be higher.

By 2014, our group had performed 232 lung transplants, most of which had been performed in patients with COPD, cystic fibrosis, interstitial lung disease, or non-cystic fibrosis bronchiectasis. Data from the ISHLT show that 1-, 3-, and 5-year survival rates after lung transplantation are 82.0%, 66.7%, and 55.3%, respectively. For procedures performed by our group, the aforementioned rates are 71.0%, 59.8%, and 55.2%, respectively.

CONTRAINDICATIONS

The contraindications below are based on the ISHLT guidelines and on the protocols used by our Lung Transplant Group.

Absolute contraindications

- A recent history of cancer is an absolute contraindication to lung transplantation, a disease-free period of 2 years being required in all cases except those of nonmelanoma skin cancer (if properly treated). A disease-free period of 5 years is recommended for most other cancer patients, including those with hematological malignancies, sarcoma, melanoma, kidney cancer, bladder cancer, or breast cancer. Certain histological types of cancer confer a high risk of recurrence regardless of treatment duration and should therefore be evaluated on a case-by-case basis.
- Significant dysfunction of another major organ (such as the heart, the liver, the kidneys, and the brain) is an absolute contraindication to lung transplantation unless a double organ transplant can be performed. As previously mentioned, procedures involving transplantation of a lung and another solid organ are not currently performed in Brazil.
- Untreated or untreatable coronary artery disease with suspected or confirmed ischemic cardiac dysfunction is an absolute contraindication to lung transplantation.
- Acute medical instability, including, but not limited to, sepsis, acute myocardial infarction, and liver failure, is an absolute contraindication to lung transplantation.

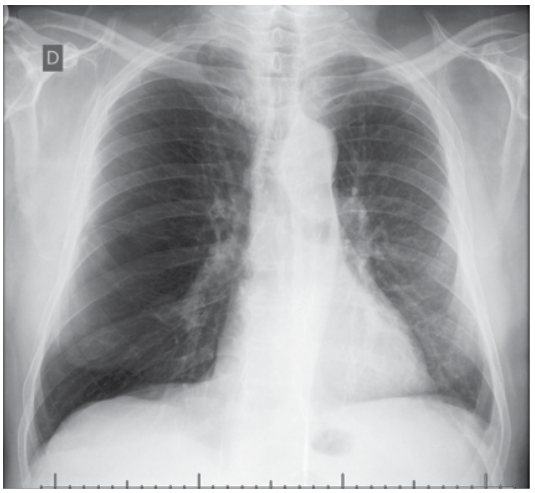

Figure 1. Chest X-ray of a left lung transplant recipient who underwent transplantation because of COPD.

- Untreatable bleeding diathesis is an absolute contraindication to lung transplantation.
- Poorly controlled chronic infection with highly virulent/resistant pathogens is an absolute contraindication to lung transplantation.
- Evidence of active infection with *Mycobacterium tuberculosis* is an absolute contraindication to lung transplantation.
- Chest wall or spinal column deformity that can lead to severe restrictive lung disease after transplantation is an absolute contraindication to lung transplantation.
- A BMI ≥ 35 kg/m^2 is an absolute contraindication to lung transplantation. At our facility, a BMI ≥ 30 kg/m^2 is an absolute contraindication to lung transplantation.
- Psychiatric or psychological conditions resulting in inability to cooperate with medical care or the health care team and in poor treatment adherence are absolute contraindications to lung transplantation.
- Inadequate social support is an absolute contraindication to lung transplantation.
- Poor functional status with low potential for rehabilitation is an absolute contraindication to lung transplantation. At our facility, lung transplant candidates undergo muscle strength assessment and the six-minute walk test, a six-minute walk distance (6MWD) of less than 200 m being a contraindication to the procedure. [3]
- Chemical abuse or dependency (including alcohol, tobacco, and illicit drug use/abuse) is an absolute contraindication to lung transplantation. At our facility, a minimum of six months of abstinence and complete cessation are required for patients undergoing lung transplantation.

Relative contraindications

- Being over 65 years of age and the presence of diminished psychological reserve, other relative contraindications, or a combination of the two are relative contraindications to lung transplantation, as is, in most cases, being over 75 years of age. At

our facility, patients over 60 years of age are not placed on the waiting list for lung transplantation.

- A BMI ≥ 30 kg/m^2 is a relative contraindication to lung transplantation. As previously mentioned, a BMI ≥ 30 kg/m^2 is an absolute contraindication to lung transplantation at our facility.
- Severe malnutrition is a relative contraindication to lung transplantation.
- Severe symptomatic osteoporosis is a relative contraindication to lung transplantation.
- Having undergone major thoracic surgery with pulmonary resection is a relative contraindication to lung transplantation.
- Being on mechanical ventilation, extracorporeal membrane oxygenation, or a combination of the two is a relative contraindication to lung transplantation. However, selected patients, without acute or chronic dysfunction of other organs, can undergo transplantation under these conditions.
- Colonization or infection with virulent pathogens or certain mycobacterial strains is a relative contraindication to lung transplantation.
- Active infection with HBV, HCV, or a combination of the two is a relative contraindication to lung transplantation. In some centers, patients infected with HBV, HCV, or both are considered for transplantation if there are no signs of cirrhosis or portal hypertension and if they are receiving appropriate treatment. At our facility, patients infected with HBV, HCV, or both are considered for transplantation if there are no signs of cirrhosis or portal hypertension and after they have received appropriate treatment and achieved an undetectable viral load.
- In some centers, patients with HIV infection are considered for transplantation if they have an undetectable viral load and adhere to treatment. At our facility, positive HIV serology is considered to be an absolute contraindication to lung transplantation.
- Infection with *Burkholderia cenocepacia*, *B. gladioli*, or *Mycobacterium abscessus* is considered to be a contraindication to lung transplantation in some centers. At our facility, postoperative complications in patients infected with any of the aforementioned bacteria have been only minor. Therefore, infection with *B. cenocepacia*, *B. gladioli*, or *M. abscessus* is not a contraindication to lung transplantation there.
- Atherosclerotic disease that is sufficiently advanced to pose a threat to lung transplant recipients is a relative contraindication to lung transplantation.
- Comorbidities such as systemic arterial hypertension, diabetes mellitus, gastroesophageal reflux disease, epilepsy, and peptic ulcer constitute a relative contraindication to lung transplantation and should be optimally treated prior to transplantation.
- Antiphospholipid syndrome is no contraindication to lung transplantation if it is not accompanied by heparin-induced thrombocytopenia.
- In patients with connective tissue disease, particularly in those with scleroderma, esophageal involvement is the major limitation to the success of lung transplantation because gastroesophageal reflux disease is a major risk factor for chronic allograft dysfunction.

INDICATIONS

In general, lung transplantation is indicated for patients who meet all of the following criteria:

- high (> 50%) risk of 2-year mortality from lung disease if lung transplantation is not performed
- high (> 90%) probability of survival at 90 days after transplantation
- high (> 80%) probability of survival at 5 years after transplantation, from a clinical standpoint, if the graft is in good condition

Obstructive diseases

Obstructive diseases include COPD and bronchiolitis obliterans.

Patients should be referred for evaluation in the following situations: progressive disease, despite optimal treatment; COPD that cannot be treated with lung volume reduction surgery or endoscopic lung volume reduction; a **B**ody mass index, airflow **O**bstruction, **D**yspnea, and **E**xercise capacity (BODE) index[4] of 5-6; $PaCO_2$ > 50 mmHg, PaO_2 < 60 mmHg, or a combination of the two; and FEV_1 < 25% of predicted.

Patients should be placed on the waiting list for lung transplantation if they meet at least one of the following criteria: a BODE index ≥ 7; FEV_1 < 15-20% of predicted; three or more severe exacerbations in the last year; one severe exacerbation with acute hypercapnic respiratory failure; and moderate to severe pulmonary hypertension.

Suppurative diseases

Suppurative diseases include cystic fibrosis, ciliary dyskinesia, and bronchiectasis.

Patients should be referred for evaluation in the following situations: FEV_1 < 30% of predicted, particularly in cases of rapid decline despite optimal treatment; 6MWD < 400 m; development of pulmonary hypertension in the absence of hypoxemia secondary to exacerbation; and clinical worsening characterized by increased exacerbations accompanied by any of the following: acute respiratory failure requiring noninvasive ventilation; increased antimicrobial resistance and poor recovery from exacerbation; poor nutritional status despite supplementation; pneumothorax; or life-threatening hemoptysis that cannot be controlled with embolization.

Patients should be placed on the waiting list for lung transplantation if they meet at least one of the following criteria: chronic respiratory failure ($PaCO_2$ > 50 mmHg, PaO_2 < 60 mmHg, or a combination of the two); need for noninvasive ventilation; pulmonary hypertension; frequent hospitalizations; rapid decline in lung function; and World Health Organization functional class IV.

In patients with bronchiectasis secondary to cystic fibrosis, the following should be taken into consideration: exocrine and endocrine pancreatic disease,

which influences the choice of immunosuppressant (tacrolimus being more toxic to the pancreas than cyclosporine), and chronic sinus disease, given that colonization of the upper airways is a common cause of pulmonary infection after transplantation (sinusectomy is commonly indicated for lung transplant recipients).

Interstitial diseases

Interstitial diseases include fibrotic restrictive lung diseases, such as idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, and nonspecific interstitial pneumonia.

Patients should be referred for evaluation in the following situations: histological or radiological evidence of usual interstitial pneumonitis or fibrotic nonspecific interstitial pneumonitis, independently of lung function; FVC < 80% of predicted or DLCO < 40% of predicted; dyspnea or functional limitation attributable to lung disease; need for supplemental oxygen, even if only during exercise; and, in cases of inflammatory interstitial lung disease (other than usual interstitial pneumonitis and fibrotic nonspecific interstitial pneumonitis), no symptom improvement, need for supplemental oxygen, functional improvement after appropriate treatment, or any combination of the three.

Patients should be placed on the waiting list for lung transplantation if they meet at least one of the following criteria: ≥ 10% decline in FVC at 6 months of follow-up; ≥ 15% decline in DLCO at 6 months of follow-up; desaturation < 88%, 6MWD < 250 m, or a > 50-m decline in the 6MWD at 6 months of follow-up; pulmonary hypertension; or hospitalization because of functional deterioration, pneumothorax, or acute exacerbation.

Vascular diseases

Vascular diseases include pulmonary arterial hypertension.

Patients should be referred for evaluation in the following situations: New York Heart Association (NYHA) functional class III or IV despite optimal treatment; rapidly progressive disease; parenteral therapy use regardless of NYHA functional class (not available in Brazil); and confirmed or suspected pulmonary veno-occlusive disease or a diagnosis of pulmonary capillary hemangiomatosis.

Patients should be placed on the waiting list for lung transplantation if they meet at least one of the following criteria: NYHA functional class III or IV despite optimal treatment, including prostanoids (which are not yet widely available in Brazil); cardiac index < 2 L/min/m^2; mean right atrial pressure > 15 mmHg; 6MWD < 350 m; or hemoptysis, pericardial effusion, or signs of right heart failure.

As previously mentioned, for lung or heart-lung transplantation referral, it is essential to determine whether the right ventricle is viable. This can be done by means of magnetic resonance imaging, myocardial scintigraphy, or both.

Pediatric population

Pediatric patients should be referred for evaluation in the same situations as should adult patients.

Certain particularities should be taken into account, primarily related to the size of the recipients, which can lead to a longer waiting time.

Treatment adherence is also important and tends to be lower in the pediatric population than in the adult population, poor treatment adherence increasing the risk of complications, including acute rejection and chronic allograft dysfunction. However, the success rates in the pediatric population are similar to those in the adult population.[5,6]

Retransplantation

The number of cases of lung transplant recipients who develop chronic graft failure and, consequently, chronic respiratory failure requiring retransplantation has increased worldwide.

EVALUATION OF TRANSPLANT CANDIDATES

Lung transplant candidates should be evaluated by a multidisciplinary team including pulmonologists, thoracic surgeons, infectious disease specialists, nurses, nutritionists, physiotherapists, psychologists, and social workers.

Required tests

- laboratory tests: complete blood count; coagulation profile; blood typing; urea; creatinine; sodium; potassium; ionized calcium; magnesium; total cholesterol, LDL cholesterol, and HDL cholesterol; triglycerides; total and direct bilirubin; total protein and albumin; lactate dehydrogenase; aspartate aminotransferase; alanine aminotransferase; alkaline phosphatase; gamma-glutamyltransferase; amylase; arterial blood gas analysis on room air; TSH and free thyroxine; serology for HIV, hepatitis A virus, HBV, HCV, syphilis, Chagas disease, cytomegalovirus (CMV), toxoplasmosis, Epstein-Barr virus, and HSV; blood glucose; glycated hemoglobin; immune panel (after placement on the waiting list); urinalysis; creatinine clearance; and sputum examination (aerobic culture, AFB smear testing, AFB culture, screening for fungi, and fungal culture)
- full pulmonary function testing, including DLCO measurement
- imaging tests: posteroanterior and lateral chest X-rays; electrocardiography; HRCT; cranial CT; sinus CT (for patients with suppurative lung disease); quantitative lung perfusion radionuclide scanning; echocardiography; left heart catheterization (for patients over 40 years of age); right heart catheterization (for patients with echocardiographic signs of pulmonary hypertension); and bone densitometry

Patients with a history of gastroesophageal reflux disease or scleroderma should undergo pH monitoring and esophageal manometry.

Whenever necessary, patients should be evaluated by a gastroenterologist, a psychiatrist, a cardiologist, a nephrologist, a neurologist, a hematologist, a urologist, or a gynecologist.

The decision to place a patient on the waiting list for lung transplantation is made by the multidisciplinary team on a case-by-case basis and is based on the results of the complete evaluation of the patient.

When a patient is placed on the waiting list for lung transplantation, an immune panel is requested in order to identify the presence of pre-transplant HLA class I and II antibodies. A > 10% positive immune panel increases the risk of hyperacute rejection, and pre-transplant virtual crossmatch is therefore required. The immune panel should be repeated every 6 months. Blood transfusions can stimulate the formation of anti-HLA antibodies. Therefore, if a patient on the waiting list for lung transplantation receives a blood product transfusion, the immune panel should be repeated.

EVALUATION OF DONOR CANDIDATES

Data from the Brazilian Organ Transplant Association show that, in 2014, Brazil had approximately 190.8 million inhabitants, with 14.2 actual donors per million population. Of those, only 0.4 per million population were actual lung donors.

Reasons for low organ donation rates include family refusal, cardiac arrest, and medical contraindications (poor donor quality).

The criteria for ideal and marginal donors are summarized below. Marginal donors meeting two or more of the criteria below should be excluded as candidates for organ donation.

Several studies have shown that the use of marginal donors does not affect outcome in the first year after lung transplantation.[7-9]

Ideal donors

- age < 55 years
- smoking history < 20 pack-years
- no chest trauma
- mechanical ventilation < 48 h
- no history of asthma
- no malignancies
- no bacteria in tracheal secretion or BAL fluid samples
- arterial blood gas analysis: PaO_2 > 300 mmHg with a positive end-expiratory pressure of 5 cmH_2O and an FiO_2 of 100%
- no chest X-ray findings of consolidation
- no bronchoscopic findings of airway secretions

Marginal donors (should be excluded as donor candidates if they meet two or more of the criteria below)

- age > 55 years
- smoking history > 20 pack-years
- chest trauma
- mechanical ventilation > 48 h
- personal history of asthma
- central nervous system tumor
- presence of bacteria in tracheal secretion or BAL fluid samples
- arterial blood gas analysis: PaO_2 < 300 mmHg with a positive end-expiratory pressure of 5 cmH_2O and an FiO_2 of 100%
- abnormal chest X-ray findings
- bronchoscopic findings of airway secretions

MANAGEMENT OF TRANSPLANT RECIPIENTS

Below, we describe how lung transplant recipients are managed by our Lung Transplant Group, our protocols being based on the ISHLT guidelines and on criteria established in the literature.

Immunosuppression

Immunosuppression is induced with a corticosteroid (methylprednisolone 500 mg i.v.) and an anti-IL-2 receptor monoclonal antibody (basiliximab 20 mg i.v.), both of which are administered at induction of anesthesia.

Immunosuppression is maintained with concomitant use of a calcineurin inhibitor (cyclosporine or tacrolimus), a cell proliferation inhibitor (azathioprine or mycophenolate), and a corticosteroid (prednisone). In some situations, mammalian target of rapamycin inhibitors (sirolimus or everolimus) can be used in association with the aforementioned treatment regimen or replace any of the aforementioned drugs, although not before postoperative month 3, because of the high risk of anastomotic dehiscence.

Prophylaxis

Bacterial infections

The antibiotics used in the intraoperative and immediate postoperative periods should be chosen on the basis of the underlying lung disease.

In smear-negative cases of nonsuppurative lung disease, the drug of choice is cefepime, which should be maintained until postoperative day 14. This treatment regimen can be modified on the basis of the results of cultures of specimens from the donor and the recipient (including donor blood, donor BAL fluid, and bronchial secretions from the donor and the recipient in the intraoperative period) or on the clinical status of the recipient.

In patients with suppurative lung disease, the treatment regimen is based on previous culture and antibiogram results.

Viral infections

Prophylaxis for viral infections includes prophylaxis for HSV and CMV infection. In cases in which donors and recipients are seronegative for CMV, recipients should receive prophylaxis for HSV infection (with oral acyclovir for 3 months). In other cases, recipients should receive prophylaxis with intravenous ganciclovir for 3 months. Seronegative patients receiving organs from seropositive donors—a group of lung transplant recipients who are at an increased risk of viral

reactivation—should receive prophylaxis with oral valganciclovir for 6 months.

Fungal infections

Prophylaxis for fungal infections includes prophylaxis for infection with *Aspergillus* spp., *Candida* spp., and *Pneumocystis jirovecii*. Prophylaxis for infection with *Aspergillus* spp. includes inhaled amphotericin (10 mg twice daily) and itraconazole (400 mg/day for 3 months). Prophylaxis for infection with *Candida* spp. includes nystatin oral suspension (for 3 months). Prophylaxis for infection with *P. jirovecii* includes trimethoprim-sulfamethoxazole (400/80 mg per day indefinitely).

MAJOR COMPLICATIONS

The major complications of lung transplantation are described below.

Primary graft dysfunction

Similar to ARDS, primary graft dysfunction is defined as a PaO_2/FiO_2 ratio of < 300 and radiological infiltrates within the first 72 h after lung transplantation.

Major risk factors for primary graft dysfunction include the use of cardiopulmonary bypass during surgery, a previous diagnosis of idiopathic pulmonary fibrosis, a previous diagnosis of pulmonary arterial hypertension, significant donor smoking history, and a high BMI.[10,11]

The management of primary graft dysfunction is similar to that of ARDS, including lung-protective ventilation strategies and general clinical support.

Acute rejection

There are two types of acute rejection: acute cellular rejection, which is the more common of the two and is characterized by perivascular and interstitial mononuclear cell infiltrates; and acute humoral rejection, which is also referred to as acute antibody-mediated rejection. Humoral rejection is more closely related to hyperacute rejection, which occurs immediately after the surgical procedure; however, it can occur later, with *de novo* donor-specific antibody formation leading to endothelial cell damage and, consequently, pulmonary capillaritis.[12]

Active surveillance for acute cellular rejection is performed by means of transbronchial biopsy, independently of patient symptoms, during the first year after lung transplantation. In addition, in the presence of clinical worsening or functional loss, acute cellular rejection is a differential diagnosis for infections and other complications.

The treatment of acute cellular rejection varies according to the degree of impairment and includes immunosuppressive dose adjustment, corticosteroid pulse therapy and, in selected cases, antithymocyte globulin.

Humoral rejection is treated with plasmapheresis (in order to remove donor-specific antibodies) and polyclonal immunoglobulin.

Chronic allograft dysfunction

It is currently known that there are different phenotypes of chronic allograft dysfunction, the most common being bronchiolitis obliterans syndrome (Figure 2), which manifests as a progressive decline in FEV_1 from baseline that cannot be attributed to acute rejection, infection, or bronchial stenosis. Major risk factors for chronic allograft dysfunction include previous viral infections, gastroesophageal reflux disease, and a history of acute rejection.

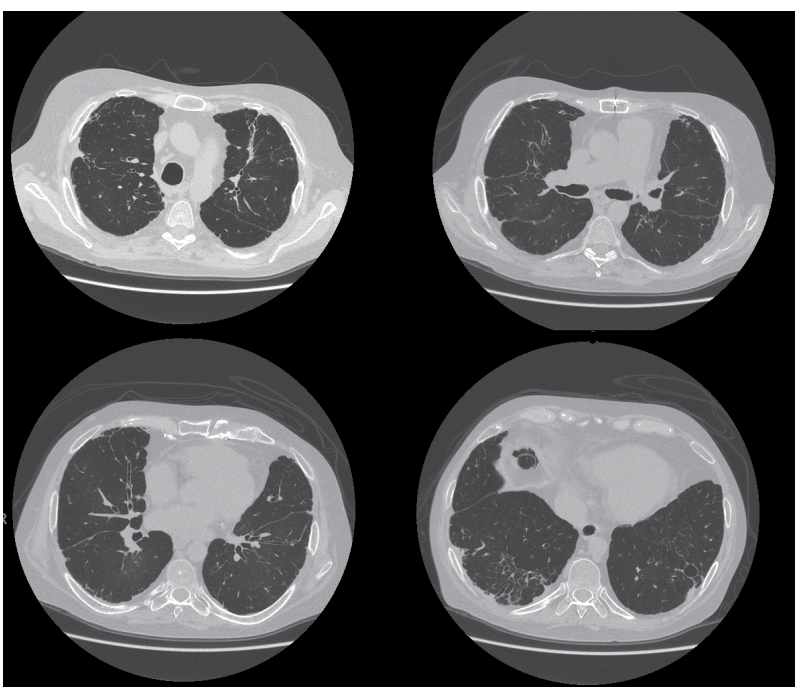

Figure 2. Chest CT scan of a patient with bronchiolitis obliterans syndrome.

Other, less common, phenotypes have been described, including chronic allograft dysfunction characterized by restrictive ventilatory impairment and acute fibrinoid organizing pneumonia, the prognosis of which is worse than that of bronchiolitis obliterans syndrome.[13-15]

The management of chronic allograft dysfunction includes optimization of immunosuppression, removal of risk factors (such as gastroesophageal reflux disease), and, in cases that are more severe, retransplantation.

Infections

Lung transplant recipients are at risk of infection in the postoperative period. However, the prevalence of pathogens depends on the time elapsed since transplantation.[16] Until postoperative month 1, the most common infections are those related to the surgical procedure, the donor, or the recipient. From postoperative month 1 to postoperative month 6, activation of latent infections (such as CMV infection and tuberculosis) is common. After postoperative month 6, the prevalence of community-acquired infections (pneumonia and urinary tract infection) increases.

Malignancies

Patients receiving immunosuppressants are at an increased risk of malignancies. The most common types of malignancies are skin cancer and lymphoproliferative disorders. There is a relationship between the development of lymphoma and Epstein-Barr virus infection; recurrent CMV infection is a risk factor for the disease.

Surgical complications

Surgical complications occur in approximately 27% of cases and include dehiscence, necrosis, and bronchial anastomotic stenosis. Vascular complications such as venous stenosis are rare, occurring in 1-2% of cases.

Paralytic ileus is the most common abdominal complication, occurring in 30-50% of patients. Gastroparesis, acute cholecystitis, and intestinal perforation can also occur, the mortality from intestinal perforation being high.[17-19]

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CASE REPORT

The challenge of managing extensively drug-resistant tuberculosis at a referral hospital in the state of São Paulo, Brazil: a report of three cases

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ABSTRACT

Here, we report the cases of three patients diagnosed with extensively drug-resistant tuberculosis and admitted to a referral hospital in the state of São Paulo, Brazil, showing the clinical and radiological evolution, as well as laboratory test results, over a one-year period. Treatment was based on the World Health Organization guidelines, with the inclusion of a new proposal for the use of a combination of antituberculosis drugs (imipenem and linezolid). In the cases studied, we show the challenge of creating an acceptable, effective treatment regimen including drugs that are more toxic, are more expensive, and are administered for longer periods. We also show that treatment costs are significantly higher for such patients, which could have an impact on health care systems, even after hospital discharge. We highlight the fact that in extreme cases, such as those reported here, hospitalization at a referral center seems to be the most effective strategy for providing appropriate treatment and increasing the chance of cure. In conclusion, health professionals and governments must make every effort to prevent cases of multidrug-resistant and extensively drug-resistant tuberculosis.

Keywords: Tuberculosis, multidrug-resistant; Extensively drug-resistant tuberculosis; Antitubercular agents; Antibiotics, antitubercular.

INTRODUCTION

The number of cases of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) has increased significantly, MDR-TB and XDR-TB having become a serious public health problem worldwide. Recent data show that the number of cases of MDR-TB tripled between 2009 and 2013.[1] In 2013, cases of MDR-TB accounted for 3.5% of all new tuberculosis cases and 20.5% of all previously treated tuberculosis cases. Cases of XDR-TB accounted for 9% of all MDR-TB cases reported in 100 countries.[1] MDR-TB is caused by *Mycobacterium tuberculosis* strains that are resistant to rifampin and isoniazid, whereas XDR-TB is caused by strains that are also resistant to any fluoroquinolone and at least one of three injectable second-line drugs (amikacin, kanamycin, and capreomycin).[1-3] The increasing recognition of MDR-TB and XDR-TB has led to the development of new therapeutic strategies combining standard and new antituberculosis drugs. The World Health Organization (WHO) has divided first-line drugs (which are more effective), second-line drugs (which are less effective, are more toxic, and require longer treatment duration), and additional drugs for reinforcement (the use of which depends on their efficacy and tolerability) into five groups.[1,4,5] Table 1 shows the five groups of drugs and the WHO recommendations for their use.

A standard or an individualized approach can be used in order to treat patients with MDR-TB. Official agencies recommend standard treatment regimens on the basis of health data (e.g., resistance patterns) in a given region.[2,3,6] In Brazil, the treatment of MDR-TB is standardized by the National Ministry of Health.[7] The WHO[1] recommends that the treatment of MDR-TB be divided into two phases: the intensive phase and the maintenance phase. In the intensive phase, which lasts 8 months, at least four potentially effective drugs should be used: an injectable drug (group 2), a fluoroquinolone (group 3), an oral drug (group 4), and an additional drug for reinforcement (group 5). In the maintenance phase, the injectable drug is discontinued, and the remaining drugs should be continued for 12 months after a negative sputum culture.[1,8,9] However, according to some authors, MDR-TB treatment should continue for at least 20 months. Recent studies have shown that continuing treatment for 18 months after a negative sputum culture prevents treatment failure, recurrence, and mortality.[8-11]

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Table 1. Antituberculosis drug groups proposed by the World Health Organization and step-by-step recommendations for creating a treatment regimen for patients with multidrug-resistant or extensively drug-resistant tuberculosis.

Groups	Drugs	Steps	What to do	Drugs to consider	Notes
1	First-line oral drugs • Isoniazid • Rifampin • Ethambutol • Pyrazinamide • Rifabutin • Rifapentine	1	Choose an injectable (group 2) drug on the basis of drug susceptibility test results or patient history of tuberculosis treatment.	amikacin, capreomycin, and kanamycin	Streptomycin is not generally used, because MDR-TB is highly resistant to it.
2	Injectable drugs • Streptomycin • Kanamycin • Amikacin • Capreomycin	2	Choose a next-generation fluoroquinolone (group 3).	levofloxacin and moxifloxacin	In case of resistance to levofloxacin, moxifloxacin should be used. Moxifloxacin should be avoided in case bedaquiline is used.
3	Fluoroquinolones • Levofloxacin • Moxifloxacin • Gatifloxacin	3	Add two or more group 4 drugs.	cycloserine, terizidone, para-aminosalicylic acid, ethionamide, and prothionamide	Ethionamide and prothionamide are the most effective group 4 drugs. Patient history of tuberculosis treatment, side effects, and cost should be taken into consideration. In general, drug susceptibility testing does not include group 3 drugs.
4	Oral second-line drugs • Ethionamide • Prothionamide • Cycloserine • Terizidone • Para-aminosalicylic acid • Sodium aminosalicylate	4	Add group 1 drugs.	pyrazinamide and ethambutol	Pyrazinamide is commonly used in most treatment regimens. Ethambutol is used on the basis of susceptibility test results.
5	Additional drugs for reinforcement • Linezolid • Ertapenem • Imipenem/cilastatin • Meropenem • Clarithromycin • Thiacetazone • Amoxicillin/clavulanate • Clofazimine • High-dose isoniazid (has a modest effect) • Bedaquiline • Delamanid	5	Consider the possibility of adding group 5 drugs in case it is impossible to use 4 effective group 2-3-4 drugs.	bedaquiline, linezolid, clofazimine, amoxicillin/clavulanate, ertapenem, imipenem/cilastatin + clavulanate, meropenem + clavulanate, high-dose isoniazid, clarithromycin, and thiacetazone	If necessary, 2 or more group 5 drugs can be used. It should be noted that there are no standardized susceptibility tests for group 5 drugs.

Adapted from the World Health Organization[1] and Zumla et al.[8] MDR-TB: multidrug-resistant tuberculosis.

The treatment of XDR-TB should be individualized on the basis of patient history of tuberculosis treatment and patterns of resistance to first- and second-line drugs.[1,6,8] For patients with XDR-TB, the WHO[1] recommends special precautions: the use of pyrazinamide and/or another group 1 drug; the use of next-generation quinolones (moxifloxacin or gatifloxacin) even if drug susceptibility test results show resistance to levofloxacin, ofloxacin, or both; whenever possible, the use of the injectable antituberculosis agent (aminoglycoside or capreomycin) to which the bacterial sample is susceptible, which should continue for 12 months or even for the duration of the treatment; the use of two or more group 5 drugs; and the use of all group 4 drugs that have not been extensively prescribed or that are considered effective.

The objective of the present study was to show the 1-year progression of three XDR-TB patients admitted to *Hospital Nestor Goulart Reis* (HNGR), which is located in the city of Américo Brasiliense, Brazil, and is a São

Paulo State Department of Health referral hospital for the treatment of MDR-TB and XDR-TB patients requiring hospitalization.

CASE REPORTS

Below, we describe the cases of three patients who were admitted to and treated at our institution.

Table 2. Treatment setting, duration, regimen, and outcome, as well as drug susceptibility test results, for the three patients in the present study prior to their admission to *Hospital Nestor Goulart Reis*, located in the city of Américo Brasiliense, Brazil.

Treatment setting	Drug susceptibility testing	Treatment duration (from month/year to month/year)	Treatment regimen										Treatment outcome
			R	H	Z	E	S	Et	O	T	C	A	L	
Patient 1														
Outpatient	Resistance to (R,H,E,S)	05/2001-11/2001	x	x	x									Failure
Outpatient	Resistance to (R,H,E,Z,S)	01/2003-07/2003				x			x	x	x	x		Nonadherence
Outpatient	Resistance to (R,H,Z)	09/2005-09/2007				x			x	x	x	x		Nonadherence
Outpatient	Resistance to (R,H,Z); Susceptibility to (E,S)	11/2007-07/2008				x			x	x		x		Nonadherence
Outpatient	Resistance to (R,H,E,Z)	08/2008-09/2010				x			x	x	x	x		Nonadherence
Outpatient	Resistance to (R,H,E,Z,S)	06/2011-10/2011				x				x		x		Referral for hospitalization (at *Sanatorinhos*, in the city of Campos do Jordão, Brazil)
Inpatient	Resistance to (A,C,K,S,E,H,O,Z,R)	10/2011-03/2013			x	x				x		x	x	Disciplinary discharge
Inpatient (HNGR)	Resistance to (A,C,S,H,O,Z,R); Susceptibility to (E)	03/2013-08/2013			x	x				x			x	Failure
Patient 2														
Outpatient		03/2011-10/2011	x	x	x	x								Failure
Outpatient	Resistance to (R,H,Z,O); Susceptibility to (A,K,Cp,S,E)	03/2012-10/2013				x				x		x	x	Failure
Patient 3														
Outpatient		01/2006-05/2006	x	x	x									Nonadherence
Outpatient	Resistance to (R,H); Susceptibility to (Z,E,S,Et)	06/2006-06/2007	x	x	x	x								Nonadherence
Outpatient	Resistance to (R,H); Susceptibility to (Z,E,S,Et)	08/2007-07/2009			x	x	x		x					Cure
Outpatient	Resistance to (R,H); Susceptibility to (Z,E,S)	09/2009-04/2010				x	x		x	X				Failure
Inpatient (at *Sanatorinhos*, in the city of Campos do Jordão, Brazil)	Resistance to (R,H,S); Susceptibility to (Z,E)	04/2010-03/2012				x				x		x	X	Failure
Outpatient	Resistance to (R,H,S); Susceptibility to (Z,E)	02/2013-02/2014			x	x				x		x	x	Failure

R: rifampin; H: isoniazid; Z: pyrazinamide; E: ethambutol; S: streptomycin; Et: ethionamide; O: ofloxacin; T: terizidone; C: clofazimine; A: amikacin; L: levofloxacin; K: kanamycin; Cp: capreomycin; and HNGR: *Hospital Nestor Goulart Reis*.

Table 3. Drug susceptibility test results, treatment regimen, body weight, erythrocyte sedimentation rate (ESR), C-reactive protein, sputum smear microscopy, and culture for Koch's bacillus over a one-year period for the three patients studied.

Patient	Drug susceptibility testing	Treatment regimen	Treatment duration	Month	Weight. kg	ESR. mm/h	CRP. mg/l	Culture	Sputum smear microscopy
1	Resistance to (A,Cp,K,S,E, H,O,Z,R)	A (Mon-Fri)+M+ E+T+Et+Lz+I+ Clr+Clv	09/2013-09/2014	Baseline	55.00	27	31.6	positive	negative
				1	54.15	22	6.7	positive	negative
				2	54.30	24	< 6.0	negative	negative
				4	54.85	12	< 6.0	negative	negative
				5	55.60	18	< 6.0	negative	negative
				6	56.00	13	< 6.0	negative	negative
				8	58.55	15	< 6.0	negative	negative
				10	57.45	12	< 6.0	negative	negative
				12	58.25	8	< 6.0	negative	negative
2	Resistance to (A,Cp,K,S,H,O, Z,R); Susceptibility to (E)	S (Mon-Fri)+ M+E+T+ Et+Lz+ I+Clr+Clv	11/2013-11/2014	Baseline	59.40	66	36.4	positive	negative
				2	58.30	7	< 6.0	positive	negative
				4	60.90	9	< 6.0	positive	negative
				6	61.95	24	6.2	negative	negative
				8	62.55	13	< 6.0	negative	negative
				10	64.15	10	< 6.0	negative	negative
				12	64.90	6	< 6.0	negative	negative
3	Resistance to (A,Cp,K,S,H,O,R); Susceptibility to (E.Z)	Cp (Mon-Fri)+M+ E+T+ Et+Lz+I+Clr+ Clv+Z	03/2014-03/2015	Baseline	36.30	89	91.0	positive	positive
				2	40.75	10	59.1	positive	negative
				4	45.60	15	17.4	negative	negative
				6	46.10	20	15.7	negative	negative
				8	47.80	15	16.1	negative	negative
				10	46.90	34	9.2	negative	negative
				12	46.70	11	36.0	negative	negative

CRP: C-reactive protein; A: amikacin; Cp: capreomycin; Clr: clarithromycin; Clv: clavulanate/amoxicillin; S: streptomycin; E: etambutol; Et: ethionamide; I: imipenem; H: isoniazid; K: kanamycin; Lz: linezolid; M: moxifloxacin; O: ofloxacin; Z: pyrazinamide; R: rifampin; T: terizidone; and Mon-Fri: from Monday to Friday.

Preadmission treatment regimens and drug susceptibility test results for the three patients (herein identified as patient 1, patient 2, and patient 3) are presented in Table 2, whereas postadmission treatment regimens, drug susceptibility test results, body weight, smear microscopy results, results of culture for Koch's bacillus, erythrocyte sedimentation rate (ESR), and C-reactive protein are presented in Table 3.

Chest X-rays (Figures 1, 2, and 3 for patients 1, 2, and 3, respectively), as well as laboratory test results at admission and after 1 year of treatment, can be found in the online supplement of the JBP (http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=43)

Patient 1

A 43-year-old male smoker (with a smoking history of 20 pack-years) presented to our institution. In addition to social drinking, he reported a history of cocaine use (he had not used it since 2011). He was unofficially employed as a car washer. He had previously been treated for tuberculosis but had not adhered to the prescribed treatment regimens. According to the patient, this was due to the fact that he was granted no social security benefit allowances for tuberculosis and had to work during the treatment period. His family income, in Brazilian reals (R$), was 800.00 (US$ 363.00). He lived in a two-bedroom household with his mother. He was admitted to HNGR on March 18, 2013. Treatment for XDR-TB was initiated on September 6, 2013.

Patient 2

A 41-year-old male smoker (with a smoking history of 20 pack-years) presented to our institution. He was a maintenance assistant. He reported a history of alcohol dependence (he had not consumed any alcohol since 2008) but no illicit drug use. He had been on sick leave while on treatment for tuberculosis, having been granted a social security benefit allowance. His family income was R$ 1,400.00 (US$ 437.00). He lived in a single room with his wife, a 1-year-old child, and two teenage children. He was admitted to HNGR on October 24, 2013. Treatment for XDR-TB was initiated on November 1, 2013.

Patient 3

A 25-year-old female smoker (with a smoking history of 5 pack-years) presented to our institution. She was unofficially employed as a clerk in a bakery. She reported social drinking but no illicit drug use. Her salary was R$ 725.00 (US$ 327.00). She had previously been treated for tuberculosis but had not adhered to the prescribed treatment regimens. According to the patient, this was due to the fact that she was granted

no social security benefit allowances for tuberculosis and had to work during the treatment period. She lived in a three-bedroom household with three other people (a 5-year-old daughter, a brother, and her mother) and slept alone in one of the bedrooms. She had received home oxygen therapy in the period between December of 2013 and her admission to HNGR. She was hospitalized on February 10, 2014. Treatment for XDR-TB was initiated on March 10, 2014.

DISCUSSION

In the present study, we reported three cases of XDR-TB patients who had previously been treated for tuberculosis. The use of a treatment regimen based on the WHO guidelines in association with a new combination of antituberculosis drugs (imipenem and linezolid) resulted in clinical and bacteriological cure, as well as in significant radiological improvement. To our knowledge, our study is the first in Latin America and the second in the world to report the use of imipenem for the treatment of patients with XDR-TB, as well as being the first in the world to report the cases of three XDR-TB patients who were cured with the use of imipenem-linezolid.

At HNGR, treatment is initiated after careful clinical and medication history taking. Smear microscopy is performed at the hospital. Cultures for Koch's bacillus and drug susceptibility testing are performed at the Adolfo Lutz Institute and repeated every two months. Laboratory tests are performed at the São Paulo State University School of Pharmaceutical Sciences and repeated every three months. At admission, chest X-rays and CT scans are taken, the former being repeated every two months. The initial proposal is inpatient treatment for 24 months, depending on the clinical, bacteriological, and laboratory response.

Both MDR-TB and XDR-TB are multifactorial and are caused by one or more of the following: inappropriate treatment regimens, inadequate drug doses, or inadequate treatment duration; mismanagement of antituberculosis drugs, affecting supply and quality; laboratories where resolution rates are low; addition of one or more drugs to a treatment regimen that has failed; treatment discontinuation or irregular medication use; and infection with primary MDR-TB strains.[1]

The chest X-rays taken at admission revealed serious pulmonary sequelae in patients 1 and 3, a finding that might be due to the fact that those patients had been treated for tuberculosis several times before, albeit erratically and, consequently, ineffectively. Patient 2 had received a basic treatment regimen under supervision. The fact that the treatment failed might be attributed to primary MDR-TB.

Patients 1 and 2 received treatment with nine different drugs, and patient 3 received treatment with ten drugs, in accordance with the WHO guidelines for the treatment of MDR-TB (Table 1) and XDR-TB,[1] as well as having received drugs that susceptibility test results showed they were sensitive to. Before their hospitalization, our patients had alternately or inconsistently used group 1 drugs, group 2 drugs, group 3 drugs, and group 4 drugs (Table 2). Patient 1 was the only patient who had used a group 5 drug (clofazimine; Table 2). For patients with XDR-TB, there are few drug options to create an acceptable and effective treatment regimen.[3] Our three patients received an injectable (group 2) drug and a next-generation fluoroquinolone (moxifloxacin). Despite relative contraindications in the WHO guidelines, streptomycin was given to patient 2 because the patient had received amikacin under supervision for approximately 20 months before hospital admission and because capreomycin was unavailable at the time. All patients received group 4 drugs (terizidone and ethionamide) and group 5 drugs (imipenem and linezolid). A case-control study showed the efficacy and tolerability of the meropenem-clavulanate/linezolid combination in the treatment of patients with MDR-TB or XDR-TB.[12] A recent study showed the efficacy of ertapenem as an alternative for the treatment (including outpatient treatment) of MDR-TB.[13] In the present study, clavulanate was used as an adjuvant to imipenem/cilastatin[1] and in combination with amoxicillin, given that clavulanate is not provided separately. Although the effect of clarithromycin on *M. tuberculosis* is uncertain, clarithromycin was used in all three patients because of its synergistic effect with linezolid.[1,14] According to the WHO guidelines,[1] ethambutol does not have a key role in the treatment of MDR-TB, even in cases of patients who are susceptible to it (e.g., patients 2 and 3 in the present study). Nevertheless, all three patients in the present study received ethambutol. Patient 3 was the only patient who received pyrazinamide, on the basis of susceptibility test results.

After the first year of treatment, the proposed follow-up consisted of maintaining the use of injectable drugs for 18 months and the use of oral drugs for 24 months (Tables 1 and 3). At this writing, patients 1 and 2 had been discharged as cured, whereas patient 2 had had clinical, radiological, and bacteriological improvement. It is of note that none of the patients had adverse drug reactions.

The pharmacological treatment of XDR-TB is costly. The Brazilian government spent approximately R$ 76,000.00 (US$ 30,000) per year on drugs alone for each of the patients included in the present study. A study conducted in South Africa showed that the treatment of one patient with XDR-TB costs US$ 26,392, which is four times higher than the treatment of one patient with MDR-TB (US$ 6,772) and 103 times higher than the treatment of one patient with tuberculosis that is susceptible to the basic treatment regimen (US$ 257).[4] In addition, drug-resistant tuberculosis results in destruction of the lung parenchyma, which has an impact on patient quality of life and makes it extremely difficult to calculate post-discharge costs for patients and governments.

In conclusion, governments must make every effort to prevent MDR-TB and XDR-TB. In extreme cases, such as those reported here, hospitalization is required in order to ensure an effective treatment for an adequate period of time.

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How many patients with idiopathic pulmonary fibrosis are there in Brazil?

José Baddini-Martinez[1], Carlos Alberto Pereira[2]

TO THE EDITOR:

Idiopathic pulmonary fibrosis (IPF) is a form of chronic fibrosing interstitial pneumonia of unknown etiology that primarily affects the elderly and for which usual interstitial pneumonia is the substrate.[1] Patients with IPF usually experience progressive loss of pulmonary function and severely impaired quality of life, evolving to death.

The treatment of IPF has always been a challenge. However, in late 2014, the US Food and Drug Administration approved two new drugs for the treatment of patients with this disease. Now it is clear that both drugs reduce the rate of decline in pulmonary function in individuals affected by the disease. In addition, clinical trials are underway to investigate new drugs with different mechanisms of action.

We are seeing the beginning of a new era in the care of IPF patients, which is promising but also implies additional needs and concerns. In particular, health-related governmental decisions should be based on robust epidemiological data, and, unfortunately, there are few such data on IPF in Brazil.

One important and still unresolved issue concerns the true incidence and prevalence of IPF and, consequently, the total number of affected patients in Brazil. When we analyzed the international literature, we found that characterizing the epidemiology of IPF is not a problem solely in Brazil. Some of the difficulties stem from the fact that the current definition of the disease came into use from 2000 onward. In addition, results vary depending on the criteria used by different authors to define a case of IPF. Nevertheless, there is a consensus that the disease affects more men than women, that it is more common after the fifth decade of life, and that its incidence has been increasing over the years, as has the associated mortality.[1] Whether the increased incidence and mortality rates are due to greater recognition of the disease, increased survival of the population, or environmental factors is an open question.

A recent systematic review suggested, in a conservative estimate, that the incidence of IPF was approximately 3-9 cases/100,000 population in North America and Europe.[2] Incidence rates seem to be lower in South America and Asia. Another, slightly earlier, review indicated that the prevalence of IPF in the United States and European countries was 14.0-27.9 and 1.25-23.4 cases/100,000 population, respectively.[3] It is reasonable to assume that various age profiles, as well as ethnic and genetic differences among the populations, may substantially contribute to the different findings.

As previously mentioned, information on the subject of IPF is scarce in Brazil. One study analyzed IPF incidence and mortality data available on the *Departamento de Informática do Sistema Único de Saúde* (DATASUS, Information Technology Department of the Brazilian Unified Health Care System) website for the 1996-2010 period.[4] There were progressive increases in both parameters during that period.[4] In 2010, the recorded incidence of IPF in Brazil was 4.48 cases/1,000,000 population, whereas mortality was 12.11 deaths/1,000,000 population. It should be pointed out that the DATASUS website does not reflect the practice of private medicine and that the accuracy of the differential diagnosis of interstitial lung diseases, as well as the completeness of death certificates, is not optimal in Brazil. On the basis of data from the 2010 Brazilian National Census[5] and the rates reported in the study cited above,[4] 923 new cases of IPF and 2,310 IPF-related deaths were expected in that year. Admittedly, these numbers sound too low, which is likely attributable not only to underreporting but also to a lack of understanding of the disease and to underdiagnosis.

In the absence of data on IPF prevalence in Brazil, we can attempt to calculate the number of affected individuals by speculating on the basis of data available from other countries. Obviously, this approach is imprecise and can lead to conflicting results, depending on the rates adopted.

For that analysis, we chose the rates obtained in two studies conducted in the United States, a country that, like Brazil, has received and still receives a significant influx of immigrants. One of the studies was published in 1994, a time when the definition of IPF was still imperfect.[6] However, its methodology was robust, and data were collected in a largely Latin-American population, which, once again, is important for the extrapolation of data for Brazil. The second study was published in 2006, and its strong points include the use of two definitions of IPF, a narrow one and a broad one, as well as the gathering of data from a single large health care plan.[7] In addition, in both studies, rates are presented by age group, which is very important for the correction of possible distortions resulting from the different population profiles of the two countries. Finally, the two studies were conducted during a period when, similar to what is currently the case in Brazil, truly effective treatments for the disease were not available. In contrast, the Brazilian population data were obtained from the 2010 National Census.[5]

When we applied the rates from the studies conducted in the United States, stratified by age group and gender,

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Table 1. Epidemiological data on idiopathic pulmonary fibrosis in Brazil, as calculated on the basis of the rates reported in two studies conducted in the United States and data from the 2010 Brazilian National Census.[5]

Calculations based on the broad definition of idiopathic pulmonary fibrosis in Coultas et al.[6]		
Age bracket	**Annual incidence**	**Prevalence**
>75 years	4,133	6,282
65-74 years	2,881	7,462
55-64 years	1,770	2,364
45-54 years	689	1,843
35-44 years	523	353
Total	**9,997**	**18,305**
Calculations based on the narrow definition of idiopathic pulmonary fibrosis in Raghu et al.[7]		
Age bracket	**Annual incidence**	**Prevalence**
>75 years	1,495	3,540
65-74 years	1,608	3,320
55-64 years	1,623	3,126
45-54 years	1,271	2,430
35-44 years	621	1,103
18-34 years	223	426
Total	**6,841**	**13,945**

to the Brazilian population data, we obtained the results listed in Table 1. From Table 1, we might assume that the annual incidence of IPF cases is between 6,841 and 9,997 cases/100,000 population, whereas its prevalence ranges between 13,945 and 18,305 cases/100,000 population. Because IPF is quite rare in young people, if we limit the analysis only to the ≥ 55-year age bracket, the projected prevalence might be between 9,986 and 16,109 cases/100,000 population.

From what has been discussed above, we can conclude that, although IPF is a rare disease, it seems to affect a significant number of Brazilians who already require specialized attention and care. With the introduction of the use of new drugs, the survival of patients with IPF will likely increase and, consequently, so will their care needs.

We point out the equal importance of the fact that speculating on the basis of calculations based on rates from other countries is highly unsatisfactory. Therefore, pulmonologists, epidemiologists, academic institutions, and government bodies, together with patients and their families, should develop initiatives to ensure a better understanding of the epidemiology and natural history of IPF in Brazil. Such initiatives should include not only the creation of databases and registries but also, once those instruments have been developed, the ongoing provision of appropriate information to these systems by medical specialists.

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Intracavitary nodule in active tuberculosis: differential diagnosis of aspergilloma

Edson Marchiori[1,2], Bruno Hochhegger[3,4], Gláucia Zanetti[2,5]

TO THE EDITOR:

A 40-year-old male presented to the emergency room with a three-month history of cough, fever, and weight loss. Twenty-four hours later, he also presented sudden hemoptysis. A chest X-ray revealed bilateral non-homogeneous opacities, predominantly in the left lung. Chest CT showed small nodules scattered throughout both lungs, with cavities in the left lung. We also noted a nodule inside a cavity, with air interposed between the nodule and the cavity wall—the air crescent sign (ACS)—suggesting an intracavitary fungus ball. The nodule showed intense enhancement after contrast administration, suggesting a diagnosis of Rasmussen aneurysm (RA; Figure 1). Fiberoptic bronchoscopy showed active bleeding from the lower left lobar bronchus. Sputum and BAL fluid were positive for AFB, subsequently identified as *Mycobacterium tuberculosis*. Treatment with antituberculosis drugs was started, and vascular occlusion with coil embolization was performed successfully. The patient was discharged from the hospital one month later.

Hemoptysis in the presence of tuberculosis is frequently due to erosion of the bronchial artery or of a branch of the pulmonary artery; it can result from numerous conditions, such as bronchiectasis, aspergilloma, tuberculosis reactivation, scar carcinoma, chronic bronchitis, broncholithiasis, microbial colonization within a cavity, and RA.[1,2] Contrast-enhanced CT of the chest and bronchoscopy remain the methods of choice for the evaluation of pulmonary hemorrhage.

The ACS is defined as a crescent-shaped collection of air that separates the wall of a cavity from an inner mass.[3] Although *Aspergillus* spp. are the most

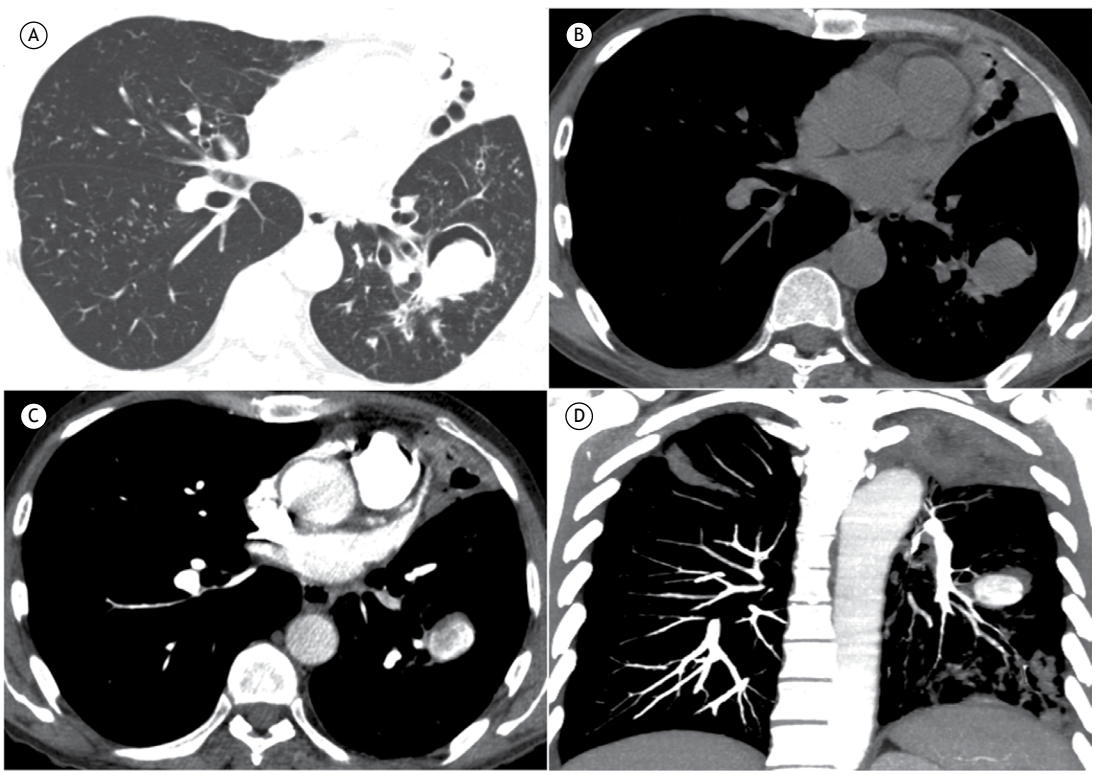

Figure 1. In A, an axial CT scan with a lung-window setting at the level of the lower lobes, showing small nodules in both lungs, a consolidation with cavitation in the lingula, and a nodule inside a cavity, with air interposed between the nodule and the cavity wall (the air crescent sign). In B, an axial CT scan with a mediastinal-window setting, demonstrating that the nodule is homogeneous. In C and D, axial and coronal reconstructions, respectively, of contrast-enhanced CT scans, showing intense enhancement of the intracavitary nodule.

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common cause of the ACS, through the colonization of pre-existing cavities or retraction of infarcted lung in angioinvasive aspergillosis, this finding has been reported in association with a variety of other conditions, including tuberculosis (blood clot or RA), hydatid cysts, cavitary lung cancer, bacterial lung abscess with inspissated pus, other fungal or fungal-like conditions (coccidioidomycosis, actinomycosis, nocardiosis, and candidiasis), and intracavitary hematoma.[3-5]

Most intracavitary nodules associated with tuberculosis correspond to aspergillomas (fungus balls caused by *Aspergillus* spp. colonization).[6] Less common etiologies include blood clots, cavitary lung cancer, and RA. Aspergilloma results from the fungal colonization of a preexisting pulmonary cavitation, generally secondary to tuberculosis or sarcoidosis. Although often indolent, with few or no symptoms, the process frequently involves hemoptysis, which can be fatal.

A change in the position of the intracavitary nodule when the patient changes position is a valuable radiological sign for the diagnosis of aspergilloma. Therefore, the classic CT evaluation of aspergilloma includes supine and prone scans in order to demonstrate whether the central mass is free or attached to the cavity wall. In contrast to a fungus ball, cavitary lung cancer and RA are fixed to the cavity wall. Contrast enhancement on CT images of the mass might also help differentiate between aspergilloma and malignancy or RA.[7]

Pulmonary artery pseudoaneurysms secondary to pulmonary tuberculosis are classified as RAs. Progressive weakening of the arterial wall occurs as granulation tissue replaces the adventitia and media of the artery. The granulation tissue in the vessel wall is then gradually replaced by fibrin, resulting in the thinning of the arterial wall, pseudoaneurysm formation, and subsequent rupture with hemorrhage.[8,9] Hemoptysis is the usual symptom at initial manifestation, and can be life threatening when massive.[8] On contrast-enhanced CT scans, RA can be identified as a markedly enhanced nodule within the wall of a tuberculous cavity.[10] The first-line treatment for RA is endovascular embolization.[8-10]

In conclusion, RA should be included in the differential diagnosis of hemoptysis in patients with tuberculosis presenting the ACS. Contrast-enhanced CT plays an important role in the evaluation of such patients.

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Reversed halo sign

Edson Marchiori[1,2], Gláucia Zanetti[2,3], Bruno Hochhegger[4,5]

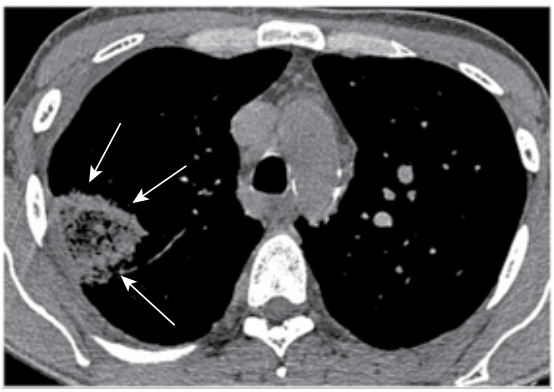

Figure 1. CT scan (mediastinal window settings) showing the reversed halo sign in the right lung (white arrows). Note the reticular pattern within the halo.

A 35-year-old man presented to the emergency room with chest pain accompanied by dyspnea. He reported having sustained a lower limb fracture and having been immobilized for 30 days.

A CT scan showed the reversed halo sign (RHS) with a reticular pattern, and the final diagnosis was pulmonary infarction. The RHS found on HRCT of the chest is defined as a rounded area of ground-glass attenuation surrounded by a ring of consolidation. This sign was initially described as a sign specific for organizing pneumonia (OP). Later studies identified the RHS in a wide spectrum of infectious and noninfectious diseases. In Brazil, the most common infectious causes of the RHS are tuberculosis, paracoccidioidomycosis, and invasive fungal diseases (invasive pulmonary aspergillosis and mucormycosis). Among the noninfectious causes, OP, both idiopathic and secondary, is the most common. Other important causes are pulmonary infarction and sarcoidosis.

Although the RHS is considered a nonspecific sign, a careful analysis of its morphological characteristics can narrow the differential diagnosis, helping the attending physician to make a definitive diagnosis. Two imaging patterns should be taken into account in order to make the diagnosis more specific: the presence of nodules on the wall of or within the halo (nodular RHS); and a reticular pattern within the halo (reticular RHS).

The nodular RHS is generally found in active granulomatous diseases, especially tuberculosis and sarcoidosis. It is also seen in some cases of paracoccidioidomycosis. Histopathological analysis of such cases has revealed that the formation of nodules is due to the presence of granulomas. With regard to the reticular RHS, the immunological status of the patient is the most important piece of clinical information needed in order to make the differential diagnosis. In immunocompromised patients, the primary diagnostic hypothesis is that of invasive fungal diseases. In immunocompetent patients, the reticular RHS corresponds, as a rule, to pulmonary infarction, usually secondary to thromboembolic disease. Suspicion of infarction from thromboembolic disease requires immediate confirmation by determination of D-dimers and CT angiography.

It should be borne in mind that the reticular and nodular patterns are not found in OP, which is the most common cause of the RHS. These considerations are important because the treatment for infectious conditions is completely different from that used for noninfectious conditions. Corticosteroid use, which is the treatment of choice for OP, can have harmful effects in patients with invasive fungal disease or active tuberculosis. Although the final diagnosis should be based on the clinical manifestations, the characteristics of the RHS can be quite useful in making the differential diagnosis. In some cases, lung biopsy may be necessary for the final diagnosis.

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Confidence intervals: a useful statistical tool to estimate effect sizes in the real world

Cecilia Maria Patino,[1,2] Juliana Carvalho Ferreira[2,3]

PRACTICAL SCENARIO

A prospective cohort study evaluated the association between the presence of asthma and the risk of developing obstructive sleep apnea (OSA) in adults. Adults were randomly recruited from a population-based list of state employees and were followed for four years. Participants with asthma, when compared with those without, had a higher risk of developing OSA in four years (relative risk [RR] = 1.39; 95% CI: 1.06-1.82; p = 0.03)

BACKGROUND

When conducting clinical research, we usually recruit a subgroup of the population of interest in order to increase study efficiency (fewer costs and less time). This subgroup of individuals, the study population, are those individuals who meet the inclusion criteria and agree to participate in the study (Figure 1). We then complete the study and calculate an effect size (e.g., a mean difference or a relative risk) to answer our research question. This process (inference) involves using data collected from the study population to estimate the true effect size in the population of interest, i.e., the source population. In our example, investigators recruited a random sample of state employees (source population) who were eligible and agreed to participate in the study (study population) and reported that asthma increases the risk of developing OSA in the study population (RR = 1.39). To take into account a sampling error due to recruiting only a subgroup of the population of interest, they also calculated a 95% confidence interval (around the estimate) of 1.06-1.82, indicating a 95% probability that the true RR in the source population would be between 1.06 and 1.82.

DEFINITION

A confidence interval is a measure of imprecision of the true effect size in the population of interest (e.g., difference between two means or a relative risk) estimated in the study population. That imprecision is due to the sampling error caused by taking subsamples of the population of interest. However, the estimate calculated in the study population is always the best estimate of the effect size in the source population.

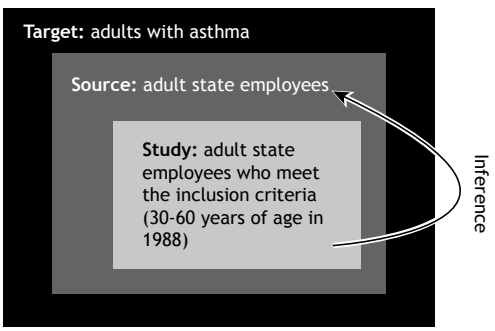

Figure 1. Research populations.

WHY DO WE NEED CONFIDENCE INTERVALS?

We need confidence intervals to indicate the amount of uncertainty or imprecision around the effect size calculated, using the study sample to estimate the true effect size in the source population. Calculating the confidence interval is a strategy that takes into account sampling error: the study effect size and its´ confidence interval represent plausible values for the source population, and the narrower the confidence interval is, the more certain we are that the estimate from the study population represents the true effect size in the source population.

CONFIDENCE INTERVALS: INTERESTING FACTS

The most common width of confidence intervals reported in the literature is the 95% confidence interval. However, if we are interested in more or less confidence, 90% or 99% confidence intervals can be used.

The confidence interval represents the uncertainty of the effect size in the source population, not in the study population. When calculating a confidence interval, the width of the interval is determined by the sample size (i.e., the individuals who agreed to be studied), the amount of measurement error of the study, and the degree of confidence required.

There is a unique relationship between the 95% confidence interval and a two-sided 5% level of significance. When the 95% confidence interval for differences in effect does not include 0 for absolute measures of association (e.g., mean differences) or 1 for relative measures of association (e.g., odds ratios), it can be inferred that the association is statistically significant ($p < 0.05$). The advantage of the 95% confidence interval over the p value is that it provides information about the size of the effect, the uncertainty of the population estimate, and the direction of the effect.

Confidence intervals should always be used in order to describe the major findings of a research study. The relevant confidence intervals should be shown not only in the text of the paper but also in the abstract.

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Examples: Journal Articles

1. Neder JA, Nery LE, Castelo A, Andreoni S, Lerario MC, Sachs AC et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomized study. Eur Respir J. 1999;14(6):1204-13.

Abstracts

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.

Chapter in a Book

3. Queluz T, Andres G. Goodpasture's syndrome. In: Roitt IM, Delves PJ, editors. Encyclopedia of Immunology. 1st ed. London: Academic Press; 1992. p. 621-3.

Official Publications

4. World Health Organization. Guidelines for surveillance of drug resistance in tuberculosis. WHO/Tb, 1994;178:1-24.

Theses

5. Martinez TY. Impacto da dispnéia e parâmetros funcionais respiratórios em medidas de qualidade de vida relacionada a saúde de pacientes com fibrose pulmonar idiopática [thesis]. São Paulo: Universidade Federal de São Paulo; 1998.

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

Homepages/URLs

7. Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/

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FLUIMUCIL® ACETILCISTEÍNA É UM MEDICAMENTO. SEU USO PODE TRAZER RISCOS. PROCURE O MÉDICO E O FARMACEUTICO. LEIA A BULA.

Fluimucil®, acetilcisteína. **Uso oral - Uso adulto:** Comprimido efervescente 200 mg e 600 mg com 16 comprimidos efervescentes. **Indicações:** Dificuldade para expectorar e existência de muita secreção densa e viscosa, tais como: bronquite crônica e suas exacerbações, enfisema pulmonar, bronquite aguda, pneumonia, colapsos/atelectasias pulmonares, mucoviscidose/fibrose cística. Também é indicado como antídoto na intoxicação acidental ou voluntária por paracetamol. **Contraindicações:** Hipersensibilidade conhecida à acetilcisteína e/ou demais componentes de suas formulações. Fluimucil® comprimido efervescente: "Atenção fenilcetonúricos: contém fenilalanina". Estas substâncias podem causar reações alérgicas (possivelmente tardias). Registro MS.: 1.0084.0075

REFERÊNCIAS: 1. Documento interno: registro do produto Fluimucil na Itália, datado de 1965. **2.** Bula do produto Fluimucil® Oral. **3.** IMS PMB – produtos com a molécula acetilcisteína isolada na forma farmacêutica comprimidos efervescentes de 200mg e 600mg. Consulta em Janeiro de 2015. **4.** Global Strategy for Diagnosis, Management, and Prevention of COPD. Updated January 2015. Pág. 36 Management Stable COPD

AO PERSISTIREM OS SINTOMAS O MÉDICO DEVERÁ SER CONSULTADO.

ATENDIMENTO AO CONSUMIDOR 0800.017.7011

203422 Anuncio Trade Fluimucil Mar/2015

Zambon 1906

Novo!

seebri™

brometo de glicopirrônio

EFICAZ NO TRATAMENTO DA DPOC DESDE A MANHÃ[1,2]
MAIS RÁPIDO[3], MAIS SELETIVO[2-4], FÁCIL DE USAR[5]

- Melhora da função pulmonar desde os 5 minutos e sustentada por 52 semanas[4]
- Prolonga significativamente o tempo até a primeira exacerbação; reduz a taxa de exacerbações em 34% e reduz em 61% o risco de exacerbações graves que levam a hospitalizações[6]
- Melhora significativamente a tolerância ao exercício aumentando o tempo, diminuindo a dispneia e o desconforto das pernas[7]
- Perfil de segurança documentado e comparável a placebo[2,4,6]
- Vem com Breezhaler®, dispositivo desenvolvido especialmente para DPOC e com feedback sensorial: OUVE, SENTE E VÊ[8]

SEEBRI™ brometo de glicopirrônio. **Forma farmacêutica e apresentações:** Cápsulas com pó para inalação contendo 63 mcg de brometo de glicopirrônio equivalente a 50 mcg de glicopirrônio. Caixas com 12 cápsulas + 1 inalador ou 30 cápsulas + 1 inalador. **Indicações:** Seebri™ é indicado para tratamento broncodilatador de manutenção para o alívio de sintomas dos pacientes com doença pulmonar obstrutiva crônica (DPOC). **Posologia:** Adultos – A dose recomendada é de uma inalação uma vez ao dia do conteúdo de uma cápsula de Seebri™ 50 mcg usando o inalador de Seebri™. Crianças (menores de 18 anos) – Não deve ser utilizado em pacientes abaixo de 18 anos de idade. População especial – Nenhum ajuste de dose é necessário para pacientes idosos, pacientes com doenças hepáticas ou com insuficiência renal leve e moderada. Deve-se ter cautela em pacientes com insuficiência renal grave, incluindo estágio final de doença renal que requeiram diálise. **Método de administração:** As cápsulas de Seebri™ devem ser administradas apenas por via inalatória oral e apenas usando o inalador de Seebri™. As cápsulas não devem ser engolidas. Seebri™ deve ser administrado no mesmo horário todos os dias. Se uma dose for esquecida, a próxima dose deve ser tomada o mais rápido possível. Os pacientes devem ser instruídos a não administrar mais que uma dose por dia. As cápsulas devem sempre ser armazenadas no blíster, e apenas removidas imediatamente antes do uso. Os pacientes devem ser instruídos em como administrar o medicamento corretamente. Os pacientes que não apresentarem melhora na respiração, devem ser questionados se estão engolindo o medicamento ao invés de inalando. **Contraindicações:** Hipersensibilidade ao glicopirrônio, que é o princípio ativo de Seebri™ ou a qualquer um dos excipientes. **Advertências e Precauções:** Uso Agudo – Não deve ser usado como medicamento de resgate. Hipersensibilidade – Se ocorrer reação de hipersensibilidade, Seebri™ deve ser descontinuado imediatamente e uma terapia alternativa deve ser instituída. Broncoespasmo paradoxal – Assim como com outras terapias inalatórias, a administração pode resultar em broncoespasmo paradoxal que pode ocasionar risco à vida. Se ocorrer broncoespasmo paradoxal, Seebri™ deve ser descontinuado imediatamente e um tratamento alternativo deve ser instituído. Efeito Anticolinérgico – utilizar com cautela em pacientes com glaucoma de ângulo fechado e retenção urinária. Insuficiência renal grave – utilizar somente se o beneficio esperado for maior que o potencial de risco em pacientes com insuficiencia renal grave incluindo aqueles no estágio final de doença renal que requeiram diálise. Gravidez –deve ser utilizado durante a gravidez apenas se os benefícios esperados justificarem o risco potencial ao feto. Lactação –deve ser considerado apenas se o benefício esperado para a mulher for maior que qualquer possível risco ao bebê. **Interações medicamentosas:** A co-administração com outros medicamentos anticolinérgicos inalatórios não foi estudada e, portanto, não é recomendada. Foi usado concomitantemente com broncodilatadores simpaticomiméticos, metilxantinas, esteróides orais e inalatórios, os quais são comumente utilizados no tratamento da DPOC, sem evidência clínica de interacções medicamentosas. **Reações adversas:** Comuns (1 a 10%): boca seca, insônia, gastroenterite; Incomuns (0,1 a 1%): dispneia, cárie dental, dor nas extremidades, dor torácica musculoesquelética, erupção cutânea (rash), fadiga, astenia, congestão nasal, tosse produtiva, irritação na garganta, epistaxe, rinite, cistite, hiperglicemia, disúria, retenção urinária, fibrilação atrial, palpitações, hiposestesia. Não conhecido: Angioedema, broncoespasmo paradoxal, hipersensibilidade, prurido. Outras reações adversas: nasofaringite, vômito, dor musculoesquelética, dor no pescoço, diabetes mellitus. Em pacientes idosos: Dor de cabeça, infecção no trato urinário. VENDA SOB PRESCRIÇÃO MÉDICA. MS – 1.0068.1117. Informações completas para prescrição disponíveis mediante solicitação ao Departamento Médico da Novartis BBSS 10.03.15 2014-PSB/GLC-0726-s.

Contraindicações: Hipersensibilidade ao glicopirrônio, que é o princípio ativo de Seebri™ ou a qualquer um dos excipientes. **Interações medicamentosas:** A co-administração com outros medicamentos anticolinérgicos inalatórios não foi estudada e, portanto, não é recomendada. Foi usado concomitantemente com broncodilatadores simpaticomiméticos, metilxantinas, esteróides orais e inalatórios, os quais são comumente utilizados no tratamento da DPOC, sem evidência clínica de interacções medicamentosas.

Referências: 1. O'Hagan P et al. The impact of morning symptoms on daily activities in chronic obstructive pulmonary Disease. Cur Med Res Op. 2014; 30 (2): 301- 314. **2.** D'Urzo A, Ferguson GT, van Noord JA, Hirata K et al. Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. Respiratory Research 2011, 12:156. **3.** Sykes DA, Dowling MR, Leighton-Davies J, Kent TC, Fawcett L, Renard E, Trifilieff A, Charlton SJ. The Influence of receptor kinetics on the onset and duration of action and the therapeutic index of NVA237 and tiotropium. J Pharmacol Exp Ther. 2012, 343(2):520-8. doi: 0.1124/jpet.112.194456. Epub 2012 Aug 1. **4.** Kerwin E, Hebert J, Gallagher N, Martin C et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. Eur Respir J 2012; 40: 1106–1114. **5.** Molinard M and D'Andrea P. Once-daily glycopyrronium via the breezhaler device for the treatment of COPD:pharmacological and clinical profile. Expert Rev Clin Pharmacol 2013, 6(5): 503-517. **6.** D'Urzo A et al. Once daily glycopyrronium for the treatment of COPD: pooled analysis of the GLOW1 and GLOW2 studies. Curr Med Res Op 2014; 30 (3):493–508. **7.** Beeh KM, Singh D, Di SL, et al. Once-daily NVA237 improves exercise tolerance from the first dose in patients with COPD: the GLOW 3 trial. Int J Chron Obstruct Pulmon Dis 2012; 7: 503-513. **8.** Seebri™ 50 µg. Bula do Produto.

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NACIONAIS

XVII Curso Nacional de Atualização em Pneumologia
Data: 21 a 23 de abril de 2016
Local: São Paulo/SP
Informações: eventos@sbpt.org.br
Fone: 0800 61 6218

VII Curso Nacional de Ventilação Mecânica
IV Curso Nacional de Sono
Data: 18 a 20 de agosto de 2016
Local: São Paulo/SP
Informações: eventos@sbpt.org.br
Fone: 0800 61 6218

XXXVIII Congresso Brasileiro de Pneumologia e Tisiologia
XI Congresso Luso-Brasileiro de Pneumologia
XIV Congresso Brasileiro de Endoscopia Respiratória
Data: 11 a 15 outubro de 2016
Local: Rio de Janeiro/RJ
Informações: eventos@sbpt.org.br
Fone: 0800 61 6218

INTERNACIONAIS

CHEST 2015
Data: 24 a 29 de outubro de 2015
Local: Montreal/Canadá
Informações: www.chestnet.org

ATS 2016
Data: 13 a 18 de maio de 2016
Local: San Francisco/CA-USA
Informações: www.thoracic.org

SEPAR 2016
Data: 10 a 13 de junho de 2016
Local: Granada/Espanha
Informações: www.separ.es

ALAT 2016
Data: 06 a 09 de julho de 2016
Local: Centro de Convenções Casa Piedra, Santiago/Chile
Informações: https://www.congresosalat.org/

ERS 2016
Data: 03 a 07 de setembro de 2016
Local: Londres, Reino Unido
Informações: www.ersnet.org

7 PESSOAS MORREM DE ASMA POR DIA, NO BRASIL.[2]

Clenil® HFA

dipropionato de beclometasona

O tratamento da asma ao alcance de todos[1]

- Reduz os sintomas e controla a inflamação[3]
- Pode ser usado em combinação com broncodilatadores de curta ação, conforme o GINA preconiza[4]

COMODIDADE POSOLÓGICA:[5]

ADULTOS:

200 mcg - 1 dose, 2-4 X ao dia

250 mcg - 2 doses, 2-4 X ao dia

250 mcg Jet® - 2 doses, 2-4 X ao dia

CRIANÇAS:

50 mcg - 2 doses, 2-4 X ao dia

NOVIDADE

AQUI TEM FARMÁCIA POPULAR

Custo Zero para seu paciente[1]

Referências Bibliográficas: 1- Ministério da Saúde. Gabinete do Ministro. Portaria nº 1.146, de 1 de junho de 2012. Altera e acresce dispositivos à Portaria nº 971/GM/MS, de 17 de maio de 2012, para ampliar a cobertura da gratuidade no âmbito do Programa Farmácia Popular do Brasil. DOU, Brasília, DF, 4 de junho de 2012,. P72-73. **2-** http://portaldasaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/noticias-anteriores-agencia-saude/2740. **3-** Diretrizes da Sociedade Brasileira de Pneumologia e Tisiologia para o manejo da asma - 2012. J. Bras Pneumo. 2012; 38 (supl. 1) S1-S46. **4-** Global Strategy for asthma management and prevention. GINA 2014. **5-** Bula do medicamento Clenil® HFA.

Clenil® HFA dipropionato de beclometasona. **USO ADULTO E PEDIÁTRICO** (somente a apresentação de 50 mcg). **COMPOSIÇÃO, FORMA FARMACÊUTICA E APRESENTAÇÕES:** Solução pressurizada para inalação (aerossol). Clenil® HFA Spray 50, 200 e 250 mcg: aerossol com 200 doses. Clenil® HFA Jet® 250 mcg: aerossol com 200 doses. **INDICAÇÕES:** tratamento e prevenção da asma brônquica e bronquite, bem como nos processos inflamatórios das vias aéreas superiores. **CONTRAINDICAÇÕES:** hipersensibilidade individual aos derivados corticosteroides, hipersensibilidade ao álcool ou a qualquer outro constituinte desta formulação, tuberculose pulmonar, herpes simples ou crises asmáticas. **CUIDADOS E ADVERTÊNCIAS:** como todo corticoide inalatório, Clenil® HFA deve ser utilizado com cautela em pacientes com tuberculose ativa ou latente e infecção fúngica, bacteriana ou viral das vias aéreas. Também utilizar com cautela em pacientes portadores de anormalidades pulmonares como bronquiecstasia e pneumoconiose, uma vez que as mesmas estão relacionadas com maior susceptibilidade à infecções fúngicas. **Uso em idosos, crianças e outros grupos de risco:** como qualquer outro medicamento recomenda-se atenção especial na administração em pacientes idosos. O tratamento de pacientes com anomalias pulmonares como bronquiectasia e pneumoconiose, com a possibilidade de infecções fúngicas, deve ser restrito. **Administração durante a gravidez ou aleitamento:** em mulheres grávidas, o medicamento deve ser utilizado no caso de efetiva necessidade e sob supervisão médica. O uso do dipropionato de beclometasona em mães amamentando requer que os benefícios da terapêutica sejam levados em consideração frente aos riscos para mãe e lactente. **Interações medicamentosas:** os pacientes devem ser avisados que o medicamento contém pequena porcentagem de álcool e glicerol. Em doses normais, não há risco para os pacientes. Há um potencial teórico de interação particularmente em pacientes sensíveis a álcool utilizando dissulfiram ou metronidazol. **Reações adversas/Efeitos colaterais:** candidíase na boca e garganta, rouquidão e irritação na garganta, rash cutâneo, urticária, prurido, eritema, efeitos colaterais sistêmicos (supressão da adrenal, retardo no crescimento de crianças e adolescentes, diminuição da densidade mineral óssea, catarata, glaucoma), edema de olhos, faces, lábios e garganta, broncoespasmo paradoxal, chiado, dispneia, tosse, hiperatividade psicomotora, distúrbios do sono, ansiedade, depressão, agressividade, mudanças comportamentais (predominantemente em crianças), dor de cabeça, náusea. **POSOLOGIA: Clenil® HFA 50 mcg: Crianças:** a dose usual inicial é de 100 mcg a 400 mcg, de 12 em 12 horas. Dependendo da severidade da condição asmática, a dose diária pode ser fracionada de 8 em 8 horas ou ainda de 6 em 6 horas. **Adultos (incluindo os idosos):** A dose inicial usual é de 200 mcg a 800 mcg, (4 jatos) de 12 em 12 horas. A dose total diária pode ser dividida em tomadas de 8 em 8 horas ou ainda tomadas de 6 em 6 horas. **Clenil® HFA 200 mcg: Crianças:** NÃO DEVE SER UTILIZADO POR CRIANÇAS. **Adultos (incluindo os idosos):** A dose inicial do produto é de 200 mcg (um jato), de 12 em 12 horas. De acordo com a necessidade do paciente, pode-se prescrever doses mais altas (até 4 jatos por dia). A dose total diária deve ser dividida em tomadas de 12 em 12 horas, tomadas de 8 em 8 horas ou ainda tomadas de 6 em 6 horas. **Clenil® HFA 250 mcg: Crianças:** NÃO DEVE SER UTILIZADO POR CRIANÇAS. **Adultos (incluindo os idosos):** A dose inicial do produto é de 2 jatos (500 mcg), de 12 em 12 horas. Dependendo da severidade da doença, doses mais altas (até 8 jatos por dia) podem ser divididas em tomadas de 12 em 12 horas ou tomadas de 8 em 8 horas ou ainda tomadas de 6 em 6 horas. **Pacientes com insuficiência renal ou hepática:** Nenhum ajuste de dose é necessário. **VENDA SOB PRESCRIÇÃO MÉDICA. SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.** Reg. M.S.: 1.0058.0111. SAC: 0800-114 525. www.chiesi.com.br

INTERAÇÕES MEDICAMENTOSAS: Há um potencial teórico de interação particularmente em pacientes sensíveis a álcool utilizando dissulfiram ou metronidazol. **CONTRAINDICAÇÕES:** hipersensibilidade individual aos derivados corticosteroides, hipersensibilidade ao álcool ou a qualquer outro constituinte desta formulação, tuberculose pulmonar, herpes simples ou crises asmáticas.

Material destinado exclusivamente à classe médica

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Chiesi
People and ideas for innovation in healthcare

Fevereiro/2015

UMA NOVA ESPERANÇA NO TRATAMENTO DA FIBROSE PULMONAR IDIOPÁTICA[1]

Aprovado pela ANVISA OFEV® (Nintedanibe) para o tratamento de pacientes com FPI

OFEV® retarda a progressão da doença através da redução do declínio anual da CVF em aproximadamente 50%, em diversos perfis de pacientes incluindo:[2]

— Com doença inicial (CVF >90% do predito)
— Sem faveolamento em TCAR
— Com enfisema concomitante

Adaptado de Richeldi et al, 2014.

INPULSIS®-1

INPULSIS®-2

Além disso, OFEV® demonstrou reduzir em 68% o risco de exacerbações adjudicadas.*

OFEV® (Esilato de nintedanibe) - uso adulto. **Apresentação:** cápsulas de 100 mg e 150 mg - embalagens com 60 cápsulas moles. Indicação: tratamento e retardo da progressão da fibrose pulmonar idiopática. **Contraindicações:** em casos de hipersensibilidade conhecida ao nintedanibe, amendoim, soja, ou a qualquer excipiente do produto e durante a gravidez. **Reações adversas:** diarreia, náuseas e vômitos, dor abdominal, diminuição do apetite, perda de peso e aumento das enzimas hepáticas. **Precauções:** diarreia deve ser tratada com hidratação adequada e medicamentos antidiarreicos (como loperamida) e pode exigir a redução da dose ou interrupção do tratamento; se vômitos persistirem mesmo com tratamento de suporte adequado (incluindo terapia antiemética), pode ser necessário reduzir ou interromper o tratamento. Valores de transaminases hepáticas e bilirrubina séricas devem ser investigados antes do início do tratamento, periodicamente ou quando clinicamente indicado. Não deve ser usado em pacientes com insuficiência hepática moderada e grave. Tratar pacientes com maior risco cardiovascular, incluindo doença arterial coronária conhecida, requer cuidados. A interrupção do tratamento deve ser considerada em pacientes com sinais ou sintomas de isquemia miocárdica aguda. Pacientes com risco conhecido para sangramento somente devem ser tratados se o benefício superar o risco. Não deve ser usado em gestantes, pois pode causar dano fetal (categoria D), ou lactantes. Recomenda-se o uso de métodos contraceptivos adequados (preservativos) durante pelo menos até 3 meses após a última dose. Não há indicação do uso em crianças e adolescentes. **Interações:** O uso dos seguintes medicamentos podem aumentar ou reduzir o efeito do tratamento com nintedanibe: cetoconazol, eritromicina, rifampicina, carbamazepina, fenitoína e erva-de-são-joão. **Posologia:** 150 mg por via oral de 12 em 12hs junto com água e alimentos. Ajustes de dose: além do tratamento sintomático, o manejo dos efeitos colaterais de pode incluir a redução da dose (para 100 mg duas vezes ao dia) ou a interrupção temporária. Havendo esquecimento da dose, não tomar uma dose adicional. Não se deve exceder a dose diária máxima recomendada de 300 mg. NECESSIDADE DE REFRIGERAÇÃO (conservar entre 2° C e 8° C) e na embalagem original para proteger da umidade. Bula aprovada pela ANVISA em 26/10/2015. **OFEV® É UM MEDICAMENTO, SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO. VENDA SOB PRESCRIÇÃO MÉDICA. MS 1.0367.0173.** Boehringer Ingelheim do Brasil Química e Farmacêutica Ltda. Rod. Regis Bittencourt (BR116), km 286. Itapecerica da Serra – SP. CNPJ /MF nº 60.831.658/0021-10, Indústria Brasileira. SAC 0800-7016633. Se persistirem os sintomas, o médico deverá ser consultado.

Referências: 1. Gary M. Hunninghake, A New Hope for Idiopathic Pulmonary Fibrosis. N Engl J Med 2014; 370:2142-2143 2. Richeldi L et al. Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. N Engl J Med 2014;370:2071-82.

CONTRAINDICAÇÃO: EM CASOS DE HIPERSENSIBILIDADE CONHECIDA AO NINTEDANIBE, AMENDOIM OU SOJA. **INTERAÇÃO MEDICAMENTOSA:** CETOCONAZOL OU ERITROMICINA PODEM AUMENTAR A EXPOSIÇÃO AO NINTEDANIBE.

FPI: Fibrose Pulmonar Idiopática
CVF: Capacidade Vital Forçada
TCAR: Tomografia Computadorizada de Alta Resolução
*Exacerbações adjudicadas: exacerbações agudas relatadas pelos investigadores e que foram confirmadas por um comitê de adjudicação cego em uma análise de sensibilidade pré-especificada.

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