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HIGHLIGHT

Brazilian guidelines for cystic fibrosis

The impact of asthma in Brazil

Sleep-disordered breathing in COPD patients

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BTA distance learning course in pulmonology

Irma Godoy[1], Fernando Luiz Cavalcanti Lundgren[2]

The Brazilian Thoracic Association (BTA) statute states that one of the purposes of the BTA is to bring together physicians and other professionals involved in pulmonology research, teaching, and care, as well as to award specialist degrees in pulmonology and other areas of scientific expertise in accordance with its own policies and those of the Brazilian Medical Association. One of the many duties of the BTA board is to create departments, sections, and permanent or provisional committees aimed at developing research, teaching, care, continuing education, and standardization in areas of expertise and related areas, as well as to approve publication of guidelines and recommendations made by these organizations.

The duties of the director of education include the following: to coordinate, together with the scientific director, all BTA courses; to coordinate the development of the examination required for a specialist degree in pulmonology and the renewal thereof; to foster education in pulmonology by focusing on its promotion, quality, and continued improvement; and to represent the BTA with educational regulatory bodies.

The BTA is committed to establishing standards of excellence in respiratory care through education and professional development activities. The BTA currently offers a range of activities through its live and web-based continuing education programs, virtual learning environment, and nationwide pulmonology-related events in several areas.

The training of future pulmonologists is an essential part of all BTA education activities. Data show that, in Brazil, there are currently 66 medical residency programs in pulmonology, with 124 openings for first-year residents. The pulmonology program was last updated with the Brazilian National Medical Residency Committee in 2006. A new proposal was sent in 2011 and has yet to be approved. There are graduate programs in pulmonology that are accredited by the BTA.

Not all institutions providing education in pulmonology offer complete training in this field, which is, unfortunately, not widely available, as well as being costly to recently graduated physicians. In addition, referral centers for specific conditions are scattered throughout the country, and, given the size of the country, access can be difficult. Therefore, there is a clear need to harmonize and improve pulmonology training in Brazil.

To contribute to reducing the differences in pulmonology training, the BTA has created its first distance learning program, the "BTA distance learning course in pulmonology". For 2017, a total of 15 lectures will be recorded and made available on a distance learning platform. The course will be available on the BTA website as of July 1, 2017 and will cover the following topics:

- What are the applications of pulmonary function tests with lung volume and DLCO measurements and how should the results be interpreted?
- What are the applications of ergospirometry and how should the results be interpreted?
- Understanding polysomnography reports
- Long-term home oxygen therapy: current status and use in special conditions
- How should a patient whose echocardiographic report suggests the presence of pulmonary hypertension be investigated?
- How should the results of right heart catheterization be interpreted?
- How should asthma control be assessed in clinical practice?
- Inflammatory markers of asthma in clinical practice
- What are the health consequences of using tobacco products and other smoking products (i.e., electronic cigarettes, water pipes, and marijuana)?
- How should pulmonary nodules be approached and monitored?
- Lung cancer biomarkers
- Home noninvasive ventilation (indications, management, and costs)
- Diagnostic approach to and management of adult patients with cystic fibrosis
- Indications for the GeneXpert test and interpretation of its results in the diagnosis of tuberculosis
- Diagnostic and therapeutic management of the various forms of acute and chronic aspergillosis

All of the professors who were invited to give lectures accepted to do so at no cost and are well-known experts in the field. They will answer any questions posted by participants within 15 days after the contents have been published on the distance learning platform. At the end of each lecture, participants must answer self-assessment questions.

Instructions on how to participate in the course:

1. In order to participate, residents and graduate students in pulmonology enrolled in programs accredited by the BTA, as well as BTA members, must enroll in the course. All relevant information is available on the distance learning platform.
2. Over a period of 15 days after the lectures have been made available on the website, lecturers will answer the questions posted on the platform.
3. All participants must answer self-assessment questions; those who answer at least 70% of the questions correctly will be certified.

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4. All BTA members are invited to watch the lectures; however, only residents and graduate students enrolled in programs accredited by the BTA are allowed to interact with the lecturers.
5. Participants are allowed to watch the lectures and answer the questions three times.

The BTA is confident that participation will be high and that the course will be of value to future pulmonologists. We thank all participating professors and students in advance, whose comments and suggestions for future modules will be most welcome.

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The paradox of asthma: neglect, burden, and big data

Rafael Stelmach[1], Álvaro Augusto Cruz[2]

English is the lingua franca of scientific communication and, as such, provides words that are pregnant with meaning and symbolism but also challenging; paradoxically, such words often pave the way for solutions and innovations. Asthma is the most prevalent chronic lung disease and is per se a paradoxical disease: clinical control and good health-related quality of life can be achieved, and the risk of death is minimal or nonexistent. However, in numerous studies conducted in Brazil or other countries where disease control and treatment adherence are poor, the word "asthma" is often accompanied by the concept words "neglect" and "burden".

In an editorial published in the JBP in 2014, Perez-Padilla et al.[1] drew attention to the neglected burden of respiratory diseases, as a result of delayed diagnosis, fragmented reporting of morbidity and mortality, and compartmentalization of respiratory care, proposing that integrated primary health care programs be implemented in low- and middle-income countries. The reported prevalence of asthma (or asthma symptoms) in such countries is low; however, there is evidence that these data underestimate specific phenotypes, which might be related to hygiene, pollution, or lack of health resources/infrastructure.[2] There is no longer any doubt that the aforementioned factors influence disease severity and prognosis in children with obstructive lung disease in early childhood.[1,2]

The incidence of asthma in Brazil is believed to be approximately 10%; however, given the lack of nationwide epidemiological data, this rate is based on scattered reports. In contrast, the prevalence of asthma in Brazil is well known because of successive population-based surveys conducted under the auspices of the International Study of Asthma and Allergies in Childhood project.[2] With regard to asthma control, Marchioro et al.[3] conducted a population-based survey and found that asthma is uncontrolled in the vast majority of asthma patients in Brazil, and that patients are more likely to use oral corticosteroids and rescue bronchodilators as the treatment of choice for asthma, despite all efforts by asthma management programs and centers in Brazil advocating maintenance treatment with inhaled corticosteroids for 20 years.[4] Another paradox is that although asthma medications are provided free of charge in Brazil—apparently the only major economy in the world in which this is done—this has no clear impact on treatment adherence or disease control, as evidenced by a nationwide survey showing that nearly 50% of all young individuals with asthma symptoms have never received a diagnosis of asthma.[5]

Not all is as gloomy as it might seem. The Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System), which was established by the 1988 Federal Constitution (the so-called "citizen" Constitution), broke with the historical logic of the dichotomy between prevention and treatment in public health. I will not dwell on the achievements and shortcomings of the SUS since it was first established, but I believe that one of its greatest achievements was the *Departamento de Informática do SUS* (DATASUS, Information Technology Department of the SUS). Albeit rarely explored by researchers in Brazil, the DATASUS is a classic example of big data, which, according to Wikipedia,[6] is a term for large and complex data sets. Big data is characterized by 5 v's: velocity; volume; variety; veracity; and value. Analysis of these large data sets can reveal new correlations to spot business trends, prevent diseases, and combat crime, among others.[6]

In the previous and current issues of the JBP, two studies used the DATASUS database (particularly the TabWin program) in order to assess trends in hospital costs and in-hospital morbidity, as well as asthma mortality, in the period between the end of the 20th century and a few years ago in Brazil. Graudenz et al.[7] showed a marked (65%) decrease in the asthma mortality rate in the 0- to 34-year age bracket; however, the asthma mortality rate remained at 9-10% in the 5- to 35-year age bracket, with a remarkable decrease in children under 5 years of age (from 3.5 deaths per 100,000 population to 0.5 deaths per 100,000 population). However, the absolute number of deaths in the 0- to 35-year age bracket remained at 2,000-2,500 per year, with a disturbing mean of more than 6 asthma-related deaths per day during the study period. In the current issue of the JBP, a descriptive study presents official longitudinal data on the impact of asthma in Brazil between 2008 and 2013.[8] The data were collected from the DATASUS database, including data on number of hospitalizations, mortality, and hospitalization costs. A geographic subanalysis was also performed, based on data from the Brazilian Institute of Geography and Statistics database. The study describes all TabWin parameters used for data collection and shows the following: 2,047 people died from asthma in Brazil (5 deaths/day), with more than 120,000 hospitalizations/year; although the absolute numbers of deaths and hospitalizations decreased by 10% and 36%, respectively, the in-hospital mortality rate increased by approximately 25% in the study period; the northern/northeastern and southeastern regions had the highest asthma-related hospitalization and in-hospital mortality rates, respectively; during the study period,

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the cost of asthma-related hospitalizations to the SUS was US$ 170 million.[8]

The results of the two aforementioned studies[7,8] corroborate the volume, veracity, and value of the DATASUS "big data" in epidemiological surveys showing past and present asthma burden and neglect in Brazil. Although asthma-related hospitalizations and deaths have decreased by nearly 70% in children under 5 years of age—which might be due to an overall reduction in child mortality in Brazil—the deaths of 3-5 patients/day (depending on the age bracket) and the 100,000 hospitalizations per year are sufficient cause for concern to warrant social media campaigns such as those launched by the Global Initiative for Asthma in Brazil in order to raise awareness of the problem.[9]

In Brazil, asthma control programs under which patients with uncontrolled asthma are identified, are monitored, and receive pharmacological treatment have been shown to be successful in reducing hospitalizations and direct and indirect costs to patients and the SUS.[10] However, in a country as large and geographically varied as Brazil, where 20 million people are estimated to have asthma, primary health care interventions are lacking. In adults, the burden of asthma is similar to that of diabetes and cardiovascular disease, being even higher in children and adolescents. However, although diabetes and cardiovascular disease have long been the targets of primary health care policies in Brazil, asthma and other chronic respiratory diseases are not.

There is no doubt that the DATASUS database and other public databases in Brazil are essential resources for generating knowledge and providing the basis for public health policies, as demonstrated in the aforementioned studies.[7,8] Analysis of data from the DATASUS database should be encouraged in graduate programs because access to the database is open and free, being less costly than population-based surveys. In a recent ecological study of time trends in all Brazilian municipalities, the authors analyzed data collected from the DATASUS database and found that asthma morbidity and mortality were associated with the proportion of individuals living in urban areas,[11] a finding that allows the planning of household and community strategies to combat asthma.

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Opaque hemithorax

Edson Marchiori[1], Bruno Hochhegger[2], Gláucia Zanetti[1]

CLINICAL HISTORY

A 69-year-old male patient presented with complaints of cough and progressive dyspnea. A chest X-ray showed complete opacification of the left hemithorax (Figure 1).

DISCUSSION

Complete opacification of a hemithorax on chest X-ray is termed opaque hemithorax (OH) and is a common finding in emergency room patients. Attending physicians encountering an OH should be able to make an immediate decision regarding the most appropriate approach.

The differential diagnosis of an OH is primarily based on the volume of the affected hemithorax, as determined by the position of the mediastinum (the position of the trachea providing the best reference for that):

- increased hemithoracic volume—mediastinal shift to the unaffected side
- reduced hemithoracic volume—mediastinal shift to the affected side
- normal hemithoracic volume—no mediastinal shift

The differential diagnosis of an OH with increased volume includes large pleural effusions (which constitute the most frequent cause of OH) and large thoracic masses, especially in children. In most cases, these conditions can be easily differentiated by ultrasound or CT.

The differential diagnosis of an OH with reduced volume includes pulmonary agenesis, pneumonectomy, and atelectasis. Bronchial obstruction by a foreign body (in children) or an endobronchial tumor (in adults) is the most common cause of atelectasis.

There are cases in which an OH presents with normal volume. In children, such cases are primarily due to extensive pneumonia affecting the entire lung parenchyma. In adults, however, such cases are primarily due to bronchial carcinoma, accompanied by pleural effusion and atelectasis.

Our patient presented with opacification of the left hemithorax with a marked mediastinal shift to the left. The absence of history of surgery or surgical scar on the chest wall, ruled out a previous pneumonectomy. A previous normal chest X-ray ruled out pulmonary agenesis. Therefore, a diagnosis of atelectasis was made, and a bronchoscopy revealed a tumor resulting in complete left main bronchial obstruction.

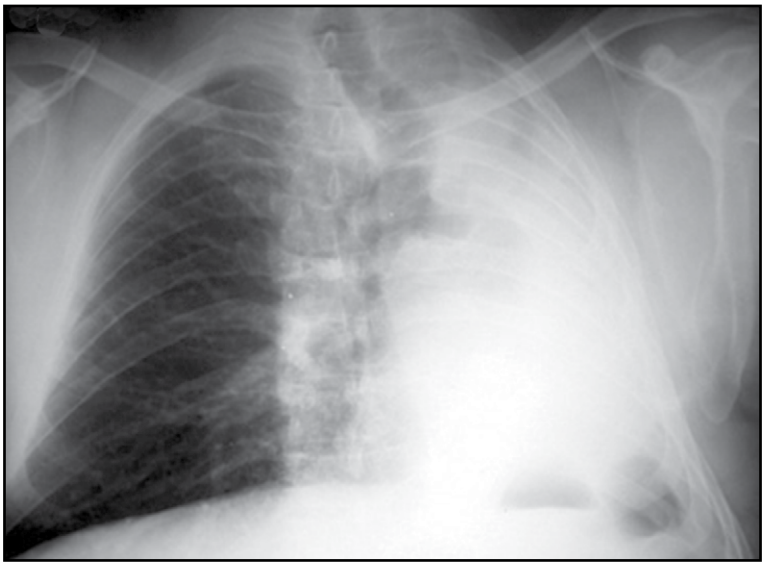

Figure 1. Anteroposterior chest X-ray showing diffuse opacification of the left hemithorax (opaque hemithorax). Note mediastinal structures, particularly the trachea, shifted to the left. Note also that the heart cannot be seen overlapping the vertebral bodies. These findings characterize an opaque hemithorax whose volume is reduced.

RECOMMENDED READING

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Subgroup analysis and interaction tests: why they are important and how to avoid common mistakes

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

A randomized clinical trial was conducted to compare the effect of vitamin C vs. placebo on improving pulmonary function in newborns of pregnant smokers; and to test if this effect differed by maternal genotype.[1] Vitamin C improved pulmonary function in newborns compared to placebo (TPTEF:TE ratio 0.383 vs 0.345; p = 0.006); and this effect was stronger in newborns with mothers with a specific genotype (p-*interaction* < 0.001).[1]

BACKGROUND

When conducting clinical trials, investigators examine the effect of interventions on outcomes in the study population and often in subgroups of patients defined by baseline characteristics (e.g., demographics, prognostic factors). The goal is to understand if the magnitude of the effect of the intervention differs within categories of a subgroup; in our example, genotype subgroups. If the effect is different within subgroups we call this effect modification of the intervention on the outcome due to the additional presence of the subgroup variable. We commonly conduct a test for interaction, using multivariable models, to evaluate for statistically significant subgroup differences. If the p value is significant, we conclude that the effect of the intervention on the outcome differs within subgroups, in our example, maternal genotype.

Understanding treatment effects across patient subgroups is important because it helps identify patient groups that respond better or worse to the intervention. However, subgroup analyses should be done with caution to avoid common mistakes that either lead to false negative or positive findings, especially when they are not pre-specified in the analysis plan before starting the study. A common mistake is to compare the effect of treatment on the outcome separately within each subgroup. For example, comparing the effect of vitamin C vs. placebo on pulmonary function in newborns among mothers with one genotype and then separately among the mothers with another genotype. This approach is incorrect because it leads to multiple testing, which means that instead of using only one calculation to test for differences in effect across subgroups (p for interaction across genotype-groups in our example), we use two or more different calculations for each subgroup analysis. Every time we add a calculation, we no longer can use the standard significant level of p < 0.05. In this case, since there are two calculations we would need to divide the p value by 2 and use p < 0.025 as the significance level.[2] Thus, we would overestimate subgroup differences if we kept the significance level at 0.05. Another challenge with subgroup analysis is that results may suggest that there are subgroup differences but the p-value is not statistically significant because the sample size within each subgroup is too small (Figure 1).

SUBGROUP ANALYSIS TIPS

1. Identify a few subgroups that seem highly relevant to your research question *a priori* and justify your choices.
2. Do not compare the effects of treatment vs. control in each subgroup. There are specific statistical tests to determine if there is an interaction between the treatment effect and the variables that define subgroups, which are best performed with the aid of a statistician.
3. Before making changes in clinical practice, subgroup results should be replicated in other studies.

Figure 1. Consider a hypothetical randomized trial with 30 participants, 15 in the treatment group (9 men and 6 women) and 15 in the control group (7 men and 8 women). To test if the effect of treatment differs between men and women, the correct approach is to use a multivariate model including an interaction term (treatment vs. sex), but with 30 participants, such a model would probably be underpowered to detect clinically significant differences. Comparing the effect of treatment vs. control in women only (6 vs. 8 participants), then in men only (7 vs. 8 participants) would also be underpowered.

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ORIGINAL ARTICLE

The impact of asthma in Brazil: a longitudinal analysis of data from a Brazilian national database system

Thiago de Araujo Cardoso[1], Cristian Roncada[1], Emerson Rodrigues da Silva[2], Leonardo Araujo Pinto[1], Marcus Herbert Jones[1], Renato Tetelbon Stein[1], Paulo Márcio Pitrez[1]

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Study carried out at Centro Infant, Instituto de Pesquisas Biomédicas, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.

ABSTRACT

Objective: To present official longitudinal data on the impact of asthma in Brazil between 2008 and 2013. **Methods:** This was a descriptive study of data collected between 2008 and 2013 from an official Brazilian national database, including data on asthma-related number of hospitalizations, mortality, and hospitalization costs. A geographical subanalysis was also performed. **Results:** In 2013, 2,047 people died from asthma in Brazil (5 deaths/day), with more than 120,000 asthma-related hospitalizations. During the whole study period, the absolute number of asthma-related deaths and of hospitalizations decreased by 10% and 36%, respectively. However, the in-hospital mortality rate increased by approximately 25% in that period. The geographic subanalysis showed that the northern/northeastern and southeastern regions had the highest asthma-related hospitalization and in-hospital mortality rates, respectively. An analysis of the states representative of the regions of Brazil revealed discrepancies between the numbers of asthma-related hospitalizations and asthma-related in-hospital mortality rates. During the study period, the cost of asthma-related hospitalizations to the public health care system was US$ 170 million. **Conclusions:** Although the numbers of asthma-related deaths and hospital admissions in Brazil have been decreasing since 2009, the absolute numbers are still high, resulting in elevated direct and indirect costs for the society. This shows the relevance of the burden of asthma in middle-income countries.

Keywords: Asthma/epidemiology; Asthma/mortality; Public health; Hospitalization.

INTRODUCTION

Asthma is a treatable chronic disease of the airways that affects all age groups and has high prevalence, morbidity, and mortality around the world.[1,2] Many patients live with uncontrolled asthma, causing impaired quality of life and resulting in direct and indirect costs for societies, particularly in developing countries.[3-5] The prevalence of asthma (including severe asthma) is high in various countries, with a relevant impact on global public health care.[6,7] The populations in which the prevalence of asthma is highest (> 20%) are observed in English-speaking countries and in Latin America.[8]

The prevalence of childhood asthma in Latin America varies widely (4-30% in children), but it is above 10% in virtually all countries.[9-12] The high burden of asthma in those countries is usually complicated by the limited access to health care and essential medications.[4,8,13] Brazil, a middle-income country of continental size, is one of the countries with the highest prevalences of asthma in children, with high rates of severe asthma.[6,7,14] We have recently shown that, in southern Brazil, 20% of school-age children have asthma, many of whom lacking control of the disease and presenting with high rates of physical inactivity, school absenteeism, and hospitalizations.[15] However, national data on the impact of asthma in developing countries are scarce. Data on mortality and number of hospitalizations regarding a particular disease are important to guide public health care policies. Large national databases are uncommon in developing countries. However, when available, such data become valuable information for improving health care policies for prevalent diseases.

Brazil has an official and longitudinal free-access database from the Brazilian Unified Health Care System, which records health indicators, such as mortality rates and number/costs of hospitalizations.[16] Thus, the aim of our study was to present longitudinal data regarding the impact of asthma in Brazil in recent years and to analyze geographic factors concerning the disease.

METHODS

We conducted a descriptive study, based on asthma information collected from the *Departamento de Informática do Sistema Único de Saúde* (DATASUS, Information Technology Department of the Brazilian Unified Health Care System) database.[16] The population studied consisted of all cases of asthma —in accordance with the International Classification of Diseases, 10th revision (ICD-10; code J.45)—in which hospitalizations and deaths were reported between 2008 and 2013. For

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the geographic analysis, variables were corrected for population numbers in 2010, according to regions and states, using another database: the *Instituto Brasileiro de Geografia e Estatística* (IBGE, Brazilian Institute of Geography and Statistics) database, which provides data regarding the Brazilian population via periodic censuses.[17] Graphics were prepared using the GraphPad Prism statistical software program, version 6 (GraphPad Inc., San Diego, CA, USA). The DATASUS database is under public domain; hence, approval of our research ethics committee was not required.

Data from the DATASUS database were subdivided into three groups for analysis: Brazil, regions, and states. The following variables were analyzed: number of deaths, number of hospitalizations, length of hospital stay, and financial costs of hospitalization.

For the general analysis, our survey was carried out from 2008 to 2013, using the Health Information System tool. For the variables analyzed, we used the tables of Epidemiology and Morbidity in the "Hospital Morbidity" group, and then the "General, by hospital location" sub-item. In the filter options, the items "years", "contents of hospitalizations", "mean length of hospital stay", "total cost", "mean cost of hospitalization", and "deaths" were selected and correlated with "asthma" (ICD-10 code, J.45). Data regarding total deaths, aiming to cover all cases of asthma-related deaths and not only those related to hospitalizations, were collected from the Brazilian National Mortality Database, using the "Vital Statistics" item (Mortality Group, 1996 to 2014) and the "General Mortality" sub-item. In the filter options, we then selected, per year, the terms "deaths" and "asthma" (ICD-10, code J.45). The criteria for the analyses of regions and states followed the standards of the general analysis, with regions and states selected only regarding the year of 2010. The variables were corrected by the populations in 2010, in accordance with the IBGE census of that year.

The results concerning asthma-related mortality of hospitalized patients refer to the total number of asthma-related deaths of hospitalized patients, divided by the total number of hospitalizations due to asthma, and multiplied by 100. In relation to the regions and states, in order to calculate the numbers of asthma-related hospital admissions and asthma-related deaths of hospitalized patients per 100,000 population, both variables were divided by the total population of the respective location and multiplied by 100,000, using only the data from 2010. All asthma-related costs of hospitalizations in Brazilian reals (R$) were converted to American dollars (USD), on the basis of the exchange rate on June 29, 2016 (USD 1.00 = R$ 3,237).

RESULTS

The total numbers of asthma-related total deaths and of hospitalizations decreased from 2008 to 2013, despite the high absolute numbers observed. In 2013, the last year analyzed, 2,047 people died from asthma in Brazil, meaning approximately 5 deaths/day and more than 120,000 hospitalizations per year. In six years, the absolute numbers of asthma-related deaths and hospitalizations decreased by 10% and 36%, respectively. However, the asthma-related mortality rate in hospitalized patients increased by approximately 25% during that period. The mean length of hospital stay due to asthma remained at approximately 3 days. These results are presented in Figure 1.

Geographically, we analyzed the numbers of asthma-related hospitalizations and deaths in

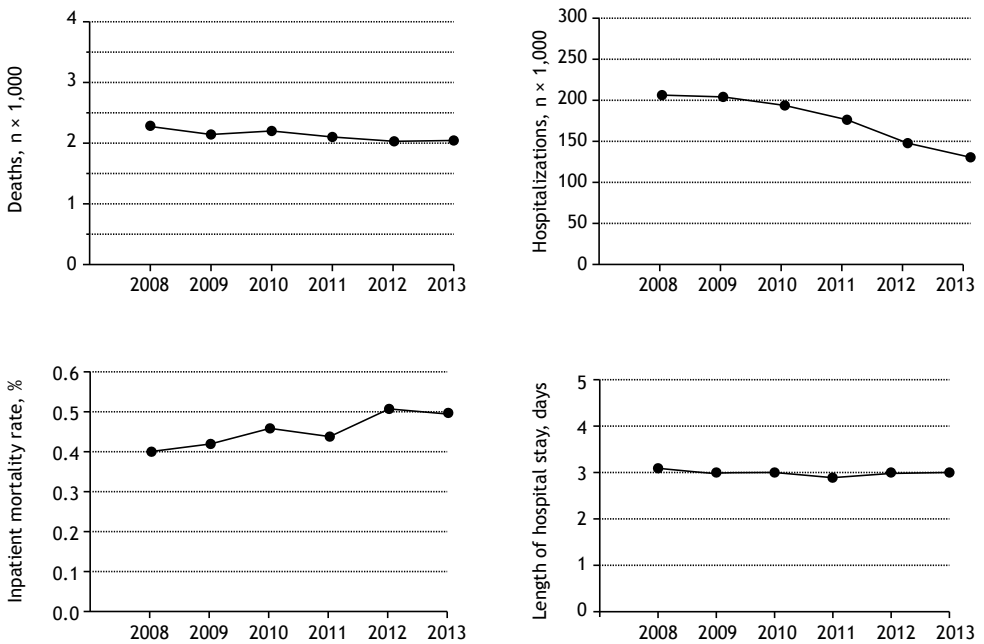

Figure 1. Overall asthma-related mortality, number of hospitalizations, inpatient mortality rate, and mean length of hospital stay in Brazil (2008-2013).

hospitalized patients in 2010 by regions and representative states. Analyzing the different regions of Brazil, we found that the northern/northeastern and southeastern regions showed the highest rates of asthma-related hospitalizations and deaths of hospitalized patients, respectively. The mean number of asthma-related hospitalizations by region in 2010 was 110 hospitalizations/100,000 population, and the proportion of deaths among hospitalized patients was 0.46% (Figure 2). The mean length of hospital stay was similar among the regions, ranging from 2.8 to 3.3 days. When we evaluated the states selected to represent the regions of Brazil (Figure 3), we observed that the states of Pará (northern region) and Bahia (northeastern region) had the largest numbers of asthma-related hospitalizations/100,000 population. The states of São Paulo (southeastern region), Goiás (central-west region), and Rio Grande do Sul (southern region) revealed numbers of asthma-related deaths among hospitalized patients above the mean. We also observed that, in some regions or states, there was a discrepancy between the number of asthma-related hospitalizations/100,000 population and the mortality rate in hospitalized patients. Figure 2 shows that the northern and northeastern regions had numbers of asthma-related hospitalizations above the mean, whereas the mortality rates were below the mean. In contrast, the southeastern region had fewer asthma-related hospitalizations but more deaths among hospitalized patients than the overall mean. In addition, Figure 3 shows the same discrepancy in the states of Pará and Bahia (more asthma-related hospitalizations per capita and fewer deaths in hospitalized patients), which was the opposite in the state of São Paulo (fewer asthma-related hospitalizations per capita and more deaths in hospitalized patients).

Finally, the asthma-related costs of hospital admissions in Brazil decreased during the period studied, despite the economic inflation (Table 1). However, the cost of hospitalizations to the public health care system reached almost USD 170 million. The mean cost of each asthma-related hospitalization was USD 160.00 (values indexed and calculated by the Brazilian public health care system). In addition, the mean cost of asthma-related hospitalizations was similar among the regions and the states of Brazil (Table 2).

DISCUSSION

Asthma, among other chronic respiratory diseases, represents an important global health problem, resulting in a negative social impact on various populations.[18] Unfortunately, for the governments of many countries, asthma is not a health care priority.[4] Brazil has a high prevalence of asthma and severe asthma, which is also observed in other countries in Latin America.[6-8,13] Nevertheless, there is a lack of official national data on the impact of asthma in Latin America. Our results show official longitudinal numbers of asthma-related deaths and hospital admissions in the largest country

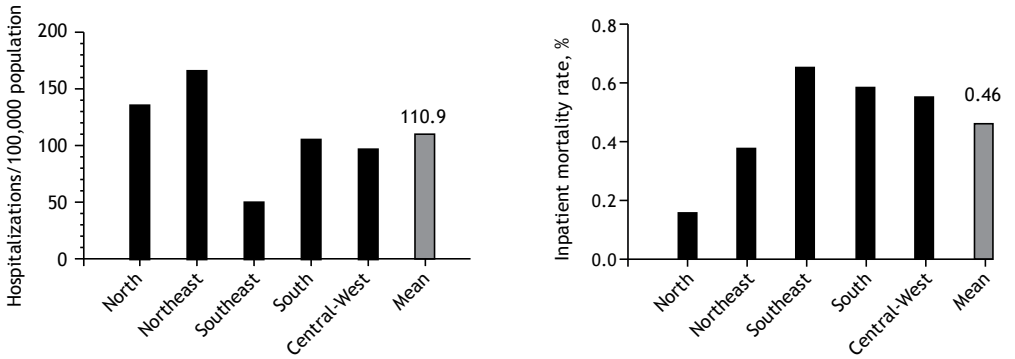

Figure 2. Number of asthma-related hospitalizations and inpatient mortality rates in the regions of Brazil (base year, 2010).

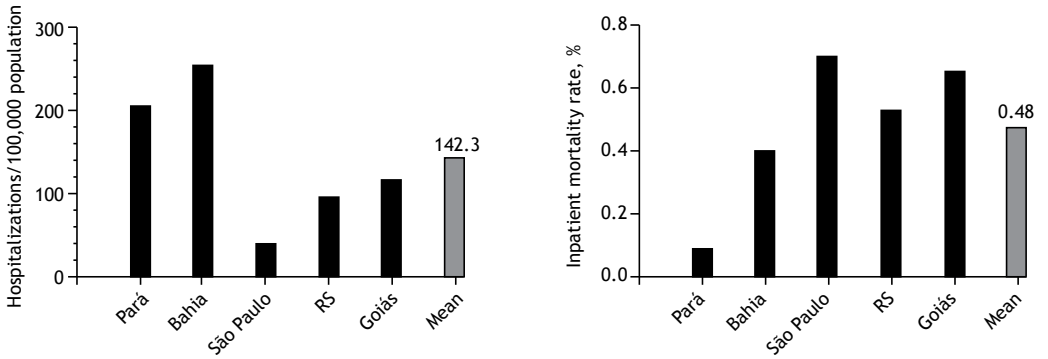

Figure 3. Number of asthma-related hospitalizations and inpatient mortality rates in the Brazilian states selected for regional analysis (base year, 2010). RS: Rio Grande do Sul.

Table 1. Total number of asthma-related hospitalizations and their costs in Brazil (2008-2013).

Year	Hospitalization, n	Cost, USD	Mean cost, USD
2008	205,276	30,195,020.86	147.09
2009	203,649	32,708,217.35	160.61
2010	193,017	31,165,431.83	161.46
2011	175,955	28,720,338.89	163.23
2012	146,559	24,153,812.17	164.81
2013	129,728	21,490,888.95	165.66
Total	1,054,184	168,433,710.05	160.48

USD: American dollars. Mean cost = total cost of hospitalizations/total number of hospitalizations.

Table 2. Total number of asthma-related hospitalizations and their costs by region and representative states in Brazil (2010).

Location	Population, n	Hospitalization, n	Total cost, USD	Mean cost, USD
Regions				
North	15,864,454	21,602	3,375,973.22	156.28
Northeast	53,081,950	88,090	13,509,808.13	153.36
Southeast	80,364,410	40,979	7,221,726.37	176.23
South	27,386,891	28,827	4,910,306.62	170.34
Central-west	14,058,094	13,519	2,147,617.49	158.86
Total	190,755,799	193,017	31,165,431.83	161,46
States				
Pará	7,581,051	15,647	2,413,448.59	154.24
Bahia	14,016,906	35,528	5,453,139.31	153.49
São Paulo	41,262,199	16,594	2,940,473.82	177.20
Rio Grande do Sul	10,693,929	10,265	1,734,000.03	168.92
Goiás	6,003,788	6,935	1,109,985.82	160.06
Total	79,557,873	84,969	13,651,047.57	162.78

USD: American dollars. Mean cost = total cost of hospitalizations/total number of hospitalizations.

of Latin America, which might help to improve national asthma care, the quality of life of patients, and the control of costs of the disease.

Asthma-related mortality in Brazil is still high. Although we observed a small reduction (10%) in the total number of deaths from 2008 to 2013, approximately 5 patients die from asthma daily in Brazil. Childhood asthma-related mortality in Brazil also decreased from 1980 to 2000,[19] suggesting a national trend toward a slow and gradual improvement in asthma-related deaths in the country. In 2000, most asthma-related deaths occurred in hospitals, and household deaths were more common in elderly patients.[20] In addition, one previous analysis of asthma-related mortality in Brazil from 1998 to 2009 showed increased mortality in less developed regions in comparison with more developed regions.[21] In the USA, one of the most developed countries in the world, with a population of over 300 million inhabitants, 3,630 deaths due to asthma were reported in 2013 (approximately 9.9 deaths/day).[22] Considering the population in the USA and in Brazil in that particular year, the asthma-related mortality rates were similar in the general population in both countries, with approximately 1 death/10,000 population. Given that asthma is a treatable disease, deaths due to asthma, often prematurely, should be a very rare fatality in this context. Public authorities, regardless of the degree of development of the country, should be continuously pursuing a reduction in asthma-related mortality.

Hospital admissions due to respiratory diseases are a negative outcome in the quality of life of patients and in the public health care system. DATASUS showed that Brazil has more than 120,000 asthma-related hospitalizations per year. However, there was a reduction of 36% of asthma-related hospital admissions during the period analyzed. This is a positive finding for the public health care system from an epidemiological point of view, and it is difficult to explain it in the context of the analysis of the present study. One possible explanation could be the implementation of a national public health care policy by the Brazilian National Ministry of Health, implemented in 2009, which provided free and easily accessible asthma medications (beclomethasone and albuterol) in the whole territory of the country.[23] This public health care policy might have facilitated the access to control and rescue medications for asthma patients across the country. In the USA, hospitalizations due to asthma remained stable between 2001 and 2009, with high economic costs,[24,25] emphasizing the importance of a permanent review of asthma control programs by health care systems. In the present study, we showed that asthma-related mortality in hospitalized patients was around 0.5%, with a 25% increase during the study period. Hence, less than 1% of hospitalized

patients die from asthma in Brazil. This finding suggests that the management of severe asthma in inpatients appears to be effective, indicating that it is imperative that comprehensive studies on the reasons why household asthma-related deaths are so high in Brazil be conducted. Another positive finding was the length of asthma-related hospital stay in Brazil. The mean length of hospital stay was 3 days, regardless of geographic factors, which is similar to that in developed countries, such as the United Kingdom.[26] We believe that little can be modified regarding the inpatient conventional therapies available against this severe clinical situation in order to reduce the number of hospital days.

When the regions of Brazil were analyzed, the northern\northeastern regions (less affluent populations) and the southeastern region (the most affluent population) showed the highest rates of asthma-related hospitalizations and deaths of hospitalized patients, respectively. The states of Pará (northern region) and Bahia (northeastern region) had the largest numbers of asthma-related hospitalizations per 100,000 population. The states of São Paulo (southeastern region), Goiás (central-west region), and Rio Grande do Sul (southern region) had a rate of asthma-related deaths among hospitalized patients above the mean. This information is important for the Brazilian public health care authorities and requires more detailed analyses in order to improve the management of asthma patients and asthma-related costs. In this context, two Brazilian cities implemented distinct public health care programs for asthma (with the creation of referral centers, easy provision of medications, strict public health care protocols, and professional training) and were successful in achieving an important decrease in the number of asthma-related hospitalizations.[27,28] Moreover, in one of these cities (Salvador, in the state of Bahia), the implemented asthma control program showed that, when patients with severe asthma had their disease under control, there was a major decrease in the direct costs of asthma in the families (−89%) and an increase in the overall family income.[29] These local initiatives demonstrate the importance of implementing further effective asthma control programs in public health care systems.

An interesting finding was the discrepancy between the number of asthma-related hospital admissions and asthma-related mortality rates in hospitalized patients among the geographic regions. The northern\northeastern regions showed asthma-related hospitalizations above the mean, which was the opposite regarding asthma-related mortality. In contrast, the southeastern region had fewer asthma-related hospitalizations but more asthma-related deaths in hospitalized patients than the overall mean. The same relationship was found in the representative states selected in the present study (i.e., Pará/Bahia and São Paulo). Once again, these data deserve an in-depth analysis by asthma control programs, considering the regional differences that are usually found particularly in large countries.

Inpatient care is the largest single component of direct asthma-related costs in public health.[30] The costs of asthma-related hospitalizations in our analysis followed the reduction in the number of hospital admissions observed, with no regional differences, especially considering the annual economic inflation of the period, which ranged from 4.4% to 6.5%.[31] Nevertheless, even with the reduction in asthma-related hospital admissions, the total cost of hospitalizations was still high. Almost USD 170 million were spent on asthma-related hospital admissions between 2008 and 2013. The mean cost of one hospitalization in Brazil is approximately USD 160.00. One may consider that the cost of one hospitalization in Brazil is low, but it is important to note that this is a value calculated by the government, which is paid to public health care providers (hospitals), and that, in fact, does not reflect the actual amount spent by the hospitals themselves. The issue of the cost of the disease stipulated by the Brazilian government (informed by DATASUS) and the "real" cost for the health care provider is another aspect that deserves public comprehensive public analysis and discussion, as well as an administrative-financial review. A recent systematic review of the costs of severe asthma in Brazil showed that the major direct expenses were related to hospitalizations and medications and that USD 733.00 were spent per patient per year, highlighting the elevated economic costs of asthma.[32]

Our study has limitations. This was a retrospective analysis of secondary data, which are subject to inadequate completion of medical records, including erroneous diagnosis of the disease. Underdiagnosis and underreporting are problems in any health care system, particularly in developing countries.[33] However, we have to consider that the data collected represent the official numbers of the Brazilian government, and limitations can be found in any country that implements this type of database. Nevertheless, we believe that DATASUS, with all its limitations, substantially helps to present relevant information on the impact of asthma in Brazil.

In conclusion, asthma-related mortality in Brazil is still very high if we take into account that asthma is a treatable disease. Despite the decrease in the number of asthma-related hospitalizations in recent years, the absolute numbers are still remarkable, resulting in relevant direct and indirect costs for the society. Finally, these results show that asthma should receive greater attention from the public health care authorities in Brazil and most other countries in Latin America.

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ORIGINAL ARTICLE

Assessment of fatigue using the Identity-Consequence Fatigue Scale in patients with lung cancer

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Study carried out in the Universidade Federal do Ceará, Fortaleza (CE) Brasil.

ABSTRACT

Objective: To evaluate the properties of the Identity-Consequence Fatigue Scale (ICFS) in patients with lung cancer (LC), assessing the intensity of fatigue and associated factors. **Methods:** This was a cross-sectional study involving LC patients, treated at a teaching hospital in Brazil, who completed the ICFS. Patients with chronic heart disease (CHD) and healthy controls, matched for age and gender, also completed the scale. Initially, a Brazilian Portuguese-language version of the ICFS was administered to 50 LC patients by two independent interviewers; to test for reproducibility, it was readministered to those same patients. At baseline, the LC patients were submitted to spirometry and the six-minute walk test, as well as completing the Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scale (HADS), Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), and Fatigue Severity Scale (FSS). Inflammatory status was assessed by blood C-reactive protein (CRP) levels. To validate the ICFS, we assessed the correlations of its scores with those variables. **Results:** The sample comprised 50 patients in each group (LC, CHD, and control). In the LC group, the intraclass correlation coefficients for intra-rater and inter-rater reliability regarding ICFS summary variables ranged from 0.94 to 0.76 and from 0.94 to 0.79, respectively. The ICFS presented excellent internal consistency, and Bland-Altman plots showed good test-retest reliability. The ICFS correlated significantly with FSS, HADS, and SF-36 scores, as well as with CRP levels. Mean ICFS scores in the LC group differed significantly from those in the CHD and control groups. **Conclusions:** The ICFS is a valid, reliable instrument for evaluating LC patients, in whom depression, quality of life, and CRP levels seem to be significantly associated with fatigue.

Keywords: Fatigue; Lung neoplasms; Symptom assessment.

INTRODUCTION

Fatigue is a subjective complaint of patients with various chronic illnesses and can affect work performance and activities of daily living, as well as social and family responsibilities.[1] Cancer-related fatigue is reportedly in the range of 70-80%.[1-3] The most severe fatigue is reported among lung cancer (LC) patients and persists for several months or years after treatment completion, having a great negative impact on the quality of life of those patients.[4-7]

The pathogenesis of cancer-related fatigue is poorly understood. In attempts to explain fatigue, models have been developed based on both physiological and psychological aspects. The mechanisms involve effects of cancer or of its treatment on the central nervous system, muscle energy metabolism, sleep/circadian rhythms,[8,9] mediators of inflammation,[10] stress,[10] immune activation,[11] and hormonal changes related to effects on the hypothalamic-pituitary axis.[12-14] Immune activation has been associated with fatigue and depression in patients with cancer or other chronic diseases.[15,16] Therefore, a better understanding of LC-related fatigue and its correlation with biomarkers, physical function, and psychological parameters is important to enable more personalized interventions.

Fatigue is also one of the most commonly reported symptoms by patients with chronic heart disease (CHD). Causes of fatigue in heart failure include low cardiac output, poor tissue perfusion, muscle metabolic abnormalities, autonomic nervous system abnormalities, deconditioning effects, and endothelial dysfunction.[17,18]

Fatigue has been most commonly assessed by self-report questionnaires.[2-5] The Identity-Consequence Fatigue Scale (ICFS) is a validated comprehensive questionnaire that identifies the energy levels of patients and is appropriate to identify both mental and behavioral consequences of cancer-related fatigue.[19,20] The objective of this study was to evaluate the measurement properties of the ICFS, as well as the intensity of fatigue and the associated factors, in LC patients. To our knowledge, this is the first

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study to evaluate fatigue using the ICFS in LC patients. Because ICFS is a generic fatigue questionnaire, it allows for comparisons to be made among different patient populations.

METHODS

This was a cross-sectional study involving 50 consecutive patients previously diagnosed with non-small cell LC (LC group) and referred to an outpatient clinic at a teaching hospital in the city of Fortaleza, Brazil, for staging and potential surgical treatment. Patients who were incapable of understanding the scale were excluded, as were those who had neurologic, vascular, or musculoskeletal diseases that limited their ability to perform the six-minute walk test (6MWT). In addition, two other groups, matched for age and gender, were studied for comparison: 50 patients with CHD recruited from the cardiology outpatient clinic in the same teaching hospital (CHD group); and 50 healthy volunteers from a local community senior center (control group).

All LC cancer participants were initially assessed in order to determine relevant demographic and clinical parameters. LC staging was obtained from the medical records of the patients. All LC patients underwent spirometry, were submitted to the 6MWT, completed questionnaires/scales (anxiety and depression, fatigue, daytime somnolence, and health-related quality of life), and had their serum C-reactive protein (CRP) levels measured. Specific questionnaires were completed in a face-to-face interview by two medical investigators. A metabolic equivalent of CRP was established in order to determine the validity of ICFS, because we hypothesized that fatigue was associated with inflammation. The participants in the CHD and control groups completed the ICFS once only.

Research tool

The ICFS is a 31-item self-report tool that assesses five domains of fatigue (feelings of fatigue, feelings of vigor, impacts on concentration, impacts on energy, and impacts on daily activities) and provides two summary scores: fatigue experiences and fatigue impacts.[19]

The "fatigue experiences" score is the average of "feelings of fatigue," "feelings of vigor," and "impacts on concentration" subscale scores. The "fatigue impacts" score is the average of "impacts on energy" and "impacts on daily activities" subscale scores. For the items in the "feelings of fatigue," "feelings of vigor," "impacts on energy," and "impacts on concentration" domains, the anchors are "not at all" (score = 0); and "almost never," "some of the time," "fairly often," "very often," and "all of the time" (score = 5). For the items in the "daily activity" domain, the anchors are "not at all" (score = 0); and "only occasionally," "some of the time but less than usual," "nearly as often as usual," and "as often as usual" (score = 4). For two items in the "impacts on energy" subscale ("I have achieved very little with the day" and "I lack the energy to do things that I normally do"), the scores are rated as follows: 0 = "I strongly agree"; 1 = "I agree"; 2 = "neutral"; 3 = "I disagree"; and 4 = "I strongly disagree." The scores are reported as a percentage of the maximum possible score available for each participant. In this study we used the Brazilian-Portuguese version of the ICFS.

Translation process

First, the English-language version of the ICFS was independently translated into Brazilian Portuguese by two of the investigators. The two translations were compared until a consensus version was agreed upon. That version was administered to a small sample of five patients with LC in order to evaluate clarity and to ensure that no terms or situations in the questionnaire were considered obscure or difficult to understand. This Brazilian Portuguese-language version was then back-translated into English by a translator who had no prior knowledge of the original scale. The author of the original scale assessed the back-translation, which was discussed with the investigators, and a final version was then obtained. The final version (Appendix) was administered to the participants in the present study. The Appendix is available online at http://jornaldepneumologia.com.br/detalhe_anexo.asp?id=50

Measurements

In order to test the inter-rater reliability of the Brazilian Portuguese-language version of the ICFS, the instrument was administered to the LC patients twice by two observers, 30 minutes apart, during the first visit (V1). The second visit (V2) occurred 7 days after V1, and the ICFS was again administered to the same patients by only one of the observers in order to test intra-rater reliability. We chose a 7-day interval because it was more practical for the participants who lived outside the city of Fortaleza and for those who had started receiving chemotherapy. A 7-day interval between visits has also been used in other intra-observer reliability studies.[21] All other assessments were carried out at V1.

The Fatigue Severity Scale (FSS)[22] is a seven-point Likert scale in which 1 means "I strongly disagree," and 7 means "I strongly agree." Higher scores indicate more severe fatigue. In the present study, we used the Portuguese-language version of the FSS validated for use in Brazil.[23]

Symptoms of depression and anxiety states were assessed using the Hospital Anxiety and Depression Scale (HADS). This scale consists of 14 items, of which 7 focus on the assessment of anxiety (HADS-A subscale), and 7 focus on the assessment of depression (HADS-D subscale). Each item can be scored from 0 to 3, the maximum score on each subscale being 21 points. This scale was selected because it was specifically developed to assess anxiety and depression in medically ill patients; therefore, it excludes items that are related to somatic symptoms.[24] We used the Portuguese-language version of the HADS validated for use in Brazil.[25]

The Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) is a patient-reported survey

of health status. It consists of eight scaled scores which are the weighted sums of the questions in each section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries an equal weight. Lower scores indicate more disability. The SF-36 has been translated and adapted for use in Brazil.[26]

The Epworth Sleepiness Scale (ESS) is a simple and reliable instrument that has been widely used in order to measure daytime sleepiness; we used the ESS version that had been translated to Portuguese and adapted for use in Brazil.[27] The subjects are required to rate their likelihood of falling asleep on a scale of increasing probability (from 0 to 3) for eight different situations in which most people find themselves during their activities of daily living. The scores for the eight questions are added together to obtain a single number.[28]

Spirometry was performed in accordance with Miller et al.[29] Measurements included FEV_1, FVC, and the FEV_1/FVC ratio. The results were compared with reference values established by Pereira et al.[30]

The 6MWT is a simple and practical standardized test for the evaluation of exercise capacity. The six-minute walk distance (6MWD) is defined as the distance a patient can quickly walk on a flat, hard surface in a period of six minutes.[31] The test was carried out indoors along a flat, straight, 30-m corridor. Patients were asked to walk at their fastest pace from one end of the corridor to the other end as many times as possible. The 6MWD was then measured.

Statistics

Data were statistically analyzed with the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA). We used descriptive analysis and frequencies in order to assess the characteristics of the sample. Kruskal-Wallis H test was used in order to compare the fatigue scores in the three groups. We used the intraclass correlation coefficient (ICC) for the analysis of reproducibility of the application and reapplication of the ICFS (V1 vs. V2). The Wilcoxon test was used in order to compare the scores obtained from the administration of the ICFS by the same observer in V1 and V2. Bland-Altman plots were used in order to improve the visualization of the test-retest reliability obtained from the various administrations of the ICFS. The ICFS was tested for internal consistency by Cronbach's alpha coefficient. In order to validate the ICFS, we used Spearman's correlation test to assess the strength of the correlations between its scores and those obtained on the FSS, HADS, SF-36, and ESS, as well as the 6MWD, spirometry values, and CRP levels. Bonferroni correction was used for multiple comparisons to alter the p value to a more stringent value in order to reduce the likelihood of a type I error. The level of significance was set at 5%. The sample size (50 subjects) was calculated on the basis of the hypothesis of a moderate correlation ($r = 0.5$) between the degree of fatigue measured by the ICFS and that measured by other instruments. That level was set at two-sided $\alpha = 0.05$ and $\beta = 0.20$.

Ethical aspects

This study was conducted in accordance with Brazilian National Health Council Resolution 196/96, which established ethical principles for human research, and was approved by the local research ethics committee. All patients gave written informed consent prior to their inclusion in the study.

RESULTS

The study sample comprised 150 patients, 50 in each group (LC, CHD, and control). The major characteristics of the patients in the LC group are summarized in Table 1. A Kruskal-Wallis H test showed that there was a statistically significant difference in the "fatigue experiences" scores among the three groups—$\chi^2(2) = 23.63$; $p = 0.001$—with a mean rank score of 80.2 in the LC group, 92.2 in the CHD group, and 51.6 in the control group (Table 2). A post hoc test showed that there was no difference between the LC and CHD groups regarding the ICFS summary variable "fatigue experiences"; both groups presented with a higher level of fatigue when compared with the control group. There was a progressive increase in the mean rank of the ICFS summary variable "fatigue impacts" scores ($\chi^2(2) = 41.74$; $p = 0.001$). A post hoc test showed that there was a significant difference when the control group was compared with the LC and the CHD groups ($p < 0.001$ for both), and when the LC group was compared with the CHD group ($p < 0.001$). No differences in the ICFS summary variables "fatigue experiences" and "fatigue impacts" were observed in regard to gender, age (≤ 65 years vs. > 65 years), LC staging (stages I/II vs. III/IV), or chemotherapy.

There were no significant differences between the ICFS summary variables "fatigue experiences" and "fatigue impacts" scores obtained by the same observer in different visits (V1 = 30.9 ± 18.4; V2 = 31.8 ± 17.1; $p = 0.8$; and V1 = 28.1 ± 15.0; V2 = 25.3 ± 12.9; $p = 0.3$; respectively). The ICCs for intra-rater reliability (V1 vs. V2) regarding the same summary variables were 0.94 (95% CI: 0.90-0.97) and 0.76 (95% CI: 0.57-0.86), respectively. Neither were there significant differences between the two observers of the study for the same summary variables scores (30.9 ± 18.4 vs. 32.5 ± 19.8; $p = 0.6$; and 28.1 ± 15.0 vs. 28.2 ± 10.0; $p = 1.0$; respectively). The ICCs for inter-rater reliability on the ICFS summary variables "fatigue experiences" and "fatigue impacts" were 0.94 (95% CI: 0.90-0.96) and 0.79 (95% CI: 0.64-0.88), respectively. Excellent inter-rater and intra-rater reliability were also identified in the Bland-Altman plots (Figures 1 and 2). The Cronbach's alpha coefficient for the ICFS was 0.88 (95% CI: 0.82-0.92), indicating excellent internal consistency.

There were significant correlations of the FSS scores with the ICFS summary variables "fatigue experiences"

and "fatigue impacts" scores (r = 0.60 and r = 0.52, respectively). Anxiety and depression scales were significantly correlated with the summary variables "fatigue experiences" (r = 0.43; p = < 0.01; and r = 0.60; p = < 0.01; respectively) and "fatigue impacts" (r = 0.62; p = < 0.01; and r = 0.63; p = < 0.01; respectively). The same summary variables correlated negatively with the mental component summary of SF-36 (r = −0.55; p < 0.01; and r = −0.48; p = < 0.01; respectively). After the Bonferroni correction for multiple comparisons, serum CRP levels showed a positive correlation with the summary variable "fatigue impacts". However, no significant correlations were found with the ESS score (Table 3).

Table 1. Characteristics of the patients with lung cancer in the study (N = 50).[a]

Variable	Result
Age, years[b]	60 ± 12.2
Gender	
Male	27 (54)
Female	23 (46)
Cancer stage[b]	
I or II	24 (48)
III or IV	26 (52)
Chemotherapy[c]	
Yes	6 (12)
No	44 (88)
FEV_1, % of predicted[b]	86.3 ± 19.8
FVC, % of predicted[b]	86.9 ± 17.8
6MWD, m[b]	478.4 ± 104.6
BMI, kg/m2[b]	25.9 ± 3.5
ICFS[d]	
Feelings of fatigue	32 (12-44)
Feelings of vigor	45 (5-60)
Impacts on energy	35.7 (28.5-50.0)
Impacts on concentration	22 (8-40)
Impacts on daily activities	14.3 (1.0-27.0)
ICFS summary variable	
Fatigue impacts[d]	24.3 (17.6-38.0)
Fatigue experiences[b]	31.9 ± 18.6
Epworth Sleepiness Scale[b]	7.1 ± 3.8
SF-36 MCS[b]	47.7 ± 13.3
SF-36 PCS[b]	45.6 ± 8.4
Fatigue Severity Scale[d]	23 (12-33)
HADS-A[d]	5 (3-8)
HADS-D[d]	4.5 (2.0-7.0)
CRP, mg/L[d]	2.9 (1.1-6.1)

6MWD: six-minute walk distance; ICFS: Identity-Consequence Fatigue Scale; SF-36: Medical Outcomes Study 36-item Short-Form Health Survey; MCS: mental component summary; PCS: physical component summary; HADS-A: Hospital Anxiety and Depression Scale-anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale-depression subscale; and CRP: C-reactive protein. [a]Values are expressed as n (%), except otherwise indicated. [b]Values are expressed as mean ± SD. [c]On the assessment day, those patients were being evaluated for a potential chemotherapy treatment. [d]Values are expressed as median (interquartile range).

DISCUSSION

The present study shows that the Brazilian Portuguese-language version of the ICFS has excellent inter-rater/intra-rater reliability, high internal consistency, and good correlations with clinical and psychological parameters. The ICFS clearly distinguished among different patient populations.

One issue for clinicians and researchers is the choice of the fatigue scale to be used. Certainly, there is still work to be undertaken in understanding the phenomenon of fatigue and how it should be measured. The ICFS was chosen by the investigators because it is a multidimensional instrument that captures multiple characteristics and manifestations of fatigue.

In the present study, the ICFS correlated with a wide range of variables. The strong correlation between the FSS and ICFS is remarkable, considering the fact that they were developed using different samples of patients, as well as that they present different structures, layouts, and response formats.

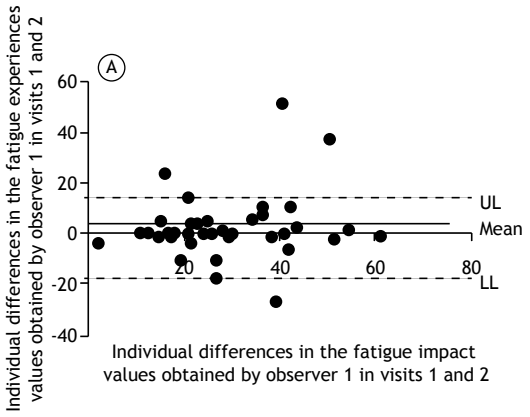
The mental component summary of the SF-36 correlated negatively with both of the ICFS summary variables. The reason is that the SF-36 mental component summary comprises the vitality subscale, which addresses energy level and fatigue. Tang et al.[32] showed an association between SF-36 and fatigue measured by FSS. The magnitude of the correlation was highest for the vitality domain.

Both ICFS summary variables correlated with anxiety and depression. Our results are consistent with those of previous reports that showed a strong correlation between depression and fatigue.[14,33] One hallmark of depression is a decreased motivation to do things that the patient once enjoyed. This is addressed by the ICFS items (e.g., "It has been hard for me to get motivated to do my regular activities.")

Table 2. Comparisons among the three groups studied (N = 50 in all).

Variable	Group			p
	Control	Lung cancer	Chronic heart disease	
Male, n (%)	27 (54)	27 (54)	24 (50)	0.8
Age, years[a]	60.5 ± 12.2	60.4± 12.0	60.3 ± 12.2	0.9
ICFS-fatigue experiences[b]	51.6	80.2	92.2	0.001*
ICFS-fatigue impacts[b]	47.5	73.7	103.7	0.001**

ICFS: Identity-Consequence Fatigue Scale. [a]Value is expressed as mean ± SD. [b]Values are expressed as mean rank score. *Control group vs. lung cancer and chronic heart disease groups. **Control group vs. lung cancer and chronic heart disease groups; and lung cancer group vs. chronic heart disease group.



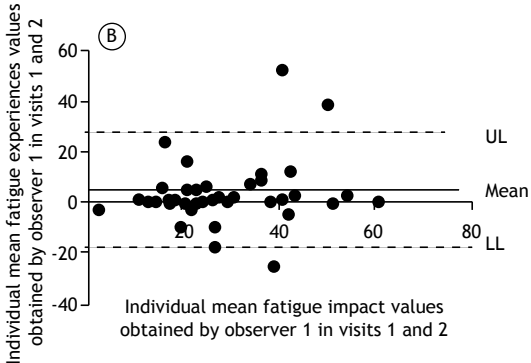
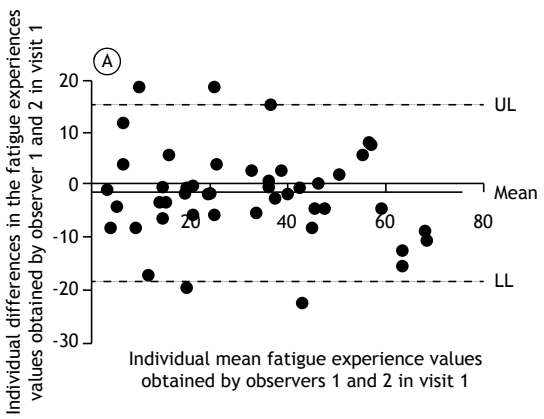


Figure 1. Bland-Altman plots. In A, intra-rater analysis of fatigue experiences: mean = −0.98; UL = 15.24; LL = −17.00. In B, intra-rater analysis of fatigue impacts: mean = 2.78; UL = 25.15; LL = −19.58. UL: upper limit; and LL: lower limit.



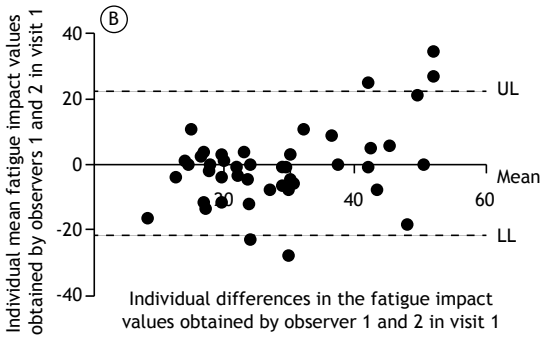


Figure 2. Bland-Altman plots. In A, inter-rater analysis of fatigue experiences: mean = −1.61; UL = 14.95; and LL = −18.18. In B, inter-rater analysis of fatigue impacts: mean = −0.04; UL = 22.38; and LL = −22.46. UL: upper limit; and LL: lower limit.

A remarkable correlation was found between fatigue and anxiety. This could be explained by the fact that people with anxiety are prone to panic, fear, and other high-stress responses which cause fatigue, increasing the levels of stress hormones.[34]

Previously, correlations between fatigue and sleep disorders have been noted in patients undergoing radiotherapy and surgery, as well as in those with a variety of cancer types, including LC.[35] In our study, under the criterion of Bonferroni correction for multiple comparisons, fatigue did not correlate with excessive daytime sleepiness. A possible explanation could be the fact that only a few patients (only 10%) presented with excessive daytime sleepiness.

We found that the presence of a systemic inflammatory response (as evidenced by elevated circulating CRP levels) was associated with increased fatigue. Some cancerous cells have been shown to secrete IL-6 and IL-8, which, in turn, induce the production of CRP.[36] Previously, de Raaf et al.[37] observed that fatigue dimensions were associated with inflammatory markers in different groups of cancer patients. We decided to measure CRP because it is a biomarker for which routine measurements are available in clinical practice.

In the present study, we measured fatigue in a multidimensional way and found a correlation between CRP levels and fatigue impacts. Previous studies measured fatigue in a unidimensional way and could not find significant correlations with inflammatory markers.[38,39] Those studies are controversial, and further research is warranted in order to investigate the relationship between elevated serum concentrations of inflammatory markers and subjective complaints of fatigue.

In contrast with our results, fatigue has been previously reported to be correlated with LC stage and the use of chemotherapy.[6,12] Because only 12% of our patients were on chemotherapy on the assessment day, it is possible that our study lacked statistical power to detect this association. A similar effect may be present in regard to cancer staging.

Our sample of LC patients reported higher intensity of fatigue than did the control group patients. By comparing the LC group with that with another chronic disease (CHD group), we found that the scores for "fatigue experiences" were similar, although those for "fatigue impacts" were lower in the former group. Patients with heart disease present with restrictions on their activities of daily living (as measured by the

Table 3. Correlations of fatigue, as measured by the scores of the Identity-Consequence Fatigue Scale summary variables (fatigue experiences and fatigue impacts), with other variables studied.

Variable	Fatigue experiences			Fatigue impacts		
	r	p	p[a]	r	p	p*
Fatigue Severity Scale	0.60	< 0.001	0.007	0.52	< 0.001	0.007
FEV_1, % of predicted	0.14	0.313	2.171	0.12	0.376	2.591
6MWD	−0.16	0.261	1.827	−0.09	0.950	6.651
HADS-A	0.43	0.002	0.014	0.62	< 0.001	0.007
HADS-D	0.60	< 0.001	0.007	0.63	< 0.001	0.007
SF-36 MCS	−0.55	< 0.001	0.007	−0.48	< 0.001	0.007
SF-36 PCS	0.29	0.239		0.16	0.102	0.714
Epworth Sleepiness Scale	0.19	0.181	1.267	0.32	0.021	0.147
CRP, mg/L	0.28	0.048	0.336	0.50	< 0.001	0.007

6MWD: six-minute walk distance; HADS-A: Hospital Anxiety and Depression Scale-anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale-depression subscale; SF-36: Medical Outcomes Study 36-item Short-Form Health Survey; MCS: mental component summary; PCS: physical component summary; and CRP: C-reactive protein. *After Bonferroni correction: α critical = 0.048.

summary variable "fatigue impacts"); one explanation for this could be that patients with heart disease have impaired peripheral circulatory perfusion and, consequently, reduced oxygen delivery and impaired muscle strength.

One limitation of this study is that it had a cross-sectional design; therefore, it provides no indication of the responsiveness of the ICFS over time. Another limitation is that subjects were recruited from a single center and might differ from LC patients under treatment elsewhere. Overall, more research is needed in order to understand the clinical significance attributable to patient reports of fatigue.

The strength of the study is the use of a more comprehensive measure of fatigue. The ICFS provides a general assessment for use in a variety of medical situations in which a complete evaluation of fatigue is desired. It is important to measure fatigue in LC patients in order to develop effective, patient-centered management strategies, as well as to improve the physical functioning, quality of life, and emotional/psychological health of these patients.

In conclusion, the present study presents evidence that the Brazilian Portuguese-language version of the ICFS is a reliable tool for measuring fatigue in LC patients.

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ORIGINAL ARTICLE

Sleep-disordered breathing in patients with COPD and mild hypoxemia: prevalence and predictive variables

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ABSTRACT

Objective: To infer the prevalence and variables predictive of isolated nocturnal hypoxemia and obstructive sleep apnea (OSA) in patients with COPD and mild hypoxemia. **Methods:** This was a cross-sectional study involving clinically stable COPD outpatients with mild hypoxemia (oxygen saturation = 90-94%) at a clinical center specializing in respiratory diseases, located in the city of Goiânia, Brazil. The patients underwent clinical evaluation, spirometry, polysomnography, echocardiography, arterial blood gas analysis, six-minute walk test assessment, and chest X-ray. **Results:** The sample included 64 patients with COPD and mild hypoxemia; 39 (61%) were diagnosed with sleep-disordered breathing (OSA, in 14; and isolated nocturnal hypoxemia, in 25). Correlation analysis showed that PaO_2 correlated moderately with mean sleep oxygen saturation ($r = 0.45$; $p = 0.0002$), mean rapid eye movement (REM) sleep oxygen saturation ($r = 0.43$; $p = 0.001$), and mean non-REM sleep oxygen saturation ($r = 0.42$; $p = 0.001$). A cut-off point of $PaO_2 \leq 70$ mmHg in the arterial blood gas analysis was significantly associated with sleep-disordered breathing (OR = 4.59; 95% **CI:** 1.54-13.67; $p = 0.01$). The model showed that, for identifying sleep-disordered breathing, the cut-off point had a specificity of 73.9% (95% **CI:** 51.6-89.8%), a sensitivity of 63.4% (95% **CI:** 46.9-77.9%), a positive predictive value of 81.3% (95% **CI:** 67.7-90.0%), and a negative predictive value of 53.1% (95% **CI:** 41.4-64.4%), with an area under the ROC curve of 0.69 (95% **CI:** 0.57-0.80), correctly classifying the observations in 67.2% of the cases. **Conclusions:** In our sample of patients with COPD and mild hypoxemia, the prevalence of sleep-disordered breathing was high (61%), suggesting that such patients would benefit from sleep studies.

Keywords: Pulmonary disease, chronic obstructive/complications; Sleep wake disorders/ epidemiology; Anoxia/etiology.

INTRODUCTION

The presence of sleep-disordered breathing among patients with COPD appears to be associated with an increased risk of exacerbations and with difficulty in therapeutic management.[1,2] Although the recommendation is that the presence of sleep-disordered breathing conditions be investigated in the history taking of such patients, these conditions frequently go unnoticed by the physician and/or the patient.[3]

Sleep-disordered breathing conditions such as obstructive sleep apnea (OSA) and isolated nocturnal hypoxemia (oxygen desaturation in the absence of OSA) occur in patients with COPD at a prevalence ranging from 8% to 39% and from 27% to 84%, respectively.[3-18] Apparently, the prevalence of sleep-disordered breathing is associated with the severity of COPD, because it has been demonstrated that subjects with COPD and an oxygen saturation less than 90% may have pronounced drops in oxygen saturation during sleep.[3,11] However, there is no consensus regarding the evaluation of sleep-disordered breathing in patients with COPD who have mild daytime hypoxemia (oxygen saturation between 90% and 94%).[4,5,19] In addition, polysomnography, a test used to diagnose OSA and nocturnal hypoxemia, is not formally indicated in this subgroup of patients with COPD, and the prevalence of these sleep-disordered breathing conditions in this subgroup is unknown.[4,5]

The objective of the present study was to infer the prevalence of and identify predictive variables associated with sleep-disordered breathing (OSA and isolated nocturnal hypoxemia) in patients with COPD and mild daytime hypoxemia (oxygen saturation between 90% and 94%).

METHODS

Subjects, methodological design, and ethical aspects

This was a cross-sectional study conducted at the Clinical Research Center of the *Clínica do Aparelho Respiratório*,

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which is a clinic specializing in respiratory diseases, located in the city of Goiânia, Brazil.

Patients with a previous diagnosis of COPD who were not on home oxygen therapy, were clinically stable, and were ≥ 40 years of age, all of whom were admitted to the Clinical Research Center of the *Clínica do Aparelho Respiratório* between April 1 and September 31 of 2013, were considered eligible for and invited to participate in the study. After giving written informed consent, patients underwent spirometry and oximetry. Subjects who had a post-bronchodilator FEV_1/FVC ratio < 70; had oximetry results showing mild daytime hypoxemia (oxygen saturation between 90% and 94%); were not knowingly pregnant or had menstruated in the last 28 days (in the case of female participants); had no history of recent myocardial infarction (within three months); had no medical history of asthma or any other concomitant lung disease; had no history of cancer diagnosis; had no history of renal failure or dialysis; had no history of insulin-dependent diabetes; and had no complaints related to snoring, witnessed apneas, or excessive daytime sleepiness were included in the study. All study subjects then underwent clinical evaluation and completed validated instruments—the Medical Research Council dyspnea scale,[20] the COPD Assessment Test,[21] and a classification of socioeconomic level.[22] Subsequently, they underwent a six-minute walk test (6MWT), completed the Epworth Sleepiness Scale,[23] and underwent polysomnography, echocardiography, arterial blood gas analysis, and posteroanterior and lateral chest X-ray. Subjects with a PaO_2 < 60 mmHg by resting arterial blood gas analysis and/or radiographic evidence of any significant abnormality not attributable to COPD were excluded from the study. Subjects who were unable to understand or complete all instruments and interviews were also excluded. The present study was conducted in accordance with Good Clinical Practice and was approved by the Ethics Committee of the *Hospital Geral de Goiânia* (Protocol no. 198.344/2013).

Procedures and definitions

Clinical stability was defined as no exacerbation in the preceding four weeks.[24] All subjects were categorized by smoking status as smokers (subjects who were currently smoking daily or less than daily); former smokers (subjects who had smoked at least 100 cigarettes or 5 packs in their lifetime and had quit smoking); or nonsmokers (subjects who had never smoked or had smoked fewer than 100 cigarettes or 5 packs in their lifetime).[25]

Subjects were classified as having COPD according to the Global Initiative for Chronic Obstructive Lung Disease 2014 criteria (chronic respiratory symptoms, a history of exposure to risk factors for the disease, and a post-bronchodilator FEV_1/FVC ratio < 70 on spirometry).[2]

Nocturnal hypoxemia was defined as an oxygen saturation < 90% for at least 5 min on polysomnography, with a nadir ≤ 85%.[14] Subjects were considered to have isolated nocturnal hypoxemia if their sleep study showed nocturnal hypoxemia but no OSA.[11]

Desaturation during the 6MWT was defined as a ≥ 4% drop in resting oxygen saturation during at least the last 3 min of the test.[26]

Polysomnography was performed with the Alice 5 Diagnostic Sleep System (Philips Respironics, Murrysville, PA, USA) in a sleep laboratory. Apnea was defined as airflow cessation ≥ 10 s, and hypopnea was considered present when at least one of three conditions occurred: a > 50% reduction in airflow; a > 50% reduction in airflow and a > 3% drop in oxygen saturation; or a > 50% reduction in airflow and electroencephalographic evidence of arousal. OSA was considered present when the apnea-hypopnea index (AHI) was ≥ 15 events/h (a definition aimed at being a more stringent diagnostic criterion and at reducing the possibility of overestimating the presence of OSA because of the possible presence of excessive daytime sleepiness in patients with COPD). Recordings were interpreted and sleep stages were determined according to the recommendations of the American Academy of Sleep Medicine.[27]

Sample size calculation

To calculate the sample size for the prevalence study, we estimated a proportion of the population with specific absolute accuracy by using the formula $n = z^2_{1-\alpha/2}P(1-P)/d^2$.[28] Because prevalence rates of sleep-disordered breathing demonstrate a wide range of values across studies (from 8% to 84%),[6-14] in the sample size calculation for the cross-sectional study, we assumed a 50% prevalence of sleep-disordered breathing as the safest choice, given that this value would yield the biggest sample size. To estimate the prevalence of sleep-disordered breathing with an absolute accuracy of 13% and a confidence level of 95%, the sample size was calculated as 57 subjects. Assuming a potential error of 10%, we decided to include at least 64 subjects in the sample.

Statistical analysis

The results were analyzed with the STATA program, version 13.1 (StataCorp LP, College Station, TX, USA), using a level of significance of 5% ($p < 0.05$). Data normality was assessed by using the Shapiro-Wilk test. Quantitative variables with normal distribution were expressed as mean and standard deviation, quantitative variables with non-normal distribution were expressed as median and interquartile range (IQR), and qualitative variables were expressed as proportions.

ANOVA was used to compare means, with Tukey's post hoc test being used to identify significant differences, whereas ANOVA with the Kruskal-Wallis post hoc test was used to compare medians. For dichotomous variables, the chi-square test or Fisher's exact test, when appropriate, was used. Logistic regression was used to calculate the odds ratios of the association between the independent or predictive variable and the outcome

variable (one of the two sleep-disordered breathing conditions studied here) with 95% CIs. The cut-off value for PaO_2 was calculated by ROC curve analysis. A correlation analysis was performed to evaluate the strength of the linear relationship between numerical variables, with Bonferroni adjustment of significance levels, and multiple linear regression was conducted to study the cause-and-effect relationship.

RESULTS

Figure 1 shows the study population flowchart. Of the 64 subjects included in the study, 14 (21.8%) had OSA, 25 (39.1%) had isolated nocturnal hypoxemia, and 25 (39.1%) did not have either of the two sleep-disordered breathing conditions.

Table 1 presents the characteristics of the study sample. All patients had mild daytime hypoxemia, according to the selection criteria of the study. The sleep-disordered breathing (OSA or isolated nocturnal hypoxemia) group did not differ from the non-sleep-disordered breathing group on any baseline characteristics, except for PaO_2 as measured by arterial blood gas analysis, PaO_2 being significantly lower both in the OSA group ($p = 0.04$) and in the isolated nocturnal hypoxemia group ($p = 0.04$) than in the non-sleep-disordered breathing group. However, there was no statistically significant difference in PaO_2 between the OSA and isolated nocturnal hypoxemia groups ($p = 1.00$).

The median of the mean oxygen saturation as measured by oximetry during wakefulness on polysomnography was significantly lower in the OSA group ($p = 0.001$) and the isolated nocturnal hypoxemia group ($p < 0.0001$) than in the non-sleep-disordered breathing group. However, between the OSA and isolated nocturnal hypoxemia groups, these medians were not statistically significantly different. The same results were found for mean oxygen saturation during total sleep time, during rapid eye movement (REM) sleep, and during non-REM sleep, as well as for minimum oxygen saturation, time in minutes of oxygen saturation < 90%, and oxygen desaturation index during total sleep time, during REM sleep, and during non-REM sleep (Figure 2).

Sleep efficiency was reduced in all groups—OSA group: median = 70.3 and IQR: 58.5-76.5; isolated nocturnal hypoxemia group: median = 69.7 and IQR: 59.8-80.6; and non-sleep-disordered breathing group: median =70.6 and IQR: 57.1-82.9 ($p = 0.89$). There were no statistically significant differences in Epworth Sleepiness Scale scores among the OSA, isolated nocturnal hypoxemia, and non-sleep-disordered breathing groups (9.2 ± 4.1; 7.2 ± 4.3; and 7.3 ± 4.4, respectively; $p = 0.35$). The number of snoring-associated arousals was statistically higher in the OSA

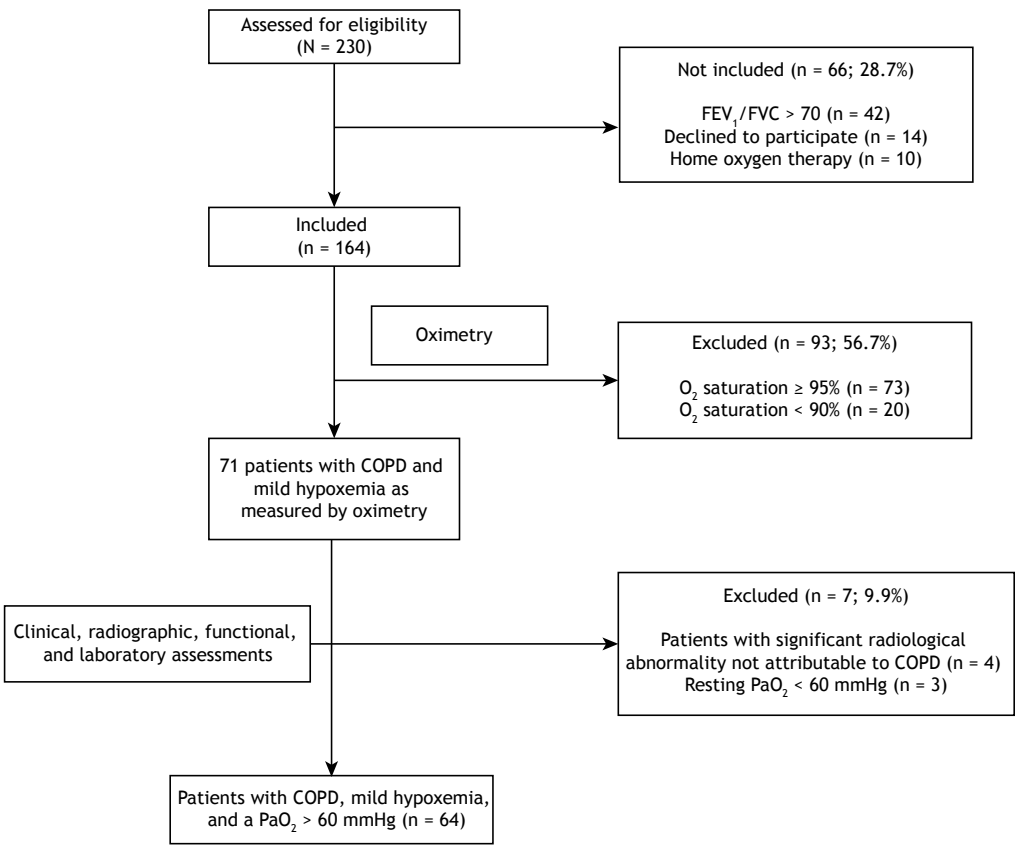

Figure 1. Study population flowchart.

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

Characteristic	Total sample (n = 64)	Subgroup			p
		OSA (n = 14)	Nocturnal hypoxemia (n = 25)	Non-SDB (n = 25)	
Age, years	69.7 ± 8.8	69.9 ± 6.1	68.9 ± 9.5	70.4 ± 9.5	0.84
Male gender, n (%)	36 (56.3)	8 (57.1)	11 (44)	17 (68)	0.23
BMI, kg/m^2	25.1 ± 5.2	26.9 ± 6.2	25.4 ± 5.9	23.8 ± 3.5	0.21
Neck circumference, cm	36.6 ± 4.9	37.8 ± 6.3	36.5 ± 4.0	35.9 ± 4.7	0.55
Socioeconomic score	17 (14-24)	19 (16-24)	16 (14-19)	17 (13-25)	0.49
Smoking history, pack-years	47.5 (26-60)	53.3 (35-60)	37 (22.5-60)	51 (30-66)	0.46
Smokers	17 (26.6)	5 (35.7)	9 (36)	3 (12)	
Former smokers/never smokers	47 (73.4)	9 (64.3)	16 (64)	22 (88)	0.11
MAP, mmHg	92.9 ± 10.5	95.2 ± 12.9	91.1 ± 9.2	93.3 ± 10.4	0.48
Hypertension, n (%)[b]	37 (57.8)	6 (42.9)	17 (68)	14 (56)	0.30
COPD classification, n (%)					
GOLD A	6 (9.4)	2 (14.3)	2 (8)	2 (8)	0.82
GOLD B	10 (15.6)	2 (14.3)	5 (20)	3 (12)	
GOLD C	2 (3.1)	0 (0)	0 (0)	2 (8)	
GOLD D	46 (71.9)	10 (71.4)	18 (72)	18 (72)	
Post-BD FEV_1, L	1.29 ± 0.6	1.45 ± 0.5	1.20 ± 0.6	1.30 ± 0.6	0.45
Post-BD FEV_1, %	50.2 ± 18.6	56.5 ± 18.4	48.2 ± 19.4	48.6 ± 17.8	0.36
Post-BD FEV_1/FVC, %	51.3 ± 12.1	57.1 ± 8.8	49.9 ± 14.4	49.5 ±10.6	0.13
PaO_2, mmHg	71.9 ± 9.8	69.0 ± 7.8	69.6 ± 9.9	76.0± 9.8	0.03*
$PaCO_2$, mmHg	35.1 ± 5.2	35.8 ± 5.9	36.3 ± 5.1	33.5 ± 4.7	0.15
O_2 saturation by ABG analysis, %	93.8 ± 2.1	93.2 ± 2.1	93.5 ± 1.9	94.5 ± 2.1	0.11
Pulmonary hypertension, n (%)	3 (4.7)	1 (7.1)	2 (8)	0 (0)	
Normal PASP, n (%)	30 (46.9)	7 (50)	14 (56)	9 (36)	0.20
Indeterminate PASP, n (%)[c]	31 (48.4)	6 (42.9)	9 (36)	16 (64)	
Desaturation during the 6MWT	17 (26.6)	4 (28.6)	8 (32)	5 (20)	0.67
6MWD, % of predicted	92.2 (82.4-107.7)	92.4 (84.8-102.8)	90.8 (82.4-107.6)	92.2 (82.1-108.3)	0.98
CAT	17 ± 7.1	14.4 ± 6.6	18 ± 6.8	17.4 ± 7.7	0.31

OSA: obstructive sleep apnea; SDB: sleep-disordered breathing; BMI: body mass index; MAP: mean arterial pressure; GOLD: Global Initiative for Chronic Obstructive Lung Disease; BD: bronchodilator; ABG: arterial blood gas; PASP: pulmonary artery systolic pressure; 6MWT: six-minute walk test; 6MWD: six-minute walk distance; and CAT: COPD Assessment Test. [a]Values expressed as mean ± SD or as median (interquartile range), except where otherwise indicated. [b]Pulmonary hypertension was defined as a PASP > 40 mmHg. [c]Indeterminate PASP was defined as the patient having no tricuspid regurgitation.

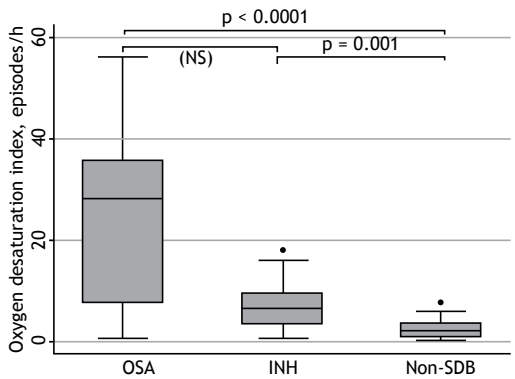

Figure 2. Oxygen desaturation index during rapid eye movement (REM) sleep and non-REM sleep in the obstructive sleep apnea (OSA), isolated nocturnal hypoxemia (INH), and non-sleep-disordered breathing (SDB) groups. NS: not significant.

group than in the isolated nocturnal hypoxemia group (p = 0.001) and the non-sleep-disordered breathing group (p = 0.0001), but there was no statistically significant difference in this number between the isolated nocturnal hypoxemia and non-sleep-disordered breathing groups (p = 0.20).

Correlation analysis showed that PaO_2 correlated moderately with mean oxygen saturation during total sleep time (r = 0.45; p = 0.0002), mean oxygen saturation during REM sleep (r = 0.43; p = 0.001), and mean oxygen saturation during non-REM sleep (r = 0.42; p = 0.001). In addition, a moderate correlation was observed between the AHI and the number of snore arousals (r = 0.53; p = 0.001). Multiple linear regression analysis was performed between the AHI as a continuous, dependent variable for OSA and clinical predictors (number of snoring-associated arousals, Epworth Sleepiness Scale score, age, body mass index, six-minute walk distance, neck circumference, oxygen saturation, PaO_2, $PaCO_2$, COPD Assessment Test score, FEV_1, FEV_1/FVC ratio, and mean arterial pressure), and no statistically significant coefficient

was found. The same results were found using other variables as dependent variables (time in minutes of oxygen saturation < 90% and time in minutes of oxygen saturation < 85%, respectively, during total sleep time, during REM sleep, and during non-REM sleep) and the same clinical predictors.

When considering the baseline characteristics, the groups differed only in PaO_2; therefore, a logistic regression analysis was conducted to determine whether PaO_2 could independently predict sleep-disordered breathing (OR = 0.93; 95% CI: 0.87-0.99; p = 0.02). After determination of the best cut-off point to identify sleep-disordered breathing (PaO_2 ≤ 70 mmHg), the model (OR = 4.59; 95% CI: 1.54-13.67; p = 0.01) had a specificity of 73.9% (95% CI: 51.6-89.8); a sensitivity of 63.4% (95% CI: 46.9-77.9); a positive predictive value of 81.3% (95% CI: 67.7-90.0); and a negative predictive value of 53.1% (95% CI: 41.4-64.4). The area under the ROC curve was 0.69 (95% CI: 0.57-0.80), and the proportion of correctly classified observations was 67.2%.

DISCUSSION

In our study sample, 60% of the patients with COPD for whom polysomnography was not formally indicated had sleep-disordered breathing. The prevalence of nocturnal hypoxemia found in the present sample (39%) can be considered high.[6-14] This is because the wide variation reported in the literature (from 27% to 84%) can be explained by the use of different definitions and inclusion criteria. For instance, Chaouat et al.[9] used severe daytime hypoxemia (PaO_2 < 60 mmHg) as an inclusion criterion and found a prevalence of 70%, whereas Vos et al.[8] included patients with OSA and patients with central hypoventilation in the group of those with nocturnal desaturation and did not use PaO_2 as an inclusion or exclusion criterion, finding a prevalence of 84%. Other studies have used pulse oximetry rather than polysomnography to diagnose nocturnal hypoxemia in small samples and found prevalence rates ranging from 47% to 52%.[10,11,13] In contrast, authors using methodologies similar to that of the present study have found similar prevalence rates.[7,12]

In the present study, PaO_2 was the independent variable predictive of sleep-disordered breathing among the patients with COPD and mild daytime hypoxemia. The high positive predictive value found (81.3%) demonstrates that the cut-off point of ≤ 70 mmHg can be useful in epidemiological settings where the prevalence of sleep-disordered breathing is high, which has been demonstrated to be the usual finding.[8-14] A previous study showed that subjects with a resting oxygen saturation ≥ 95% seldom have isolated nocturnal hypoxemia, which suggests that the investigation of this condition is unnecessary in this subgroup of patients.[11] According to the current indications for the use of home oxygen therapy in COPD, patients with an oxygen saturation < 90% (PaO_2 < 60 mmHg) should be evaluated and often require home oxygen therapy.[29] In our study sample, the subgroup of patients with COPD and daytime oxygen saturation between 90% and 94% (mild daytime hypoxemia) had a high prevalence of sleep-disordered breathing and benefited from polysomnography, although polysomnography in this context is not formally recommended by the literature. Several authors have attempted to predict nocturnal hypoxemia on the basis of patient characteristics or daytime physiological measurements.[6,7,10-14] However, this remains a controversial point, because although some authors have concluded that nocturnal desaturation cannot be predicted by any daytime functional measurement or anthropometric measurement, others have demonstrated that resting oxygen saturation and/or resting PaO_2 can predict nocturnal desaturation, although not accurately (correlation coefficients of 0.51-0.78).[6,7,10-13] This moderate correlation and the limited prediction ability found in the present study have been confirmed by other authors, suggesting that other factors can influence oxygenation during sleep.[6,7,11,13] Chaouat et al.[9] found that a high body mass index (BMI) was associated with nocturnal desaturation, and several authors have demonstrated that a high $PaCO_2$ can predict nocturnal desaturation.[7,11,14] The present study found no association between $PaCO_2$ and nocturnal hypoxemia. This could be due to a selection bias, given that the patients in our sample had less severe COPD than did those included in other studies evaluating patients with a PaO_2 < 60 mmHg.[7,9,11,14] The same may be true for BMI. It has been demonstrated that overweight and obesity can reduce FVC and expiratory reserve volume because of the loss in baseline lung volume.[28] However, the subjects in the present sample had a mean BMI of 25.1 kg/m^2, which is considered normal. Scott et al.[30] showed that desaturation during the 6MWT was associated with nocturnal hypoxemia (OR = 3.77, 95% CI: 1.87-7.62). Although it is possible to suggest that a lower baseline oxygen saturation may leave subjects prone to having desaturation at night and during exercise, the physiological factors related to the two conditions are different. During exercise, increased peripheral oxygen extraction, worsening of the ventilation/perfusion ratio, and dynamic hyperinflation are the causes of hypoxemia,[31] whereas, during sleep, reduced ventilation due to decreased responsiveness of the respiratory center, reduced accessory muscle contribution, decreased functional residual capacity, and increased closing volume, especially during REM sleep, are the factors producing hypoxemia.[32] The present study and two other studies also failed to demonstrate that desaturation during exercise can predict nocturnal hypoxemia.[10,13]

Although the prevalence of OSA found in the present study (21.8%) is within the range reported in the literature, it is higher than that reported in some studies, which is probably due to the prevalence of males and advanced age subjects in our sample, as the prevalence of OSA is higher in males and increases with age.[32]

The relatively high prevalence of OSA found in the patients with COPD and mild hypoxemia (22%) and the reduced prevalence of clinical characteristics classically associated with OSA—systemic arterial hypertension (SAH), a high BMI, a large neck circumference, and daytime sleepiness—in this subgroup are noteworthy. The OSA group did not show a higher prevalence of SAH or have a higher level of systemic arterial pressure compared with the other groups. In addition, the results for BMI, neck circumference, and the Epworth Sleepiness Scale in the OSA group were not statistically different from those in the other groups. Venkateswaran & Tee,[33] in comparing COPD patients with and without OSA, also found similar results. Because of systemic inflammation, patients with COPD may have a reduction in BMI and a predisposition to SAH,[34] and, because of the respiratory disease, they may have decreased sleep efficiency.[11] Therefore, the high prevalence of SAH, the lower BMI, with a consequently smaller neck circumference, and the lower sleep efficiency observed in all groups can explain the absence of a typical clinical profile of OSA in patients with COPD.

Measurement of oxygen saturation is routinely used for the evaluation of patients with COPD because of its many advantages over blood gas analysis (it is noninvasive, painless, and inexpensive, provides immediate results, and is widely available).[35] In view of the findings of the present study, and in the light of the established value of oximetry as an indication for oxygen supplementation and for hospitalization in cases of acute exacerbation,[36] oximetry could also be used to screen patients with stable COPD for sleep-disordered breathing. When oximetry readings are between 90% and 94%, blood gas analysis could be requested. A PaO_2 finding of ≤ 70 mmHg is associated with the presence of sleep-disordered breathing and would be an indication for requesting polysomnography.

Despite being considered the gold standard for the diagnosis of OSA syndrome, polysomnography is an expensive and technically complex test; therefore, laboratories specializing in polysomnography are scarce. To overcome this obstacle, clinical screening questionnaires should be used to identify patients at high risk for OSA, who would benefit from receiving a diagnosis and treatment as soon as possible. Studies demonstrate that portable devices have proven to be able to provide a diagnosis equivalent to that provided by in-laboratory polysomnography, at least in patients with a high likelihood of OSA.[37,38]

The present study has several limitations. All polysomnography tests were single-night measurements. Sleep changes associated with the initial experience of patients in a sleep laboratory are well known; therefore, in some studies, the first night is only used for acclimatizing patients. If sleep is disturbed in COPD patients, arousals may prevent deep sleep and desaturation. As a result, we could have underestimated nocturnal oxygenation by evaluating a single night's sleep. However, most studies that used polysomnography to diagnose nocturnal hypoxemia in patients with COPD made a single-night assessment,[6,7,9,10,13,14] and some authors have shown that there are no significant differences in mean oxygen saturation between consecutive and non-consecutive nights in the sleep laboratory.[35] Thus, the use of single-night polysomnography may not have affected our results. Our study was designed to assess the prevalence of sleep-disordered breathing in a subgroup of COPD patients with minor functional impairment (mild hypoxemia). The exclusion of COPD patients with moderate or severe hypoxemia may have introduced a selection bias, because patients, according to daily clinical practice, have various levels of hypoxemia, ranging from normoxemia to severe hypoxemia. In addition, for proper analysis of prevalence, there would be the need for an external control group.

In conclusion, the prevalence of sleep-disordered breathing in our sample of patients with COPD and mild hypoxemia was found to be high (61%), and a PaO_2 finding of ≤ 70 mmHg on arterial blood gas analysis was significantly associated with sleep-disordered breathing (OR = 4.59; 95% CI: 1.54-13.67; p = 0.01). These results indicate that this subgroup of patients with COPD and mild hypoxemia would benefit from sleep studies.

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ORIGINAL ARTICLE

Simple motor tasks independently predict extubation failure in critically ill neurological patients

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ABSTRACT

Objective: To evaluate the usefulness of simple motor tasks such as hand grasping and tongue protrusion as predictors of extubation failure in critically ill neurological patients. **Methods:** This was a prospective cohort study conducted in the neurological ICU of a tertiary care hospital in the city of Porto Alegre, Brazil. Adult patients who had been intubated for neurological reasons and were eligible for weaning were included in the study. The ability of patients to perform simple motor tasks such as hand grasping and tongue protrusion was evaluated as a predictor of extubation failure. Data regarding duration of mechanical ventilation, length of ICU stay, length of hospital stay, mortality, and incidence of ventilator-associated pneumonia were collected. **Results:** A total of 132 intubated patients who had been receiving mechanical ventilation for at least 24 h and who passed a spontaneous breathing trial were included in the analysis. Logistic regression showed that patient inability to grasp the hand of the examiner (relative risk = 1.57; 95% CI: 1.01-2.44; $p < 0.045$) and protrude the tongue (relative risk = 6.84; 95% CI: 2.49-18.8; $p < 0.001$) were independent risk factors for extubation failure. Acute Physiology and Chronic Health Evaluation II scores ($p = 0.02$), Glasgow Coma Scale scores at extubation ($p < 0.001$), eye opening response ($p = 0.001$), MIP ($p < 0.001$), MEP ($p = 0.006$), and the rapid shallow breathing index ($p = 0.03$) were significantly different between the failed extubation and successful extubation groups. **Conclusions:** The inability to follow simple motor commands is predictive of extubation failure in critically ill neurological patients. Hand grasping and tongue protrusion on command might be quick and easy bedside tests to identify neurocritical care patients who are candidates for extubation.

Keywords: Ventilator weaning; Airway extubation/adverse effects; Critical care; Neurosurgery.

INTRODUCTION

Extubation failure and need for reintubation occur in 2-25% of mechanically ventilated patients in the ICU. These rates vary depending on the type of patient and the weaning protocol used.[1] In the last decades, several studies have focused on predictors of successful ventilator weaning.[2,3] More recently, several authors have emphasized the need for better predictors of extubation outcome in patients with neurological injuries.[4-7] Predictors of extubation success in critically ill neurological patients range from subjective signs to more complex assessments that are mainly based on objective respiratory parameters.[2,8,9] However, there is no consensus regarding the best predictors of successful weaning and extubation in such patients, and results have varied across studies,[8,10] certain predictors having failed to guide the decision making process. Parameters such as being able to stick out the tongue, having a gag reflex, and being able to follow specific commands have been investigated as more reliable tools to assess the level of consciousness and the ability to protect the airway.[4-7,9,11,12] However, in a neurological critical care setting, adequate parameters for extubation have yet to be defined.

The objective of the present study was to evaluate the usefulness of simple motor tasks such as hand grasping and tongue protrusion as predictors of extubation failure in critically ill neurological patients. This was done in an attempt to provide simple clinical tools to identify candidates for extubation in the neurological ICU.

METHODS

This was a prospective cohort study conducted in the ICU of *Hospital Cristo Redentor*, in the city of Porto Alegre, Brazil, between October of 2010 and December of 2011. *Hospital Cristo Redentor* is a 290-bed regional referral center for trauma care and neurosurgery, approximately 300 patients being referred to the hospital every day. The ICU is a closed unit comprising 29 beds, care being provided by physicians in routine practice and on duty, as well as by five physiotherapists working during the day shift.

The inclusion criteria were as follows: being an ICU patient; having been on mechanical ventilation for ≥ 24 h; being ≥ 18 years of age; having a neurological disorder

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or brain injury; and being eligible for weaning. The exclusion criteria were as follows: having a spinal cord injury; having thoracic or abdominal trauma; having a peripheral neuromuscular disorder; and being a patient whose legal guardian(s) or caregiver(s) did not give written informed consent. Figure 1 shows a schematic diagram of patient selection. The study was approved by the local research ethics committee and was conducted in accordance with the provisions of the Declaration of Helsinki. Written informed consent was obtained from the legal guardians or caregivers of all participating patients.

All participating patients had been on mechanical ventilation (Evita 4; Drägerwerk AG & Co. KGaA, Lübeck, Germany; or Servo-i; MAQUET Holding B.V. & Co. KG, Rastatt, Germany) for ≥ 24 h. The criteria for extubation were as follows: adequate oxygenation (PaO_2 > 60 Torr [8 KPa]; FiO_2 < 0.4; positive end-expiratory pressure < 6 Torr [0.8 KPa], and PaO_2/FiO_2 > 150); cardiovascular stability (HR < 130 bpm and mean blood pressure > 60 Torr [8 KPa], with minimal or no use of vasopressors); axillary temperature < 37.5°C; hemoglobin level > 8 g/dL; Glasgow Coma Scale (GCS) score ≥ 8; normal acid-base balance; and normal electrolyte balance.[13] Patients who passed a spontaneous breathing trial (SBT) were extubated. The criteria for a failed SBT were as follows: SaO_2 < 90%; RR > 35 breaths/min; HR > 130 bpm; a > 20% decrease or increase in systolic or diastolic blood pressure; diaphoresis; and psychomotor agitation.[14] All SBTs were performed with a T-piece, supplemental oxygen, and an FiO_2 ≤ 0.4 for 30-120 min.

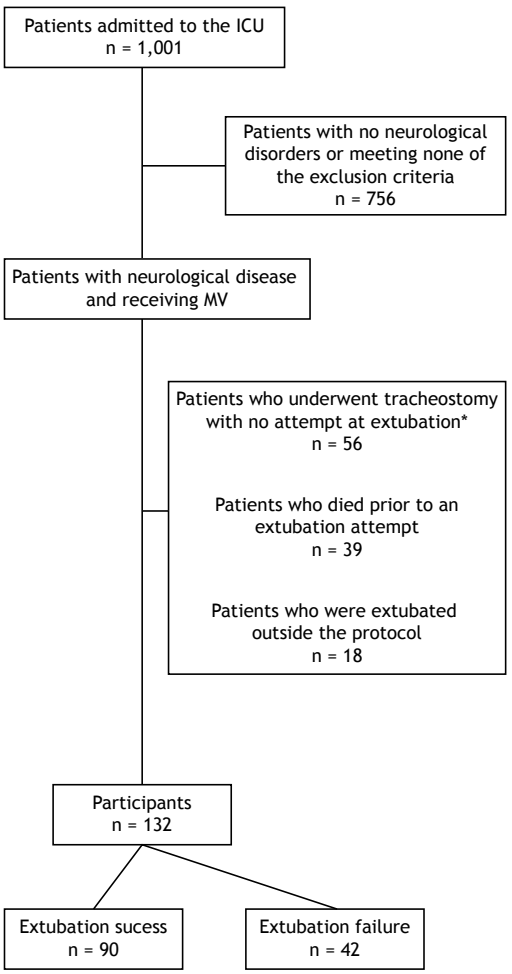

Figure 1. Schematic diagram of patient selection. MV: mechanical ventilation. *Patients with a Glasgow Coma Scale score of < 8.

Before weaning, MEP and MIP were measured with a digital manometer (MVD-500, version 1.1; Globalmed, Porto Alegre, Brazil), being defined as the most positive and negative values, respectively, produced by three consecutive respiratory efforts against a unidirectional valve after 30 s of occlusion. All results were recorded on a data collection sheet. The frequency-to-tidal volume ratio (f/V_T), minute volume, and RR were measured with a spirometer attached to the endotracheal tube (model RM 121; Datex-Ohmeda, Inc., Madison, WI, USA). The GCS score was obtained immediately before the SBT. Given that intubated patients are unable to speak, their verbal response score is 1 (no response). The best motor response was defined as the ability to grasp and release the hand of the examiner on command twice consecutively, a score of 6 indicating the presence of motor response and a score of < 6 indicating the absence of motor response. In addition, all patients underwent a tongue protrusion test of motor function consisting of sticking out their tongue on command. For patients who were unresponsive to verbal commands, the examiner demonstrated tongue protrusion.

For each patient, information was collected on the following: demographic characteristics; diagnosis at ICU admission; GCS scores at admission and at extubation; Acute Physiology and Chronic Health Evaluation II (APACHE II) score; length of ICU stay (in days); duration of mechanical ventilation (in days); cardiorespiratory variables after 30 or 120 min of spontaneous breathing; and incidence of ventilator-associated pneumonia.

Extubation failure was defined as the need for reintubation within 48 h of extubation. All of the patients who were successfully extubated were monitored throughout their hospital stay (until discharge) for complications requiring reintubation or tracheostomy, as well as for pneumonia and death. The diagnosis of pneumonia was established by a staff physician and was based on the criteria established by the local department of infection control, in accordance with the Brazilian National Health Surveillance Agency criteria and the American Thoracic Society guidelines for the management of adults with ventilator-associated pneumonia.[15,16]

Continuous variables were expressed as mean and standard deviation or median and interquartile range, whereas categorical variables were expressed as absolute numbers and proportions. Comparisons between groups at baseline were performed with the Student's t-test or the Mann-Whitney U test for continuous variables and the chi-square test or

Fisher's exact test for categorical variables. When necessary, the chi-square test was followed by analysis of adjusted residuals. The primary outcome measure was extubation failure or success. The relative risk was calculated as a measure of strength of association between predictive variables and the binary outcomes of interest. Sensitivity, specificity, and likelihood ratios for predicting extubation failure were also calculated. Variables with a value of $p < 0.2$ were included in a Poisson regression model in order to compare extubation success and failure rates. Data were analyzed with the Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago, IL, USA). The significance level was set at $p < 0.05$.

RESULTS

A total of 132 patients were included in the analysis. The demographic characteristics, ventilator settings, and clinical parameters are described in Table 1. Mean patient age was 47.8 ± 17.1 years, and 71.2% were male. Mean APACHE II score was 18.8 ± 5.41. Median duration of mechanical ventilation was 8 days (interquartile range, 3-11.7 days). As can be seen in Table 1, the most common reasons for ICU admission and orotracheal intubation were traumatic brain injury (n = 62), subarachnoid hemorrhage (n = 15), postoperative complications of tumor surgery (n = 8), and hemorrhagic stroke (n = 43).

Of the 132 patients included in the analysis, 42 (31.8%) failed extubation and were reintubated within 48 h. When the patients were grouped by GCS score, failure rates were 57.8% in the 8-9 group and 15.7% in the 10-11 group ($p < 0.001$). Attempts at extubation failed because of a change in the level of consciousness (in 7%), accumulation of bronchial secretions (in 31%), and inability to maintain airway patency (in 62%). A second attempt at extubation was made in 10 (23.8%) of the 42 patients who failed extubation, 30 (71.43%) of whom underwent tracheostomy and 2 of whom (4.76%) died.

No significant differences were found between the successful extubation group and the failed extubation group regarding hemodynamic variables and arterial blood gases at extubation. The length of ICU stay, the length of hospital stay, and ICU outcomes were significantly different between the successful extubation group and the failed extubation group, as was the incidence of ventilator-associated pneumonia (Table 2).

As can be seen in Table 3, there were statistically significant differences between the successful extubation group and the failed extubation group regarding the ability to respond to commands, as assessed by GCS scores and the tongue protrusion test of motor function ($p < 0.001$). The patients who were unable to stick out their tongue on command were nine times as likely to fail extubation as were those who were able to do that (relative risk = 9.5; 95% CI: 3.59-25.1; $p < 0.001$). Motor response as assessed by GCS scores also showed a high relative risk coefficient, and the patients who were unable to grasp the hand of the

Table 1. Demographic characteristics, ventilator settings, and clinical parameters in a sample of 132 mechanically ventilated patients in the ICU.[a]

Variable	Total (n = 132)	Extubation success (n = 90)	Extubation failure (n = 42)	p
Age, years	47.8 ± 17.01	47.7 ± 17.2	48.2 ± 16.7	0.875*
Male gender, n (%)	61 (72.6)	66 (73.3)	28 (66.7)	0.561†
APACHE II score	18.87 ± 5.41	18.2 ± 5.7	20.4 ± 4.4	0.024*
GCS score at admission	7.77 ± 2.14	7.94 ± 2.13	7.40 ± 2.16	0.79*
GCS score at extubation	9.66 ± 1.29	10.1 ± 0.95	8.81 ± 0,52	< 0.001*
Reasons for ICU admission, n (%)				0.073†
SAH	15 (11.4)	7 (7.8)	8 (19)	
ICH	43 (35.6)	32 (35.6)	15 (35.7)	
POC of tumor surgery	8 (6.1)	8 (8.9)	0 (0.0)	
TBI	62 (47)	43 (47.8)	19 (45.2)	
PEEP, cmH_2O	5.27 ± 0.46	5.25 ± 0.45	5.31 ± 0.47	0.516
FiO_2, %	34 ± 0.49	34 ± 0.41	34 ± 0.63	0.921*
V_T, mL	522 ± 134	533 ± 139	499 ± 122	0.180*
MV, days[b]	8.0 (3-11.75)	6 (3-10)	11 (6-14)	< 0.001‡
PSV	3.57 ± 3.17	2.81 ± 2.32	5.21 ± 4.06	< 0.001*
PCV	4.80 ± 3.62	4.38 ± 3.64	5.69 ± 3.46	0.055
MIP, cmH_2O[b]	65.5 (46-83)	70 (52-87)	48 (37-67)	< 0.001‡
MEP, cmH_2O[b]	59 (44-75)	63 (48-83)	50 (41-65)	0.006‡
f/V_T, breaths/min/L[b]	45 (34-56)	43 (31-53)	52.5 (38.8-58)	0.038‡

APACHE II: Acute Physiology and Chronic Health Evaluation II; GCS: Glasgow Coma Scale; SAH: subarachnoid hemorrhage; ICH: intracerebral hemorrhage; POC: postoperative complication; TBI: traumatic brain injury; PEEP: positive end-expiratory pressure; V_T: tidal volume; MV: mechanical ventilation; PSV: pressure support ventilation; PCV: pressure-controlled ventilation; and f/V_T: frequency-to-tidal volume ratio. [a]Values expressed as mean ± SD, except where otherwise indicated. [b]Values expressed as median (interquartile range). *Student's t-test. †Pearson's chi-square test. ‡Mann-Whitney U test.

examiner on command were three times as likely to fail extubation as were those who were able to do that (relative risk = 3.38; 95% CI: 2.07-5.53; p < 0.001).

The likelihood ratios for predicting extubation failure were 2.06 for a motor score of < 6 and 7.35 for the inability to stick out the tongue (Table 4). A likelihood ratio > 1 indicated a progressively higher probability of extubation failure, a motor score of < 6 indicated a lower probability of extubation failure, and the inability to stick out the tongue on command indicated a moderate probability of extubation failure, being a more specific variable for risk prediction. After a Poisson regression multivariate analysis, only a motor score of < 6 (relative risk = 1.57; 95% CI: 1.01-2.44; p = 0.045) and the inability to protrude the tongue on command (relative risk = 6.84; 95% CI: 2.49-18.8; p < 0.001) remained significantly associated with extubation failure.

DISCUSSION

In ICU patients receiving mechanical ventilation, evaluation of predictors of extubation outcome is an important step in the weaning process.[3] However, in the neurocritical care setting, the most widely used weaning and extubation parameters are not accurate enough to predict the risk of extubation failure.[6,7,11,17] Evidence-based guidelines recommend that extubation be considered after reversal of the underlying cause of respiratory failure.[13] However, in patients with neurological injuries, motor and cognitive sequelae can considerably affect their ability to protect the airway, regardless of their ability to maintain spontaneous ventilation.[18]

Most studies investigating clinical or mixed populations have reported mean extubation failure rates ranging from 15% to 25%.[4,19,20] The extubation failure rate in our study was 31.2%, which is similar to those reported by Vallverdú et al. (i.e., 35%)[9] and Namen et al. (i.e., 38%)[21] but higher than those found in populations with a similar profile (i.e., approximately 17%).[6,11,22] Extubation failure rates vary across studies examining weaning and extubation in critically ill neurological patients in whom neurological injury constituted the primary cause of respiratory failure and who were considered for weaning on the basis of predictors established for the general population. This variability reinforces the need for evaluation criteria to define the parameters that are associated with the risk of extubation failure. In our study, extubation failure was found to be associated with a longer ICU stay, a longer hospital stay, a higher incidence of ventilator-associated pneumonia, and a higher mortality rate, a finding that is consistent with those of previous studies.[1,19,22-25]

In the present study, there were significant differences between the successful extubation group and the failed extubation group regarding APACHE II scores, MIP values, MEP values, and the rapid shallow breathing index, which was used in order to assess f/V_T. However, when f/V_T and the aforementioned variables were included in the logistic regression model, they were found to be inaccurate in predicting the risk of extubation failure in our population of neurological patients.

Our findings show that, in a population of patients with acute neurological disease, the inability to respond to commands is significantly associated with the probability of extubation failure. In addition, the inability to protrude the tongue, regardless of whether or not the patient was able to grasp the hand of the examiner on command (limb motor response), was associated with a high risk of extubation failure, being an independent predictor of extubation failure.

Although a GCS cut-off score of 8 has been used for risk assessment, verbal response cannot be reliably assessed when an artificial airway is present.[26,27] In this sense, our findings support the concern that a cut-off score ≥ 8 might not be a reliable parameter, given that mathematical combinations can result in a score of 8 even when the patient is unable to respond to commands.[4-6]

In a prospective observational cohort study of 122 patients, Mokhlesi et al.[28] found that a GCS score of <

Table 2. Extubation outcomes.[a]

Variable	Success (n = 90)	Failure (n = 42)	p
Length of ICU stay, days	12 (7-17)	17 (14-23)	< 0.001*
Length of hospital stay, days	25 (17-30)	30 (21-51)	0.009*
ICU outcome[b]			0.017†
Discharge	84 (93.3)	36 (85.7)	
Death	1 (1.1)	5 (11.9)‡	
Transfer to another hospital	5 (5.6)	1 (2.4)	
Hospital outcome[b]			0.015†
Discharge	77 (85.6)	28 (66.7)	
Death	4 (4.4)	8 (19)‡	
Transfer to another hospital	9 (10)	6 (14.3)	
VAP[b]	31 (34.4)	23 (54.8)	0.027†

VAP: ventilator-associated pneumonia. [a]Values expressed as median (interquartile range), except where otherwise indicated. [b]Values expressed as n (%). *Mann-Whitney U test. †Pearson's chi-square test. ‡Analysis of adjusted residuals revealed a statistically significant association (level of significance, 5%). Length of ICU stay, length of hospital stay, mortality, and VAP incidence were significantly higher in the extubation failure group.

Table 3. Motor variables, by extubation outcome.[a]

Variable	Success (n = 90)	Failure (n = 42)	p*
Best motor response (hand grasping)			< 0.001
< 6 (unable to respond)	15 (16.7)	25 (59.5)	
= 6 (able to respond)	75 (83.3)	17 (40.5)	
Laterality of motor response			0.132
Bilateral	39 (43.3)	10 (25)	
Right	29 (32.2)	18 (45)	
Left	22 (24.4)	12 (30)	
Eye opening response			< 0.001
4- spontaneous	41 (45.6)	14 (33.3)	
3- to speech	37 (41.1)†	8 (19)	
2- to pain	9 (10)	17 (40.5)	
1- no response	3 (3.3)	3 (7.1)	
Tongue protrusion test			< 0.001
Positive	62 (68.9)	4 (9.5)	
Negative	28 (31.1)	38 (90.5)	

[a]Values expressed as n (%). *Pearson's chi-square test. †Analysis of adjusted residuals revealed a statistically significant association (level of significance, 5%).

Table 4. Variables predictive of extubation failure, after Poisson correction.

Variable	Sensitivity, %	Specificity, %	Likelihood ratio	Relative risk (95% CI)
Best motor response				
< 6*	83.3	59.5	2.06	1.57 (1.01-2.44)
Tongue protrusion test				
Negative	68.9	90.5	7.35	6.84 (2.49-18.8)

*The best motor response was defined as the ability to grasp and release the hand of the examiner on command twice consecutively, a score of 6 indicating the presence of motor response and a score of < 6 indicating the absence of motor response. A likelihood ratio > 1 indicates a high probability of extubation failure, a motor score of < 6 indicates a low probability of extubation failure, and a negative tongue protrusion test indicates a moderate probability of extubation failure.

10 was a predictor of extubation failure. Vidotto et al.[7] prospectively evaluated 92 patients who had undergone elective craniotomy and found that reintubation was required in 12% of those with a GCS score of 10-11 and in 56% of those with a GCS score of 8-9. These rates are very similar to the extubation failure rates found in the present study for GCS scores of 8-9 and 10-11 (i.e., 15.7% and 57.8%, respectively). In contrast, Coplin et al.,[22] evaluating the implications of extubation delay in a cohort of 136 brain-injured patients, found a success rate of 80% for patients with a GCS score ≤ 8 and a success rate of 91% (10 out of 11 patients) for patients with a GCS score ≤ 4, with a significant increase in the incidence of pneumonia, length of ICU stay, and length of hospital stay in patients whose extubation was delayed on the basis of assessment of neurological function. We agree that delayed extubation in patients capable of spontaneous breathing and airway protection increases the risk of infections and the costs of care. However, our findings show that there is an increased risk of extubation failure in patients who are unable to perform simple motor tasks on command.

Salam et al.[4] evaluated the ability of 88 clinical patients who had passed an SBT to complete four simple tasks (open eyes, follow with eyes, grasp hand, stick out tongue) before extubation and found that those who were unable to complete all four tasks were four times as likely to require reintubation as were those who completed the four tasks. Frutos-Vivar et al.,[20] in a prospective study evaluating the mental status of 900 patients immediately prior to extubation, subjectively defined (by the ability of patients to cooperate) as poor, moderate, or excellent, found no statistically significant difference in poor patient cooperation between patients who were reintubated and those who were not (39% vs. 32%). However, because the ability of patients to cooperate was subjectively evaluated, the methods cannot be reliably reproduced.

In the present study, the ability of patients to respond to commands was determined on the basis of their GCS motor response scores (i.e., their ability to grasp the hand of the examiner) and their ability to protrude their tongue on command. In patients whose motor score was < 6, the extubation failure rate was 59.6%; in those who were unable to stick out their tongue on command, the extubation failure rate was 90.5%. These findings support concerns about assessing patient mental status with the GCS, given

that all of the patients included in the study had GCS scores ≥ 8.[4-6]

According to Stocchetti et al.,[18] neurological patients commonly have cranial nerve deficits and are unable to protect their airway. In cases of traumatic brain injury, subarachnoid hemorrhage, intracerebral hemorrhage, and posterior fossa surgery, as well as in many other neurological disorders, the inability to swallow and to clear airway secretions has a considerable impact on the ability of patients to breathe without assistance, and a simple inspection of the tongue, both at rest and protruded, can aid in identifying cases of loss of airway protective reflexes. However, bedside assessment of tongue protrusion might not be sufficient to determine the risk of dysphagia or aspiration, which can only be assessed by videofluoroscopy. Nevertheless, it is not feasible to perform videofluoroscopy in orotracheally intubated patients, and the findings of the present study show that the inability to stick out the tongue on command is associated with a moderate risk of extubation failure.

Anderson et al.[6] evaluated neurological assessment variables and extubation outcomes in patients in a neurocritical care unit and found that the presence of an endotracheal tube, fastening tape, and orolingual edema can prevent patients from protruding their tongue on command and therefore excluded this parameter from their analysis of 378 weaning and extubation processes. In the presence of edema—or if the presence of an endotracheal tube is a major factor limiting tongue protrusion—airway patency and the ability to protect the airway might be impaired, and this impairment has an impact on extubation outcomes. In our study, multivariate regression analysis showed that the inability to protect the airway was significantly associated with extubation failure.

According to Anderson et al.,[6] the type of command used is an essential component of the assessment process; eye opening to verbal command and following the examiner with the eyes might be excitatory responses to stimuli rather than volitional events, whereas grasping the hand of the examiner might be a primitive reflex, therefore being inaccurate in evaluating the ability of patients to respond to commands. The ability of patients to perform a simple motor task (i.e., hand grasping) is routinely evaluated in the ICU and was used in our study in order to differentiate between a reflex response and the ability to respond to commands, the test being considered positive when patients were able to grasp and release the hand of the examiner on command twice consecutively.

The inability to follow simple motor commands is predictive of extubation failure in critically ill neurological patients. The best motor response scores on the GCS and a simple bedside assessment of the ability of patients to protrude their tongue can inform clinical decisions regarding extubation. If our results are confirmed in other studies, the aforementioned parameters might be used as quick and easy screening tests to identify critically ill neurological patients who can be successfully extubated.

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ORIGINAL ARTICLE

Ultrasound-guided intrapleural positioning of pleural catheters: influence on immediate lung expansion and pleurodesis in patients with recurrent malignant pleural effusion

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ABSTRACT

Objective: To evaluate the role of intrapleural positioning of a pleural catheter in early lung expansion and pleurodesis success in patients with recurrent malignant pleural effusion (RMPE). **Methods:** This was a retrospective study nested into a larger prospective cohort study including patients with RMPE recruited from a tertiary university teaching hospital between June of 2009 and September of 2014. The patients underwent pleural catheter insertion followed by bedside pleurodesis. Chest CT scans were performed twice: immediately before pleurodesis (iCT) and 30 days after pleurodesis (CT30). Catheter positioning was categorized based on iCT scans as posterolateral, anterior, fissural, and subpulmonary. We used the pleural volume on iCT scans to estimate early lung expansion and the difference between the pleural volumes on CT30 and iCT scans to evaluate radiological success of pleurodesis. Clinical pleurodesis success was defined as no need for any other pleural procedure. **Results:** Of the 131 eligible patients from the original study, 85 were included in this nested study (64 women; mean age: 60.74 years). Catheter tip positioning was subpulmonary in 35 patients (41%), anterior in 23 (27%), posterolateral in 17 (20%), and fissural in 10 (12%). No significant differences were found among the groups regarding early lung expansion (median residual pleural cavity = 377 mL; interquartile range: 171-722 mL; p = 0.645), radiological success of pleurodesis (median volume = 33 mL; interquartile range: −225 to 257 mL; p = 0.923), and clinical success of pleurodesis (85.8%; p = 0.676). **Conclusions:** Our results suggest that the position of the tip of the pleural catheter influences neither early lung expansion nor bedside pleurodesis success in patients with RMPE.

Keywords: Pleurodesis; Pleural effusion, malignant; Tomography; Catheters.

INTRODUCTION

Chest tubes are used to remove liquid or air from the pleural space. Quite often, patients with recurrent malignant pleural effusion (RMPE) undergo chest tube insertion not only to allow lung reexpansion but also as an access route for bedside pleurodesis. Therefore, in the RMPE scenario, the purpose of using a chest tube is to promote proper emptying of pleural fluid and to allow adequate contact between pleural surfaces, an important fact for successful pleurodesis. In addition, the chest tube must allow easy distribution of the sclerosing agent over the pleural surface.[1]

Large-bore tubes (≥ 24 Fr) have been widely used as an access route for bedside pleurodesis.[2] However, pain is an issue both during tube insertion and during the time the tube is in place.[3] Smaller chest tubes (≤ 14 Fr) cause less pain, are easier to insert, and appear to reduce the risk of complications.[4] Moreover, three randomized trials concluded that large-bore and small-bore tubes have equivalent efficacy in the palliation of RMPE.[5-7]

Because of the lack of evidence, positioning a chest tube is considered an issue by many. Manuals, guidelines, and review articles have suggested that the tube should lie posteriorly in the pleural cavity and directed to its apex; this statement makes sense anatomically speaking.[4,8,9] Although it is easier to insert a small-bore chest tube or a pleural catheter, it is not so easy to locate its tip inside the pleural cavity. There is little evidence in the literature addressing this issue. Therefore, the objective of the present study was to evaluate the role of intrapleural positioning of a pleural catheter in early lung expansion and pleurodesis success in patients with RMPE.

METHODS

This was a retrospective study nested into a larger prospective cohort study whose aim was to evaluate the role of elastance in the success of pleurodesis in patients with RMPE (ClinicalTrials.gov Identifier: NCT01819363). All variables and outcomes were defined beforehand and were prospectively collected. The main study has been

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completed, but the manuscript had yet to be sent for publication when the present one was submitted. All participating patients gave written informed consent, and the study was approved by the local research ethics committee (CAPPesq HCFMUSP-0654/11).

Patients were recruited between June of 2009 and September of 2013 at the University of São Paulo Medical School *Hospital das Clínicas*, a tertiary university teaching hospital located in the city of São Paulo, Brazil. The inclusion criteria were symptomatic RMPE (highly suspected or confirmed either by cytology or pleural biopsy), complete or partial lung expansion (≥ 70%) after pleural drainage, and a Karnofsky Performance Status index > 30. Highly suspected RMPE was considered when exudates from patients with confirmed metastatic cancer presented with lymphocytic predominance and low adenosine deaminase values. The exclusion criteria were age < 18 years, previous pleural procedures, hemorrhagic diathesis, current infection, massive skin infiltration, and inability to understand quality-of-life questionnaires.

After being included, the participating patients were positioned in orthostatic position, and chest ultrasonography was performed by the attending physician (a board-certified thoracic surgeon) in order to select the best site for catheter placement. The preferred site was the most inferior position that was closest to the mid-axillary line; nevertheless, the placement varied considerably depending on ultrasound findings. After local anesthesia (lidocaine 2%), pleural drainage was carried out with a 14-Fr pigtail catheter (C-UPTP-1400-WAYNE; Cook Medical, Bloomington, IN, USA) using the trocar technique. Whenever possible, we tried to push the tip of the catheter cranially and posteriorly.

Two days after pleural drainage, the patients were evaluated for lung expansion by means of a chest X-ray. The patients who presented with lung expansion ≥ 70% of the affected hemithorax (as adjudicated by two different raters) were considered eligible for pleurodesis; the remaining patients were excluded from the study. Prior to pleurodesis, the elected participants underwent an initial CT (iCT) of the chest. Then, pleurodesis was carried out using 30 mL of 0.5% silver nitrate solution or 3.6 g of talc in 60 mL of saline solution instilled through the catheter. The pleural catheter was removed 3-5 days after pleurodesis if the volume drained in 24 h was smaller than 200 mL. All patients were followed closely at our outpatient clinic, with particular attention to adverse events and recurrences. On the 30th day after pleurodesis, the participants underwent another CT of the chest (CT30).

Outcome measure

The independent variable in the present study was the position of the intrapleural catheter, which was categorized as posterolateral, anterior, fissural, or subpulmonary positioning according to the location of the fenestrated portion of the catheter (tip of the pigtail catheter). Examples of each category are depicted in Figure 1. Two independent raters (board-certified thoracic surgeons), blinded to the outcome of the patients, analyzed the images and classified the patients into the abovementioned categories. When there was a disagreement between the raters, a third researcher evaluated the CT images and solved the impasse.

The dependent variables were early lung expansion and pleurodesis success. Both were evaluated according to residual pleural fluid or residual pleural cavity volumes as measured by CT of the chest. A radiologist specializing in thoracic radiology calculated the pleural volumes. The analyses were made with the software Aquarius Intuition Viewer® (TeraRecon, Foster City, CA, USA) using the segmentation analysis and tracking tool, which is suitable for the analysis and characterization of masses and segmented structures on CT scans; the area of interest is selected, and the program calculates its volume. Even after this initial calculation, it is possible for the radiologist to make any necessary corrections with the addition of targeted areas that were not included in the first assessment. We calculated the volumes in mL. Early lung expansion was determined with the calculation of the pleural volume at iCT. Pleurodesis success was confirmed by the difference between the measurements of pleural volumes at CT30 and those at iCT. Pleurodesis success was also evaluated along the follow-up period as a binary variable (success or failure). Pleurodesis failure was defined as the need for any new procedure involving the pleura during the follow-up period. New procedures were indicated by the medical team of the pleural disease group when the patient presented recurrence of symptoms (dyspnea or chest pain) associated with radiological evidence of RMPE reaccumulation on chest X-ray or CT. We classified the adverse events according to the Common Terminology Criteria for Adverse Events version 4.0[10] as major events (score ≥ 3) or minor events (score ≤ 2).

Statistical analysis

Descriptive statistical analysis was used to summarize the characteristics of the patients studied, the success rates of pleurodesis, the residual pleural volume right after pleural drainage, and the reaccumulation of pleural effusion after pleurodesis. Numerical variables were tested for their distribution with the use of the Shapiro-Wilk and kurtosis tests. The pleurodesis success rates were compared among the groups, and the chi-square test was used to calculate the level of significance. The initial pleural volumes were compared among the groups using the Kruskal-Wallis test, as was the difference between final and initial pleural volumes. All analyses were carried out with a level of significance set at $p < 0.05$.

RESULTS

During the study period, 131 patients were treated at our outpatient clinic and considered eligible for the original prospective study. Among these, 46 patients were excluded from the analysis: 25 due to death

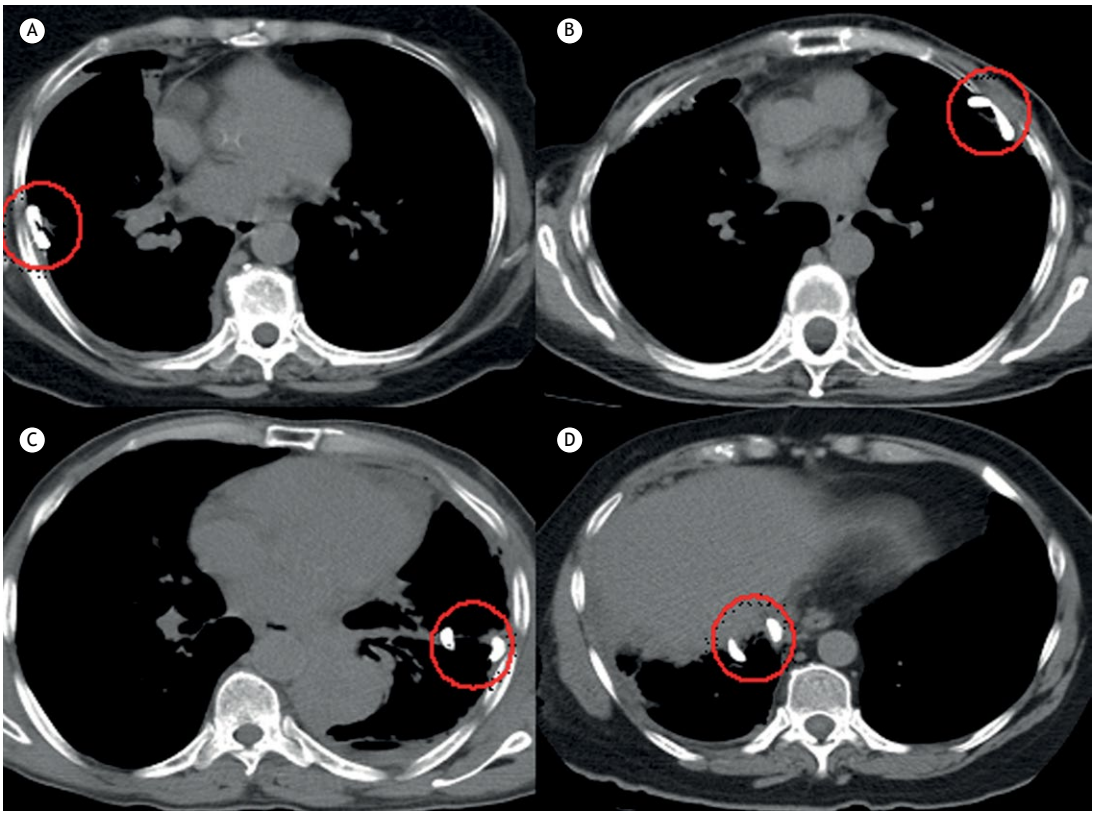

Figure 1. Positioning of the pleural catheter on CT scans. A: posterolateral; B: anterior; C: fissural; and D: subpulmonary.

(none related to the procedures) prior to 30 days after the procedures (i.e., no CT30 results), 15 due to lung expansion < 70%, and 6 lost to follow-up. Therefore, 85 patients fulfilled the inclusion criteria and participated in the original study and in the present nested study. There was a predominance of women (64 vs. 21 men). The mean age was 60.74 years. The median Karnofsky Performance Status index was 70. Breasts and lungs were the most common primary sites of neoplasia (44 and 20, respectively). The characteristics of the patients studied are presented in Table 1.

Bedside pleurodesis was associated with significant morbidity in our series. Adverse events of any kind were identified in 13 patients (15.2%), and some patients had more than one event, as well as major and minor complications. Minor complications occurred in 12 patients (14.1%). The most common ones were fever, pain, and oliguria, in 3 patients each; pneumonia, in 1; and adynamic ileus, in 1. Major complications occurred in 5 patients (5.8%): acute respiratory distress (before and after pleurodesis in 1 and 1, respectively), as well as empyema, pulmonary thromboembolism, and sepsis, in 1 patient each.

Catheter tip positioning was subpulmonary in 35 patients (41%), anterior in 23 (27%), posterolateral in 17 (20%) and fissural in 10 (12%). The two initial raters agreed in 79 cases (92.9%). Disagreements involved the subpulmonary and anterior groups (3 patients each). All of those cases were solved by the third investigator, and a consensus was reached.

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

Characteristic	Result
Gender	
Female	64 (75)
Male	21 (25)
Age, years	60.74 ± 12.4
KPS index[b]	70
Etiology	
Breast	44 (52.0)
Lung	20 (23.5)
Genitourinary	14 (16.5)
Gastrointestinal	5 (6.0)
Indefinite	2 (2.0)
Sclerosing agent	
Talc	51 (60)
Silver nitrate	34 (40)
Oncotic cytology	
Positive	62 (73)
Negative	5 (6)
Suspected	18 (21)

KPS: Karnofsky Performance Status. [a]Values expressed as n (%) or mean ± SD, except where otherwise indicated. [b]Value expressed as median.

The median pleural volume on iCT scans was 377 mL (interquartile range [IQR]: 171-722 mL). There were no

significant differences among the groups (p = 0.645). The median pleural volumes in the posterolateral, anterior, fissural, and subpulmonary groups were, respectively, 470 mL (IQR: 185-644 mL), 340 mL (IQR: 157-1,048 mL), 296 mL (IQR: 92-679 mL), and 367 mL (IQR: 177-714 mL; Figure 2).

The median difference between the pleural volumes on CT30 and iCT scans was 33 mL (IQR: −225 to 257 mL). There were no significant differences among the groups (p = 0.923). The median difference between those volumes in the posterolateral, anterior, fissural, and subpulmonary groups were, respectively, 73 mL (IQR: −217 to 219 mL), 93 mL (IQR: −446 to 268 mL), −15 mL (IQR: −322.2 to 334.2), and −27 mL (IQR: −225 to 259 mL; Figure 3).

Pleurodesis was successful in 73 patients (85.8%), with a similar distribution in the posterolateral, anterior, fissural, and subpulmonary groups (88.2%, 78.3%, 90.0%, and 88.7%, respectively; p = 0.676; Figure 4).

As mentioned before, we used two agents to induce pleurodesis. We found no significant difference between the use of talc or silver nitrate regarding their clinical effectiveness (82.7% vs. 91.4%; p = 0.247). The median difference between the pleural volumes on CT30 and iCT scans was 58 mL (IQR: −124 to 278 mL) and 81 mL (IQR: −402 to 245 mL) using talc and silver nitrate, respectively (p = 0.08). We also compared the clinical effectiveness between the patients with confirmed RMPE and those with highly suspected RMPE. Again, there was no significant difference (88.8% and 78.4%, respectively; p = 0.22).

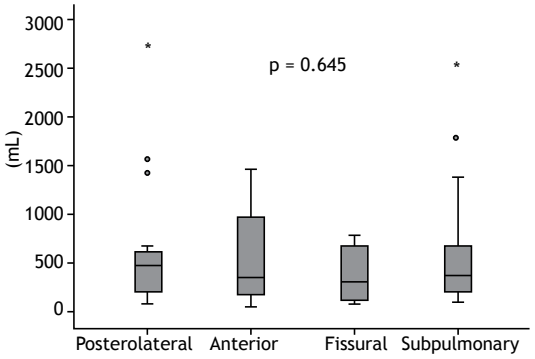

Figure 2. Initial pleural volume on CT scans.

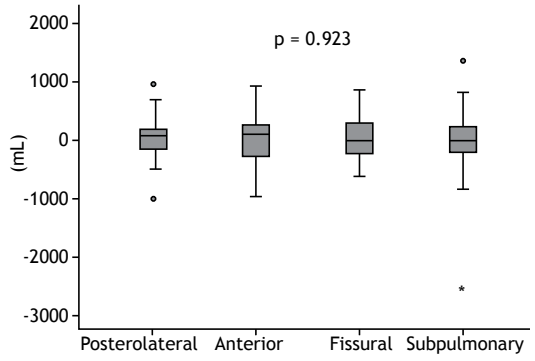

Figure 3. Difference between pleural volumes (based on final and initial CT scans).

DISCUSSION

The results of the present study suggest that the position of the pleural catheter tip influences neither the emptying of pleural effusion nor the success of pleurodesis, either radiologically or clinically, in patients with RMPE. The pleural fluid volume measured on CT scans performed after drainage was similar among the groups representing all different intrapleural positions of the tip of the catheter. Likewise, we found no differences among the groups with regard to the accumulation of effusion 30 days after pleurodesis.

Various approaches have been used in the treatment of RMPE. These patients have poor life expectancy; thus, a less invasive method, which can be performed on an outpatient basis, should be the best option.[11] In this scenario, bedside pleurodesis with a small-bore chest tube is a good approach. The use of ultrasonography guidance helps to decrease the complication rate due to catheter insertion.[1] The success rate of bedside pleurodesis ranges between 81% to 96%, and major complications occur in 7.5% of the cases.[12-15] In the present study, we found similar results, since pleurodesis was successful in 73 patients (85.8%) and major complications occurred in 5 patients (5.8%).

To the extent of our knowledge, there is only one study that explored the correlation between the success of pleurodesis and the positioning of the chest tube tip. Ishikawa et al.[16] conducted a prospective study in which 20 patients with lung cancer and RMPE underwent pleural drainage with a new curved chest tube developed by them. The new chest tube had a diameter of 18 Fr and smooth curved distal parts in order to allow a better positioning of its tip into the pleural cavity. To evaluate the position of the tip, frontal and lateral chest X-rays were taken after the insertion and before the removal of the tube. The position was classified as paravertebral gutter in posterobasal position (15 patients, 75%), posterior and superior position of the pleural space (4 patients, 20%), or pleural space other than the two previous positions (1 patient, 5%). A drainage efficacy of more than 90% on X-rays was achieved in 86.7% of the patients in the paravertebral group; however, only 25% of those

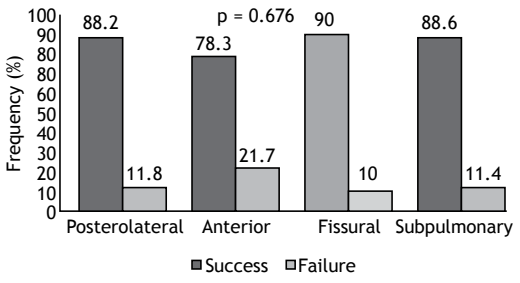

Figure 4. Pleurodesis success according to the positioning of the tip of the catheter.

in the posterior-superior group had the same efficacy (p = 0.024). Bedside pleurodesis was successful in all of those cases; nevertheless, the patients who were not in the paravertebral group achieved no full radiographic resolution within a four-week follow-up. Unfortunately, we have found no other studies addressing that new device or the relevance of the intrapleural position of the chest tube.

On the basis of the findings of Ishikawa et al.,[16] we sought to direct the tip of the chest tube superiorly and posteriorly. Nonetheless, small-bore catheters are much more flexible, making it difficult to predict where they will eventually lie in the pleural space. This fact is confirmed by the finding that the catheter was positioned posterolaterally in only 20% of our patients, in spite of our effort to push it in such a direction. Probably, after pleural effusion drainage and lung expansion, the tip assumes different random positions. However, this discussion now seems less relevant because we found, in the present study, that the position of the tip had no influence on clinical or radiological outcomes.

Our broad inclusion and exclusion criteria allowed a good generalizability of our results, which we believe might be applicable for patients with RMPE treated at other tertiary care facilities. Moreover, the pleural catheter that we used is one of the most popular catheters worldwide. One threat to the generalizability of the present study is the fact that more than 50% of the patients had breast cancer. In addition, in relation to the initial lung expansion, since we only included patients with RMPE, we cannot say that our results can be generalized to other types of pleural effusion.

The major limitation of our study is the fact that it is a secondary analysis of data collected for a different purpose. Moreover, the number of cases with clinical failure of pleurodesis was small (9 patients), hindering a powerful statistical analysis of this outcome. We also found a very wide distribution of values of pleural volumes measured on CT, reflecting the heterogeneity of our study population (various primary cancers at various stages of treatment) and broad inclusion criteria. However, the main strength of the study is the very precise method we used in order to measure lung expansion after drainage and to estimate pleural fluid reaccumulation. The CT scans allowed us to measure pleural volumes with certainty, making our conclusions stronger.

In conclusion, the present study demonstrated that, regardless of the ultrasound-guided positioning of the small-bore pleural catheter, pleural drainage and pleurodesis were efficient in our sample of patients. Therefore, the position of the tip of the pleural catheter seems to be of low relevance and should not hinder the instillation of a sclerosing agent or pleurodesis.

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ORIGINAL ARTICLE

Hearing thresholds in patients with drug-resistant tuberculosis: baseline audiogram configurations and associations

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Study carried out in the Ogun State Drug Resistant Tuberculosis Treatment Center in the Sacred Heart Hospital (Special), Lantoro, Abeokuta, Nigeria.

ABSTRACT

Objective: To use baseline audiogram parameters in order to ascertain whether drug-resistant tuberculosis (DR-TB) has effects on hearing, as well as to describe the configurations of the audiograms and to determine whether there are parameters that can be associated with those configurations. **Methods:** This was a prospective study involving patients diagnosed with DR-TB at a tuberculosis treatment center in the state of Ogun, in Nigeria. The patients included in the study were submitted to pure tone audiometry at baseline (within two weeks after treatment initiation). For comparative analyses, data regarding demographic and clinical characteristics were collected from the medical records of the patients. **Results:** The final sample comprised 132 patients. The mean age of the patients was 34.5 ± 12.6 years (range, 8-82 years), and the male:female ratio was 2:1. Of the 132 patients, 103 (78.0%) resided in neighboring states, 125 (94.7%) had previously experienced antituberculosis treatment failure, and 18 (13.6%) were retroviral-positive. Normal audiograms were found in 12 patients (9.1%), whereas sensorineural hearing loss was identified in 104 (78.8%), the two most common configurations being ascending, in 54 (40.9%), and sloping, in 26 (19.7%). Pure-tone averages at low frequencies (0.25-1.0 kHz) and high frequencies (2.0-8.0 kHz) were 33.0 dB and 40.0 dB, respectively. Regarding the degree of hearing loss in the better ear, 36 patients (27.3%) were classified as having normal hearing and 67 (50.8%) were classified as having mild hearing loss (26-40 dB), whereas 29 (21.9%) showed moderate or severe hearing loss. Among the variables studied (age, gender, retroviral status, previous treatment outcome, and weight at admission), only male gender was associated with audiometric configurations. **Conclusions:** In this sample of patients with DR-TB, most presented with bilateral, mild, suboptimal sensorineural hearing loss, and ascending/sloping audiometric configurations were associated with male gender.

Keywords: Audiometry, pure-tone; Hearing loss, high-frequency; Drug-related side effects and adverse reactions; Tuberculosis, multidrug-resistant.

INTRODUCTION

Drug-resistant tuberculosis (DR-TB) refers to infection with an isolate of *Mycobacterium tuberculosis* that is resistant to one of the first-line antituberculosis drugs, namely isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin. On the basis of their degree of resistance to such medications, mycobacteria can be classified as single drug-resistant, multidrug-resistant (MDR), or extensively drug-resistant. The reported prevalence of DR-TB is variable, strains resistant to isoniazid plus rifampin (i.e., MDR-TB strains) being identified in 0.6% to 2.9% of newly diagnosed cases of tuberculosis in sub-Saharan Africa.[1,2] In addition, DR-TB is common among retroviral-infected individuals; the incidence of rifampin-resistant tuberculosis among HIV-infected individuals in Nigeria was 7.0% over a period of three years (2009-2012).[3] The emergence of DR mycobacterial strains is an important factor that fuels the tuberculosis epidemic and its associated morbidity and mortality.[4]

Although DR-TB can be a primary infection when a patient acquires a *M. tuberculosis* strain that is already resistant, it arises more often through the selection of mutated strains by inadequate therapy. The most powerful predictor of the presence of DR-TB is a history of a previous antituberculosis treatment.[5] Other factors, such as a shortage of drugs, leads to inadequacy of initial antituberculosis regimen and fuels the emergence of DR-TB, especially in resource-poor settings. Furthermore, increased costs of treatment and complications associated with the usage of antituberculosis medications considerably contribute to the complexity of DR-TB treatment.[5]

The adverse effects of antituberculosis treatment include skin rashes, gastrointestinal disturbances, and hepatotoxicity, whereas aminoglycosides can cause nephrotoxicity and ototoxicity.[6] Sensorineural hearing impairment has been noted as the most common form of manifestation of ototoxicity.[7] This is detected by monitoring hearing threshold parameters in patients on antituberculosis drugs as part of the DR-TB management

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protocol. Hearing impairment resulting from ototoxicity is detected by comparing hearing threshold measurements during treatment with an initial hearing assessment obtained from the patient on admission prior to the commencement of therapy (baseline audiometry). However, tuberculosis can affect the ears in other ways as part of its extrapulmonary manifestations, causing infections, such as tuberculous otitis media, facial nerve paralysis, and various types and degrees of hearing loss (HL).[8] The effects that mycobacteria have on hearing, unlike the effects of the medications, can be assessed subjectively from baseline audiometry obtained prior to treatment initiation.

The objective of the present study was to use baseline audiogram parameters in order to ascertain whether DR-TB has effects on hearing, to describe the configurations of the audiograms, and to determine whether there are clinical parameters that can be associated with those configurations. We believe this will assist in the initial characterization of the hearing thresholds and clarify the audiological effects of tuberculosis.

METHODS

This was a prospective study involving patients followed at the Ogun State Drug Resistant Tuberculosis Center in the Sacred Heart Hospital (Special), located in Lantoro, Abeokuta, Nigeria, between November of 2014 and October of 2015. The center receives DR-TB patients from its home state of Ogun and from neighboring states (Lagos, Oyo, Ondo, Ekiti, Kwara, Kogi, Edo, and Delta).

The patients who were diagnosed with DR-TB—by means of GeneXpert MTB/RIF® (Cepheid, Sunnyvale, CA, USA) and a positive sputum culture for *M. tuberculosis*—were admitted and treated at the center. The cases were managed by a team of experts, which included a pulmonologist, an otolaryngologist, clinicians (trained in tuberculosis management), a psychiatrist, nurses, and a social worker. The pulmonologist performed the initial clinical assessments of the patients and confirmed the diagnosis of DR-TB aided by the investigations. Other experts also performed different roles in the management of the cases. The study protocol was approved by the Research Ethics Committee of the Sacred Heart Hospital, and all participating patients gave written informed consent.

As part of the management protocol for DR-TB, the otolaryngologist evaluated the initial (baseline) audiometry of the patients at or within two weeks after their admission and treatment initiation in order to assess their hearing thresholds. The rationale for and significance of such assessments were explained to the patients, and only those who consented had their data included in the study. Patients were questioned concerning ear diseases—present, previous or recurrent ear discharges—symptoms—HL, noise in the ears (tinnitus), echoes, and history of vertigo—and self-estimation of hearing—good or poor—in order to detect hearing impairments and difficulty in hearing. The two ears were thereafter examined using an otoscope (HEINE Optotechnik, Herrsching, Germany) in order to detect pathologies, such as perforated tympanic membrane, ear discharge, wax impaction, and presence of a foreign body. The patients with ear lesions, such as wax impaction, were treated before their hearing assessment was carried out.

The inclusion criteria were having anatomically normal ears or presenting with structural abnormalities resulting from the tuberculosis infection, as well as having performed baseline audiometry within two weeks after treatment initiation. Data for patients with a sequel of perforated tympanic membrane suspected to be related to suppurative otitis media and not resulting from the tuberculosis infection were excluded from the study.

Each patient was seated in a quiet room with an ambient noise level of 27 dB (sound pressure level), was instructed on how to perform the test, and was told what type of responses would be expected. A calibrated diagnostic audiometer (Amplivox 240; Amplivox Ltd., Eynsham, UK), a head band, and a bone stimulator were used in order to produce pure-tone sounds, ranging from 0.25-8.00 kHz and 0.25-4.0 kHz, for the determination of air conduction and bone conduction thresholds, respectively. Hearing thresholds were measured as sound intensity in decibels based on consistent responses of the patient at each frequency tested. The responses were plotted as a chart in order to produce the audiogram for each ear. The types and laterality of the audiograms were also recorded. The types of audiogram were classified as normal, conductive HL, sensorineural HL, or mixed HL. Sensorineural HL was subclassified as sloping, flat, or ascending, based on the form of the tracings moving from the lower to the higher frequencies on the audiograms. Laterality was based on the side of the abnormal audiogram, and a discordant audiogram represented different types of abnormalities in the two ears. The degree of HL was also noted in the better ear in each patient. We adopted the World Health Organization classification of HL,[9] using the pure-tone average, as follows: 0-25 dB, normal hearing; 26-40 dB, mild HL; 41-60 dB, moderate HL; 61-80 dB, severe HL; and ≥ 81 dB, profound HL.

Demographic parameters, such as usual place of domicile, and clinical parameters, including a history of tuberculosis treatment (cure or failure) and retroviral status, were retrieved from the medical records of the patients. These and the audiometric data were entered into a spreadsheet and analyzed using the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). The descriptive characteristics of the patients were summarized in tables and presented as absolute numbers and proportions (categorical variables) or as means and standard deviations (continuous variables). Variables (age, gender, retroviral status, previous treatment failure, and body weight) were compared with the audiogram configurations of the patients. The chi-square test was

used in order to detect significant differences between the variables ($p < 0.05$).

RESULTS

Over a period of one year, 142 patients were followed. However, 10 patients were excluded from the study (5 were unable to perform baseline audiometry on account of being too weak to withstand the stress of audiometric assessment; 2 presented with inconsistent, unreliable responses during audiometry; and 3 underwent audiometry after two weeks of treatment). Therefore, the sample comprised 132 patients. The mean age of the patients was 34.5 ± 12.6 years (range, 8-82 years). The male:female ratio was 2:1. Of the 132 patients, 103 (78.0%) did not reside in Ogun state and 18 (13.6%) were retroviral-positive. Self-reported hearing status was as follows: 111 patients (84.1%) described their hearing as good; 13 (9.8%) were undecided, and 8 (6.1%) described it as poor. Failure of previous tuberculosis treatment (with different combinations of drugs, including rifampin, isoniazid, pyrazinamide, and ethambutol) was reported by 125 patients (94.7%). After two months of first-line treatment, there was no sputum conversion in 44 patients (33.3%), whereas, after three months of first-line treatment, there was neither sputum conversion nor clinical improvement despite good treatment compliance in 75 patients (56.8%), as shown in Table 1.

Table 2 presents the audiometric characteristics of the patients, showing that < 10% of the patients had normal audiograms. Sensorineural HL was identified in 104 patients (78.8%), among whom the most common configurations were ascending (seen in 40.9%) and sloping (seen in 19.7%). The pure-tone averages (arithmetic mean of air conduction thresholds) at low frequencies (0.25-1.0 kHz) and high frequencies (2.0-8.0 kHz) were 33.0 dB and 40.0 dB, respectively. The analysis of the degree of HL in the patients revealed that 27.3% had normal hearing in the better ear, half (50.8%) of the patients had mild HL (26-40 dB), and the remaining patients had higher degrees of HL.

In Table 3, the factors that could be associated with ascending and sloping audiogram configurations were explored. Among all of the factors studied, only male gender was associated with both audiometric configurations, whereas age, positive retroviral status, previous treatment failure, and body weight < 50.0 kg at admission were not associated with the audiometric configurations.

DISCUSSION

The present study has revealed that only 12 (9.1%) of our DR-TB patients had normal hearing in both ears, 36 (27.3%) had normal hearing in one ear, and the majority of the patients had hearing impairment in both ears. The main type of hearing impairment was sensorineural HL—especially showing ascending or sloping audiogram configurations, of mild magnitude—which was associated with the male gender. Thus, the prevalences of increased hearing thresholds, i.e. reduced hearing at the baseline level in one ear and in both ears were 90.9% and 72.7%, respectively. These prevalences are certainly very high, arousing suspicion of a direct effect of mycobacteria on the ears of DR-TB patients. However, this should be interpreted with some caution, since such results might be a reflection of the general trend of hearing in that community, especially because there were no

Table 1. Clinical and demographic characteristics of the patients.

Characteristic	n	%
Age, years[a]	8-82	34.5 ± 12.6
Gender		
Male	87	65.9
Female	45	34.1
Place of residence		
Ogun state (rural)	12	9.1
Ogun state (urban)	17	12.9
Outside Ogun state	103	78.0
Weight at admission, kg[a]	17.0-85.0	50.6 ± 10.1
Retroviral status		
Negative	114	86.4
Positive	18	13.6
Previous antituberculosis treatment failure		
Treatment naive	7	5.3
CAT I	44	33.3
CAT II	75	56.8
Others	6	4.6

CAT I: category I represents no sputum conversion for two consecutive months after the end of the second month of first-line treatment or no clinical improvement despite good drug compliance; and CAT II: category II represents no sputum conversion for consecutive months after the end of the third month of first-line treatment or no clinical improvement despite good drug compliance. [a]Values expressed as range and mean ± SD.

Table 2. Audiometric profile of the patients.

Profile	n	%
Audiogram laterality		
Right-sided	8	6.1
Left-sided	5	3.8
Bilateral	115	87.1
Discordant	4	3.0
Type		
Normal	12	9.1
Conductive hearing loss	6	4.5
Sensorineural hearing loss	104	78.8
Flat audiogram configuration	24	18.2
Ascending audiogram configuration	54	40.9
Sloping audiogram configuration	26	19.7
Mixed hearing loss	10	7.6
Degree of hearing loss in the better ear		
Normal hearing	36	27.3
Mild	67	50.8
Moderate	25	18.9
Severe	4	3.0

Table 3. Factors associated with ascending and sloping audiogram configurations.

Factor	Ascending audiogram configuration, %		χ^2	p
	No	Yes		
Age ≤ 33 years	44.7	9.1	0.752	0.391
Male gender	49.2	16.7	5.042	0.036
HIV positive	10.6	3.0	0.322	0.805
Previous treatment failure	48.5	12.1	0.498	0.919
Weight < 50.0 kg	41.7	8.3	0.945	0.624
Factor	**Sloping audiogram configuration, %**		**χ^2**	**p**
	No	Yes		
Age ≤ 33 years	30.3	15.9	1.972	0.160
Male gender	43.2	22.7	4.360	0.037
HIV positive	10.6	3.0	3.814	0.121
Previous treatment failure	37.1	23.5	2.075	0.814
Weight < 50.0 kg	29.5	20.5	0.703	0.704

controls for comparison. Moreover, noise pollution levels in that community are high,[10,11] and this might have a bearing on the average hearing thresholds in that population.

A vast majority (94.7%) of our patients had previous drug treatment failures. The treatment regimens previously used, which varied in content and duration of use, included the standard first-line antituberculosis drugs used in Nigeria (rifampin, isoniazid, pyrazinamide, and ethambutol). These medications were used in a six-month regimen, comprising a two-month intensive phase and a four-month continuation phase. The possibility that previous hearing problems could be worsened by the use of aminoglycosides is an issue to be explored. Researchers had reported an incidence of ototoxicity of up 1.7% among tuberculosis patients on standard antituberculosis drug combination treatment.[12] Therefore, the increased hearing thresholds found in the present study might be partly related to ototoxic effects of a previous treatment with rifampin or isoniazid.

The reported prevalence of ototoxicity among DR-TB patients under treatment in Europe and Asia was 28.0%[13] and 70.1%,[14] respectively. It is noteworthy that those quoted figures are not baseline audiometric values, and ototoxicity is based on stringent criteria, including audiometric permanent hearing threshold shifts, at particular frequencies. It may suffice to posit that the level of hearing of most of the DR-TB patients in our cohort was suboptimal. However, a more serious concern regarding such high prevalences of suboptimal hearing is the long-term effects and repercussions they could have on the hearing of patients who are still going to be on aminoglycoside therapy for months. There is a tendency for HL to become aggravated, with consequent increases in the proportion of patients with hearing impairment. Considering other medications aside from aminoglycosides in the treatment of tuberculosis is expedient, and research is ongoing in this respect.

Most audiologists define the "baseline" audiogram as one obtained within two weeks after the initiation

of treatment.[15] This is based on the assumption that significant threshold shifts would not have occurred within two weeks, even if patients had started therapy. In addition, it may not be possible to perform this test immediately after admission due to logistics, and it is better not to delay the initiation of therapy in our local setting. Despite the exclusion of the data of the patients with obvious middle ear disease, such as recurrent ear discharge and perforated tympanic membranes due to suppurative ear infections, 4.5% of the patients presented with audiometric evidence of conductive HL. This might be due to subclinical malfunctioning of the middle ear conducting mechanisms. The most common type of audiometric pattern found in our sample was sensorineural HL, which denoted the affectation of the hair cells or the cochlear nerves. Tuberculosis has been reported to affect peripheral nerves, causing neuropathies, especially during the late stages of infection, although the pathogenesis of this aspect of the disease remains controversial.[16] However, various reports concerning differential affectation of cochlear hair cells are related to pathologies due to drug-induced ototoxicity, as well as to age-related and noise-induced HL.

In considering audiograms, three configurations of sensorineural HL have been described, namely ascending, flat, and sloping configurations. In our study, the most common configuration was the ascending configuration, with low-frequency HL (LFHL), which is also called reverse slope audiogram. The LFHL denotes affectation of hair cells at the apical turn of the cochlea. This type of HL is not easily identified symptomatically in a clinic setting, because the symptoms are subtle, and audiologists therefore often describe it as asymptomatic. Low-frequency sounds are more intense and suspiciously carry less information than do high-frequency sounds.[17] A person with a moderate degree of LFHL may not exhibit any outward sign of HL, such as missing speech sounds or aberrant speech production patterns. Such patients thus maintain a relatively intact intelligibility. Furthermore, low-frequency information may be carried by high-frequency fibers through temporal coding, limiting suggestive clues to LFHL to subtle symptoms, such as difficulties in hearing in a group setting or in a noisy place. Notable causes and associated factors for LFHL include a mutation of the Wolfram syndrome gene 1 (an autosomal recessive disorder called Wolfram syndrome 1),[18] Mondini dysplasia,[19] sudden HL,[20] Ménière's disease, and viral infections.[21]. It might be precipitous to assume that mycobacteria affect the hair cells in a manner similar to that of viral infections, and this phenomenon therefore needs further clarification.

The sloping audiogram configuration, which represents high-frequency HL (HFHL), has been associated with noise-induced hearing impairment and age-related HL (presbycusis). Although some of the patients in our sample were elderly (≥ 60 years of age), not all of the patients in this age group had HFHL. However, age-related hearing changes tend to start manifesting about the fifth decade of life in Nigerians.[22] Advancing age and the high level of noise in our community might have caused HFHL in some of the patients in our sample. The bulk of the patients had the same pattern in both ears, suggesting similar pathologies. Although tuberculosis primarily affects the lung parenchyma, its effects on other organs of the body are usually systemic. The systemic effects could be due to immune-mediated or vasculitis-related cytopathy,[16] rather than to the direct invasion of mycobacteria in the ears.

Most audiologists are conversant with the World Health Organization classification of the degree of HL.[9] In the present study, most of the patients had a mild degree of HL, which might not be noticeable at the outset. Continuous exposure to the same stimuli leads to progression and worsening of the clinical condition of patients, whereas the administration of injectable aminoglycosides will lead to the aggravation of the symptoms. Commencing as an initial temporary threshold shift, ototoxicity ultimately leads to a permanent threshold shift, which is irreversible. It is thus suggested that patients with any form of HL should not take the highly ototoxic aminoglycosides from the outset, or, alternatively, such patients should have more frequent audiometric monitoring in order to detect threshold shifts rapidly and to make adjustments accordingly before a permanent threshold shift sets in. However, the practicability of these suggestions in resource-poor environments is doubtful. Nevertheless, the present study underscores the necessity of initial audiometric hearing threshold measurements. We advocate serial audiometric measurements for all patients under therapy for any form of tuberculosis infection.

While medical litigation against the healthcare giver may not be particularly common in our environment for now, the possibility cannot be dismissed. There were some patients with HL that will necessitate sound amplification, assistive hearing devices, or aural rehabilitation. Such patients should be started on therapy with a drug such as capreomycin, which appears to have less toxicity[13] than other aminoglycosides, such as kanamycin. However, such patients need to be educated about their hearing problems, the pre-existence of the HL before the initiation of therapy should be emphasized, and necessary actions will need to be taken. The readily available assistance we rendered to such patients included hearing aids for free.

Discovering factors associated with a disease can aid the clinician in the disease management. Among the factors that were explored concerning the two most common audiometric configurations in the present study, only male gender was found to be associated with both ascending and sloping audiometric configurations. Although this may portend some hormonal influence, that might be oversimplifying the situation. Some studies noted comparatively increased hearing thresholds in males (in comparison with females), especially in those between 20 and 69 years of age.[23-25] Park et al. reported that hearing thresholds at frequencies of 3

kHz, 4 kHz, and 6 kHz showed a statistical difference between the two genders for people over 30 years of age, the 4-kHz frequency accounting for the largest significant difference in a population sample in South Korea.[26] The factors that have been attributed to this include occupational and leisure exposure to noise, as well as the use of analgesics or nonsteroidal anti-inflammatory drugs, which more commonly occur in males.[27]

None of the other factors studied was found to be associated with either ascending or sloping configurations. Theoretically, it should be expected that older patients, those with previous drug regimen failure, those with lower body weight at admission, and those coinfected with HIV will present with worse hearing thresholds. It was reported, however, that the absolute risks and risk factors for adverse events (possibly including HL) were similar between HIV-infected and HIV-uninfected patients treated for DR-TB in a cohort of 57 patients in Namibia.[28] It has been reported that hearing deficits in HIV-infected individuals could be a central (rather than a peripheral) auditory change that pure tone audiogram detects.[29] Similarly, antiretroviral-naïve HIV-infected patients are not more likely to show an increase in having severe adverse drug reactions when on a second-line antituberculosis regimen.[30] This underscores the need for further research into the subject, especially regarding the link resulting from DR-TB and HIV infection.

The factors associated with hearing impairment and audiometric configurations in DR-TB patients can be clarified further by means of randomized controlled studies. Such studies should carry out comparative analyses among normal individuals, patients with tuberculosis, and those with DR-TB. The lack of this type of analysis remains the major limitation of the present study. It is also noteworthy that evaluating the body mass index of the patients at admission would have represented the nutritional status better than their body weight.[31] In addition, the baseline audiometric assessment should be ideally performed before the commencement of therapy. These limitations notwithstanding, the present study suggests that, at presentation, most of the patients with DR-TB in Nigeria had mild, suboptimal, sensorineural hearing levels bilaterally and ascending or sloping audiometric configurations, the male gender being the only factor associated with such configurations.

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ORIGINAL ARTICLE

Effective tobacco control measures: agreement among medical students

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ABSTRACT

Objective: To determine the level of agreement with effective tobacco control measures recommended by the World Health Organization and to assess the attitudes toward, knowledge of, and beliefs regarding smoking among third-year medical students at University of São Paulo School of Medicine, located in the city of São Paulo, Brazil. **Methods:** Between 2008 and 2012, all third-year medical students were invited to complete a self-administered questionnaire based on the Global Health Professionals Student Survey and its additional modules. **Results:** The study sample comprised 556 students. The level of agreement with the World Health Organization recommendations was high, except for the components "received smoking cessation training" and "raising taxes is effective to reduce the prevalence of smoking". Most of the students reported that they agree with banning tobacco product sales to minors (95%), believe that physicians are role models to their patients (84%), and believe that they should advise their patients to quit cigarette smoking (96%) and using other tobacco products (94%). Regarding smoking cessation methods, most of the students were found to know more about nicotine replacement therapy than about non-nicotine therapies (93% vs. 53%). Only 37% of the respondents were aware of the importance of educational antismoking materials, and only 31% reported that they believe in the effectiveness of encouraging their patients, during medical visits. In our sample, the prevalence of current cigarette smoking was 5.23%; however, 43.82% of the respondents reported having experimented with water-pipe tobacco smoking. **Conclusions:** Our results revealed the need to emphasize to third-year medical students the importance of raising the prices of and taxes on tobacco products. We also need to make students aware of the dangers of experimenting with tobacco products other than cigarettes, particularly water-pipe tobacco smoking.

Keywords: Tobacco products; Health policy; Education, medical, undergraduate; Health knowledge, attitudes, practice.

INTRODUCTION

A decade ago, the World Health Organization created the Framework Convention on Tobacco Control, the first international public health convention aimed at decreasing tobacco-related morbidity and mortality.[1] Smoking remains an important public health problem, because it is the major preventable cause of premature morbidity and mortality. In the last century, tobacco use killed 100 million people, and, if current smoking patterns continue, it will kill around 1 billion people in the 21st century.[1] Tobacco use has also been recognized as one of the leading risk factors for noncommunicable diseases.[1] To achieve abstinence, smokers need repeated attempts to quit smoking, because lapses and relapses are frequent during treatment. For this reason, nicotine dependence is being regarded as a chronic disease.[2]

Based on evidence and best practices, the World Health Organization also developed guidelines that provide some measures to help countries to implement and manage tobacco control policies. These measures are known as MPOWER, an acronym for **M**onitoring tobacco use; **P**rotecting people from tobacco smoke; **O**ffering help to quit tobacco use; **W**arning about the dangers of tobacco; **E**nforcing bans on tobacco advertising; and **R**aising taxes on tobacco products.[3]

Medical schools need to train their future doctors in public health policies on tobacco control in order to reduce smoking initiation and smoking-related morbidity and mortality. In the future, we expect aspiring physicians to be able to play an important and unique role in preventing smoking initiation and decreasing the prevalence of smoking by advising, encouraging, and assisting helping their patients to quit smoking.

For these reasons, article 12 of the Framework Convention on Tobacco Control guidelines[4] states that the curricula of medical schools must include tobacco control, providing students with effective and appropriate training.

The aims of the present study were to determine the level of agreement with the World Health Organization

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MPOWER components among third-year medical students at the University of São Paulo School of Medicine, located in the city of São Paulo, Brazil, and to assess their attitudes, knowledge, and beliefs about smoking.

METHODS

Between 2008 and 2012, third-year medical students at the University of São Paulo School of Medicine were invited to complete a self-administered questionnaire based on a standardized school-based survey for third-year medical —the Global Health Professionals Student Survey—and its additional modules.[5] The participation was voluntary, and the completion of the questionnaire occurred during regular classes. During the study period, the medical curriculum remained the same. All students who agreed to participate gave written informed consent. The local research ethics committee of the institution approved the study. (Process no. 0277/08).

Students who reported having smoked 100 or more cigarettes in their lifetime and, at the time of the survey, were still smoking were classified as current cigarette smokers. We classified as experimentation with water pipe and other forms of tobacco use those students who reported having ever experimented with those products (e.g., having taken at least a few puffs).

Descriptive analyses and comparisons of the proportions of positive responses between smokers and nonsmokers were carried out. We used the chi-square test or Fisher's exact test, when appropriate, to verify associations between variables. Values of $p < 0.05$ were considered statistically significant. The data were analyzed with the Statistical Analysis System, version 9.0 (SAS Institute Inc., Cary, NY, USA).

RESULTS

Of a total sample of 900 students, 556 (62%) completed the questionnaire. The number of answers often varied because not all respondents answered all of the questions in each MPOWER component. The mean age of male and female respondents (n = 548) was 22.24 ± 2.85 years and 21.90 ± 2.17 years, respectively.

All of the smokers in the sample agreed about the importance of monitoring and registering the smoke status of their patients in medical charts (Table 1). Over 90% of the aspiring physicians agreed with protecting the population against environmental tobacco smoke exposure. However, few students reported having received smoking cessation training to help them with their future patients who smoke. Almost the majority of the students had been warned about the harmful health effects of tobacco smoking. More than 80% of all the respondents supported the total ban of sponsorships, promotions, and advertising of tobacco products. Nevertheless, only a few students agreed on the importance of increasing taxes as an effective measure to reduce the prevalence of smoking. There were no statistically significant differences between males and females regarding any of the six MPOWER components.

The majority of the responding students agreed with the measure that protects minors from buying tobacco products (Table 2). Almost all smokers and nonsmokers agreed that they should receive specific training on smoking cessation and that it is important to advise their patients to quit smoking. Although the proportion of nonsmokers who believed that health professionals are role models for their patients and the public was greater than was that of smokers who had the same belief (84.60% vs. 78.57%), the difference was not significant. More than 90% of the respondents agreed that physicians should routinely advise their patients to quit smoking and using other tobacco products, and they believed that the attitude of giving this sort of advice increases the chances of smoking cessation. Nonsmoking students believed that health professionals who smoke are less likely to advise their patients to quit smoking ($p < 0.05$). Half of the smokers and less than half of the nonsmokers reported having discussed the reasons that lead someone to start smoking. Less than 40% of the respondents reported having been taught about the importance to offer their patients educational materials about smoking cessation.

Regarding the issues related to treatment, both smoking and nonsmoking students showed a greater

Table 1. Agreement with the MPOWER[a] measures among undergraduate medical students, by smoking status.[b]

Measure	Group[c]		p*	Total
	Smoker n/N (%)	Nonsmoker n/N (%)		n/N (%)
Monitoring: registry in medical charts	28/28 (100.00)	499/507 (98.42)	NS	527/535 (98.50)
Protecting: smoking ban in all public enclosed places	27/27 (100.00)	477/502 (95.02)	NS	504/529 (95.27)
Offering: received smoking cessation training	9/28 (32.14)	111/505 (21.98)	NS	120/533 (22.51)
Warning: taught about health risks of smoking	27/28 (96.43)	493/507 (97.24)	NS	520/535 (97.20)
Enforcing: total ban of advertising, promotion, and sponsorship	22/28 (78.57)	411/500 (82.20)	NS	433/528 (82.01)
Raising: raising taxes is effective to reduce the prevalence of smoking	11/28 (39.29)	169/506 (33.40)	NS	180/534 (33.71)

NS: not significant. [a]World Health Organization.[3] [b]Some denominators vary because of missing data. [c]Cigarette smokers/nonsmokers. *Chi-square test.

knowledge about nicotine replacement therapies than about other types of smoking cessation therapies. Only one-third of the respondents believed in the importance of encouraging smokers, during medical visits, to try to quit smoking. There were no statistically significant differences between males and females regarding the attitudes toward and knowledge about smoking.

The prevalence of current cigarette smoking was low (5.23%); however, the prevalences of experimenting with cigars, pipes, cheroots, and other tobacco products (21.23%) and experimenting with water-pipe tobacco smoking (43.82%) were higher (Table 3). These prevalences were significantly higher among males.

Table 4 shows that less than 20% of the respondents were exposed to secondhand tobacco smoke in their households. Although the difference was not significant, the analysis revealed that males were less exposed to passive smoking than females: zero days of secondhand tobacco smoke exposure (79.83% vs. 82.97%) and five or more days of secondhand exposure (9.44% vs. 7.57%).

DISCUSSION

Future physicians should be empowered to assume their role in tobacco control. To make this happen, they must learn about the six most effective public policy measures for controlling the tobacco epidemic and be trained in smoking cessation over the medical course.

The present study revealed a high level of agreement with the majority of the MPOWER components. In the third year of the medical school, we found that students had already been properly informed about the importance of monitoring and registering the smoking status of the patients in medical charts as a means to track down and measure the prevalence of smoking among the population; a similar outcome was found in a study carried out at the University of Malta.[6]

The students in our sample were more aware of the importance of protecting people from secondhand tobacco smoke (95,2%) than were medical students in Germany (80%), Poland (74,5%), and Spain (73,9%).[7] In addition, they showed having sufficient knowledge about the damages caused by smoking, reporting that they had been taught and warned about the health risks of smoking at their medical school. This knowledge could have also come from public health policies; since 1988, Brazil has adopted health warnings on all packages of tobacco products. In 2001, the first round of pictorial warnings covering 100% of one side of cigarette packs and at points of

Table 2. Attitudes toward, knowledge of, and beliefs regarding smoking among medical undergraduate students, by smoking status.[a]

Issues related to smoking education in the medical curriculum	Group[b]		p*	Total
	Smoker	Nonsmoker		
	n/N (%)	n/N (%)		n/N (%)
1. Should sales to minors be banned?	26/28 (92.86)	479/502 (95.42)	NS	505/530 (95.28)
2. Should health professionals receive specific training in smoking cessation techniques?	26/28 (92.86)	482/503 (95.83)	NS	508/531 (95.67)
3. Do health professionals serve as role models for their patients and the public?	22/28 (78.57)	423/500 (84.60)	NS	445/528 (84.28)
4. Should health professionals routinely advise their smoking patients to quit?	28/28 (100.00)	481/503 (95.63)	NS	509/531 (95.86)
5. Should health professionals routinely advise their patients who use tobacco products other than cigarettes to stop using those products?	28/28 (100.00)	471/503 (93.64)	NS	499/531 (93.97)
6. Should health professionals provide information about smoking cessation to patients?	28/28 (100.00)	501/503 (99.60)	NS	529/531 (99.62)
7. Do the possibilities to quit smoking increase if a health professional provide advice?	26/28 (92.86)	454/495 (91.72)	NS	480/523 (91.78)
8. Are smoking health professionals less likely to advise smoking patients to quit smoking?	12/27 (44.44)	321/502 (63.94)	< 0.05	333/529 (62.95)
9. Have you discussed the reasons why people smoke during your medical school classes?	14/28 (50)	248/507 (48.92)	NS	262/535 (48.97)
10. Have you been taught about the importance of providing educational materials to support smoking cessation during your medical school classes?	9/28 (32.14)	190/505 (37.62)	NS	199/533 (37.34)
11. Have you heard about smoking cessation treatment with nicotine replacement therapy (patch and gum)?	26/28 (92.86)	473/507 (93.29)	NS	499/535 (93.27)
12. Have you heard about smoking cessation treatment with bupropion or nortriptyline?	17/28 (60.71)	266/505 (52.67)	NS	283/533 (53.10)
13. Do you believe that encouraging smokers to think about quitting and trying to stop smoking, during medical visits, is an effective method for smoking cessation?	9/28 (32.14)	159/507 (31.36)	NS	168/535 (31.40)

NS: not significant. [a]Some denominators vary because of missing data. [b]Cigarette smokers/nonsmokers. *Chi-square test.

Table 3. Prevalence of smoking and tobacco experimentation among medical undergraduate students, by gender.[a]

Tobacco use	Female n/N (%)	Male n/N (%)	p*	Total n/N (%)
Current cigarette smokers[b]	5/227 (2.20)	23/308 (7.47)	< 0.01	28/535 (5.23)
Other forms of experimentation (cigars, pipes, cheroots, chewed, and sniffed)[c]	23/235 (9.79)	94/316 (29.75)	< 0.0001	117/551 (21.23)
Water-pipe tobacco smoking experimentation[c]	86/235 (36.60)	155/315 (49.21)	< 0.005	241/550 (43.82)

NS: not significant. [a]Some denominators vary because of missing data. [b]Defined as lifetime smoking ≥ 100 cigarettes and currently reporting to be a cigarette smoker. [c]Defined as having ever used the product once. *Chi-square test.

Table 4. Prevalence of secondhand smoke exposure at home in the last seven days among medical undergraduate students, by smoking status.[a]

Secondhand smoke exposure, days	Group[b]		p*	Total
	Smoker n/N (%)	Nonsmoker n/N (%)		n/N (%)
0	20/28 (71.43)	413/502 (82.27)	NS	433/530 (81.70)
1-2	1/28 (3.57)	11/502 (2.19)	NS	12/530 (2.26)
3-4	2/28 (7.14)	39/502 (7.77)	NS	41/530 (7.74)
≥ 5	5/28 (17.86)	39/502 (7.77)	NS	44/530 (8.30)

NS: not significant. [a]Some denominators vary because of missing data. [b]Cigarette smokers/nonsmokers. *Chi-square test.

sale began to appear. We are currently in the third round of the warning images.[8-10]

The enforcement of the total ban of promotion and sponsorship of tobacco products was a consensus among the students. This generation has been protected against the tobacco industry advertising, because Brazil has banned sponsorship of all tobacco advertising, except at the points of sale, since 2000.[8-10] In contrast, our sample of students showed little knowledge about some of the topics related to smoking cessation training. Our poor result was similar to that in a study carried out in Italy.[11] Perhaps these findings can be explained by the fact that the respondents were still at the beginning of their medical course, and the treatment approach to smoking cessation has yet to be taught.

On the subject related to the importance of raising tobacco taxes, the results showed that few medical students agreed with this important recommendation, showing their little knowledge on the topic. Increasing taxes on and prices of tobacco products is one of the most effective measures for reducing smoking initiation among the youth, and it is also significantly effective in reducing consumption.[4] The Brazilian Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Diseases carried out two surveys (in 2006 and 2013) among smokers aged 18 years or older that showed that the prevalence of smoking decreased from 15.72% to 11.30%.[12] According to the International Tobacco Control Policy Evaluation Project/Brazil, taxes increased the prices of tobacco products by 30% in 2007, and taxes on retail pricing increased to 65% in 2009. This might have had an impact on the decrease in the prevalence of smoking.[8] Young people are two or three times more affected by tax and price rises than older smokers.[13] These measures reduce their chances of moving from tobacco experimentation to addiction. Medical students are the health practitioners of the future, and they need to know that this is the most important public health measure for tobacco control.[4,10] This subject must be taught in medical schools, and more discussions on this topic should be encouraged in order to strengthen the understanding of the positive impact of these measures by future doctors. We can observe in the present study and in another one carried out in four European countries[7] that there is a trend toward awareness of and agreement on an underage tobacco sales ban. Our research raised another interesting point because almost all of the respondents recognized that specific training in smoking cessation techniques is relevant to their education. The same result was found in a study carried out in India.[14]

The results showed a trend when the medical students recognized that they serve as role models for the general population. The respondents thought they should routinely offer advice or information to their patients who smoke cigarettes and use other tobacco products about quitting smoking and that the possibilities of smoking cessation increase with motivational intervention. Therefore, to improve the effectiveness of medical students as role models, medical schools need to have a comprehensive undergraduate curriculum that teaches issues related to tobacco smoking prevention and cessation. These results were also found in other studies.[7,14,15]

Physicians dedicate their lives to taking care of the greatest human patrimony; because of that, unfortunately, they have little time to take care of their own health. The findings showed a statistical significance on the issue related to their beliefs regarding the importance of the smoking status of health care professionals. Nonsmoking students more often believed, when compared with their smoking colleagues, that health professionals who smoke have

fewer chances to counsel their smoking patients to stop smoking. Because nicotine is an addictive substance, it is important to highlight the ethical role played by medical schools in offering smoking cessation treatment to their motivated students.[12,16,17]

Less than half of respondents said that, during their classes, they had discussed the reasons why people smoke; this corroborates the findings of another study, which showed slightly higher results than ours.[6] We emphasize that teaching about tobacco use triggers is essential for a comprehensive and correct approach to smoking.

Only a little over a third of the respondents reported having been taught that educational materials are an effective support for smoking cessation. This fact shows that this issue had not been addressed as effectively as it was in the University of Malta.[6]

The questions related to the pharmacological treatment for supporting smoking cessation revealed that the majority of the respondents had good knowledge of nicotine replacement therapies, and this result is similar to those seen in Germany and lower than those found in Spain.[7] In addition, more than half of the respondents in our survey had heard about nonnicotinic therapies for smoking cessation, our results being far more significant than those found in the European study.[7]

In the present study, the prevalence of cigarette smoking among the respondents was lower when compared with the results of a study carried out in India (5.23% vs. 13.4%)[14]; in addition, the proportion of our medical students experimenting with tobacco products other than cigarettes was almost half of that reported in the same study (21.23% vs. 40.5%). However, the frequency of experimenting with water-pipe tobacco smoking was significantly higher among our medical students (43.82%) than it was among medical students in Turkey and in Lebanon (28.6% and 29.5%, respectively).[18]

Although the vast majority of our medical students recognized the importance of smoking cessation counseling (regarding all forms of tobacco products), more than 40% had already tried water-pipe tobacco smoking. Among young people, there is a common belief that water-pipe tobacco smoking is less harmful to health than are traditional cigarettes. Educational and warning campaigns about the harms caused by the use of and experimentation with these types of products are urgent.

In 2009, the state of São Paulo, Brazil, enacted the Antismoking Law, creating smoke-free environments and banning the use of any smoking product, derived or not from tobacco, in all public and private enclosed places. Our study was conducted between 2008 and 2012, i.e., most of the study was carried out after that law came into force in the state, where our school of medicine is located. During that period, several educational campaigns were conducted to warn the population about the harms of secondhand tobacco smoke. This could have had a positive effect on the results in the present study.[9,19]

The main limitation of the present study was that it involved third-year medical students, who might not have received all the information and training regarding tobacco cessation programs. It is expected that such topics should be covered by the end of medical undergraduate courses. Studies comparing the medical curriculum in the third year with that in the last year have yet to be conducted.

Public tobacco control polices require that future physicians be prepared to take their key role in preventing smoking initiation and promoting smoking cessation. The results of the present study are encouraging; however, we need to emphasize to our students the importance of raising the prices of and taxes on tobacco products. We also need to make students aware of the dangers of experimenting with tobacco products other than cigarettes, particularly water-pipe tobacco smoking. Another point that deserves more attention and should be addressed even in the third-year medical curriculum involves the reasons why people smoke and the importance of providing educational materials to the population. Finally, it is strongly recommended that medical schools implement training in nicotine dependence treatment and reinforce the importance of a continuous, during medical visits, to motivate smokers to quit smoking.

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Effects of emissions from sugar cane burning on the trachea and lungs of Wistar rats

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ABSTRACT

Objective: To evaluate the effects of exposure to emissions from sugar cane burning on inflammatory mechanisms in tissues of the trachea and lung parenchyma in Wistar rats after different periods of exposure. **Methods:** This was an experimental open randomized study. The animals were divided into four groups: a control group (CG) underwent standard laboratory conditions, and three experimental groups were exposed to emissions from sugar cane burning over different periods of time, in days—1 (EG1), 7 (EG7), and 21 (EG21). After euthanasia with 200 mg/kg of ketamine/xylazine, fragments of trachea and lung were collected and fixed in 10% formalin. Histological analyses were performed with H&E and picrosirius red staining. **Results:** No inflammatory infiltrates were found in the tissues of CG rats. The histological examination of tissues of the trachea and lung parenchyma revealed that the inflammatory process was significantly more intense in EG7 than in the CG ($p < 0.05$ and $p < 0.01$, respectively). In comparison with the CG and EG1, angiogenesis in the lung parenchyma and collagen deposition in tracheal tissues were significantly greater only in EG21 ($p < 0.001$ and $p < 0.01$, respectively). **Conclusions:** In this sample, emissions from sugar cane burning induced acute focal and diffuse inflammation in the lamina propria of tracheal tissues, with no loss of ciliated epithelial tissue. In the lung parenchyma of the animals in the experimental groups, there was interstitial and alveolar edema, together with polymorphonuclear cell infiltrates.

Keywords: Saccharum; Smoke; Inflammation; Respiratory system.

INTRODUCTION

Sugar cane, *Saccharum officinarum*, is widely cultivated in Brazil for the production of ethanol and sugar, being essential to the country's economy.[1,2] Harvesting of sugar cane, when performed manually, is preceded by burning of sugar cane fields to remove dry leaves, facilitate cutting, and reduce the risk of bites and stings by venomous animals.[3-7]

Sugar cane combustion releases a large quantity of particulate matter (PM), in addition to gases, such as ozone, carbon monoxide, nitric oxide, sulfur oxide, formaldehyde, benzopyrene, and polycyclic aromatic hydrocarbons,[6-8] all of which contribute to air pollution and adversely affect human health.[2,9,10]

The PM and toxic compounds generated by sugar cane burning are harmful to the respiratory tract, because as they are inhaled and deposited in the lower airways, they are phagocytosed by alveolar macrophages, which release cytotoxic cytokines, thus inducing inflammation.[4,8] The stress caused by smoke can trigger a series of cellular reactions that aim to restore stability; however, when this stress is chronic, it causes irreversible cellular damage.[11] Coarse PM from smoke damages the upper airways, which are directly exposed to the external environment, whereas fine PM from smoke accumulates in the bronchi and bronchioles, leading to permanent damage and fibrosis.[12,13] Alveolar structures are susceptible to responses of an inflammatory nature and can cause pathological reactions with obstructive and restrictive consequences,[11,12,14-16] generally associated with the process of tissue remodeling.[14]

Although the risks from exposure to smoke, such as tobacco smoke or emissions from fossil fuel burning, are known, there have been few studies on this topic. Therefore, the objective of the present investigation was to use an experimental model to evaluate the effects of exposure to emissions from sugar cane burning on inflammatory mechanisms in tissues of the trachea and lung parenchyma after different periods of exposure.

METHODS

This was an experimental open randomized study. In the study, 28 male Wistar rats weighing 250-300 g were housed in cages with sawdust bedding, maintained on a 12/12-h light/dark cycle at 25-28°C, and provided free access to standard rodent chow and filtered water. The animals were divided into four groups: a control group (CG) of 4 animals underwent standard laboratory

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conditions for 24 h; and three experimental groups of 8 animals each were exposed to emissions from sugar cane straw burning for consecutive periods of 1, 7, and 21 days (EG1, EG7, and EG21, respectively). For the purposes of the study, a combustion chamber with a portable air extraction device was built where 200 g of sugar cane straw were burnt, generating a continuous stream of smoke that was piped into the cages of the experimental animals for 2 h daily at the same time of day (Figure 1).

The animals were euthanized by i.p. administration of 5% ketamine/xylazine diluted with 2 mL of physiological saline. After this procedure, the trachea was exposed and cannulated, a laparotomy was performed to separate the organs, and the abdominal aorta and inferior vena cava were sectioned. The trachea was then occluded by suture to maintain the lungs at functional residual capacity. A trans-sternal thoracotomy was performed through the diaphragm to remove the trachea and lungs. The collected organs were washed with physiological saline for macroscopic examination and were fixed in 10% buffered formalin.

Tissue fragments obtained from the material were processed conventionally and embedded in paraffin to prepare slides containing 5-µm sections. The sections were stained with H&E and picrosirius red for analysis under light microscopy (BX51; Olympus Optical, Tokyo, Japan) at a magnification of ×100. A digital camera (C-7070; Olympus) was used to obtain photomicrographs. To perform a semi-quantitative microscopic analysis, the histological changes found were classified as mild, moderate, or marked.

For a morphometric analysis, three photomicrographs were obtained of non-overlapping fields of the tissues studied. In the tracheal sections, areas containing hyaline cartilage, lamina propria, and ciliated epithelium were selected. In the lung parenchyma, bronchioles, alveoli, and blood vessels were evaluated. The nuclear area was quantified (in pixels) to evaluate the inflammatory process, using Adobe Photoshop CS5 software (Adobe Systems Inc.; San Jose, CA, USA). Collagen deposition was quantified by picrosirius red staining, positive staining corresponding to the presence of type I collagen. Angiogenesis was assessed by counting the number of blood vessels per quadrant of each panoramic photomicrograph, using BioEstat 5.3 software.

A statistical analysis was carried out using the Shapiro-Wilk normality test. After confirmation of normality, ANOVA with Tukey's post hoc test was used. In cases of non-normality, the Kruskal-Wallis test and Dunn's post hoc test were used. Results were expressed as group means and standard deviations and as box plots. The level of significance was set at 5%.

The study was approved by the Animal Research Ethics Committee of the *Faculdade Adventista da Bahia* (Protocol no. 013/2014).

RESULTS

Macroscopic examination of the trachea revealed no changes in tissue color or integrity in any of the groups. The lungs of EG7 and EG21 rats showed focal and diffuse macroscopic changes in different lobes, these changes being related to tissue color and texture.

The histological findings for each group are described below.

In the CG, there were no inflammatory infiltrates or structural tissue changes in the trachea (Figure 2). The lung parenchyma showed no alveolar, septal, or bronchiolar changes and was of normal appearance (Figure 3).

In EG1, a mild inflammatory infiltrate was present in the trachea in 87.5% of the cases. However, in 12.5% of the samples analyzed, the inflammatory response was intense and predominantly focal (Figure 2). In the lung parenchyma, an inflammatory process, consisting of 50% of polymorphonuclear cells, was present in 75% of the cases, and the diffuse form predominated over the focal one. Infiltrates were found in perivascular areas (ranging from mild to moderate) and in peribronchiolar areas. In addition, mild interstitial edema was observed, and there was no collagen deposition (Figure 3).

In EG7, inflammatory infiltrates of varying intensity—mild (in 62.5% of the cases), moderate (in 50.0%),

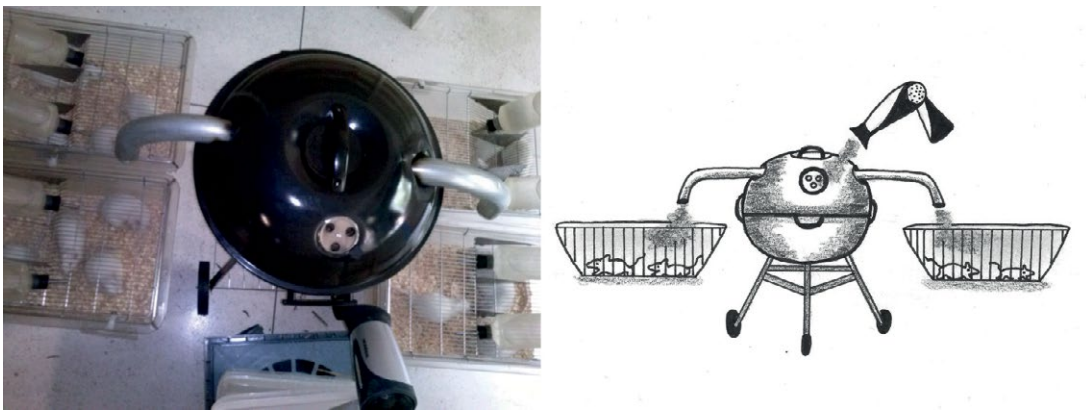

Figure 1. Photograph (in A) and schematic (in B) of the combustion chamber.

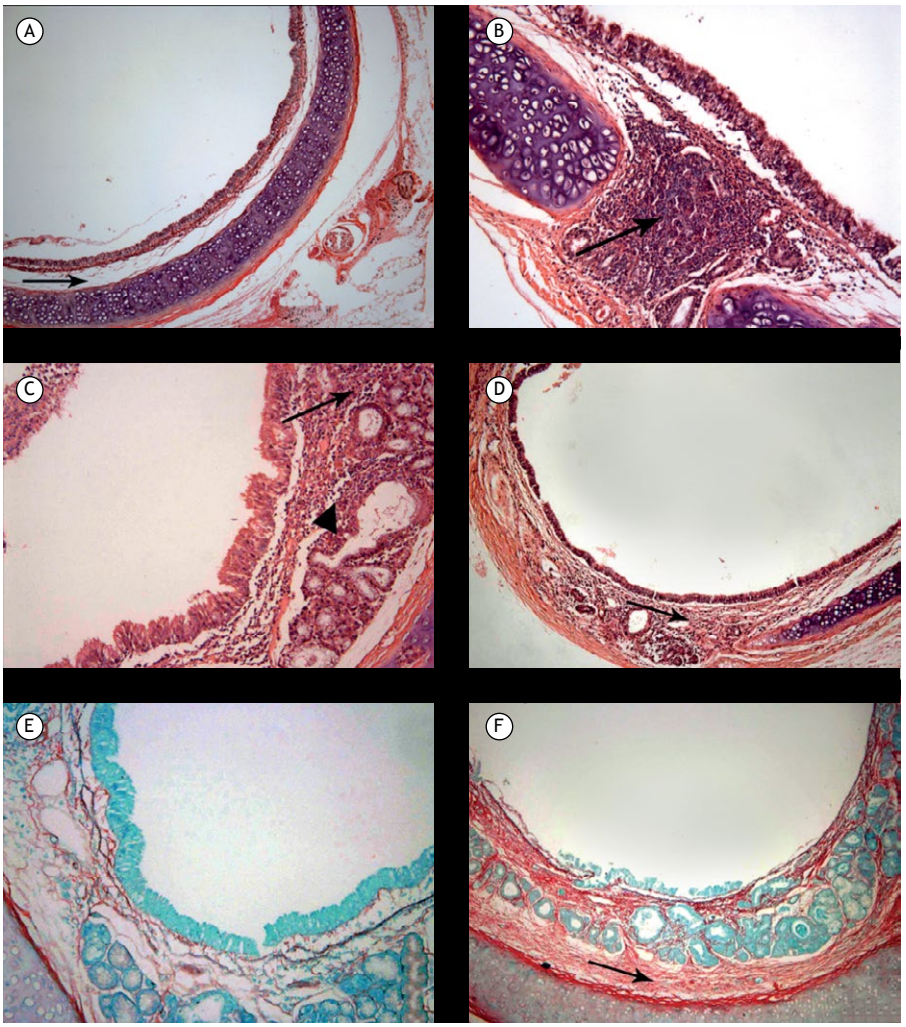

Figure 2. Photomicrographs of tracheal sections from animals in the different groups studied (H&E and picrosirius red; magnification, ×100). A (control group), Photomicrograph showing hyaline cartilage of normal appearance, with preservation of ciliated epithelium and no inflammatory infiltrates in the lamina propria (arrow). B (group exposed to emissions from sugar cane straw burning for 1 day), Photomicrograph showing intense focal inflammatory infiltrate in the lamina propria (arrow). C (7-day exposure group), Photomicrograph showing moderate diffuse acute inflammatory infiltrate in the lamina propria of the mucosa (arrow) and in the submucosal region adjacent to the seromucous glands (triangle), with ciliary preservation. D (21 day-exposure group), Photomicrograph showing mild to moderate diffuse inflammatory infiltrate in the lamina propria of the mucosa (arrow). E (7-day exposure group), Photomicrograph showing mild staining for collagen. F (21-day exposure group), Photomicrograph showing increased acidophilia of the connective tissue, indicating collagen deposition (arrow).

and intense (in 25.0%)—were present in the tracheal tissue (Figure 2). The onset of collagen deposition was demonstrated by the increased acidophilic reaction in the trachea after picrosirius red staining (Figure 2). Microscopic examination of the lung parenchyma revealed an inflammatory process in 87.5% of the cases and a polymorphonuclear cell infiltrate in 62.5%. A mild to intense diffuse inflammatory process was present in 75% of the cases. A perivascular infiltrate pattern was present in 62.5% of the specimens. In addition, perivascular and peribronchiolar collagen deposition was found (Figure 3).

In EG21, a diffuse inflammatory infiltrate was observed in 75% of the cases, being of mild (in 25%) to moderate (in 50%) intensity. No intense inflammatory infiltrates were found (Figure 2). After picrosirius red staining, there was increased acidophilia, indicating the presence of collagen (Figure 2). Histological examination of the lung parenchyma revealed mild to intense diffuse inflammatory infiltrates, with a predominance of mononuclear cells, in 100% of the cases. There was mild perivascular and peribronchiolar inflammation in 50% and 25% of the cases, respectively. Necrosis was observed in 37.5% of the cases and angiogenesis was observed in 100% ($p < 0.001$) when EG21 was compared with the CG and EG1; in addition, perivascular and peribronchiolar collagen deposition was seen, as was alveolar collagen deposition (Figure 3).

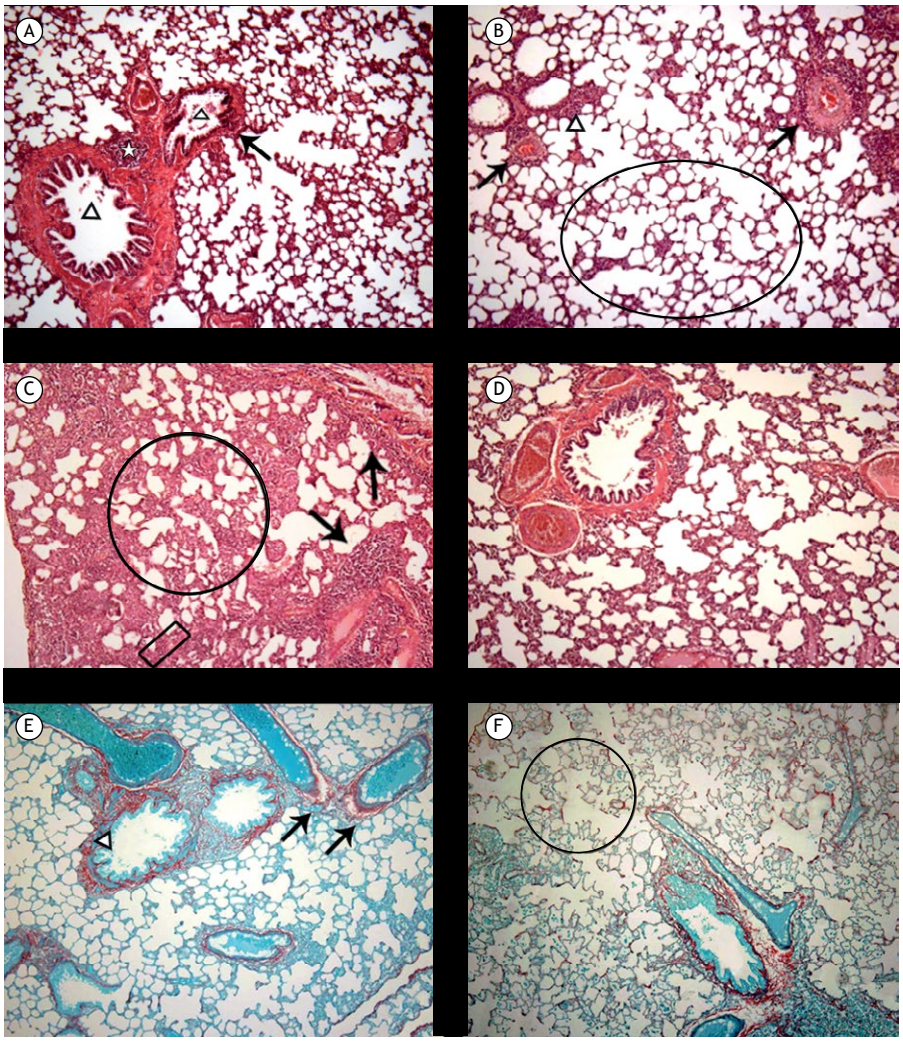

Figure 3. Photomicrographs of tissue sections from animals in the different groups studied (H&E and picrosirius red; magnification, ×100). A (control group), Photomicrograph showing terminal bronchioles (triangle), respiratory bronchioles (arrow), alveolar ducts, and bronchus-associated lymphoid tissue (star) without tissue changes. B (group exposed to emissions from sugar cane straw burning for 1 day), Photomicrograph showing focal perivascular (arrows) and peribronchiolar (triangle) inflammatory infiltrates and diffuse infiltrate in the lung parenchyma (circle). C (7-day exposure group), Photomicrograph showing changes in alveolar architecture (circle) and intense, diffuse peribronchiolar and perivascular inflammatory infiltrates (arrows). D (21-day exposure group), Photomicrograph showing moderate diffuse alveolar inflammatory infiltrate, together with alveolar edema and septal losses. E (7-day exposure group), Photomicrograph showing perivascular (arrows) and peribronchiolar (triangle) collagen deposition. F (21-day exposure group), Photomicrograph showing perivascular and peribronchiolar collagen deposition and alveolar collagen deposition (circle).

Morphometric and statistical analysis (Figure 4) demonstrated the presence of an inflammatory process in the tracheal tissue of experimental group rats. The mean nuclear area (in pixels) was 379.78 ± 105.65 in the CG, 650.36 ± 147.74 in EG1, 899.18 ± 183.65 in EG7, and 751.96 ± 143.64 in EG21. In comparison with the CG, EG7 showed a more significant inflammatory response ($p < 0.05$). The data obtained from the morphometric analysis are complementary to the findings of the semi-quantitative analysis.

Morphometry after picrosirius red staining revealed no collagen deposition in the CG and showed a slight progressive, but not statistically significant, increase in acidophilia in EG1 and EG7. However, tracheal tissue collagen deposition was found to be greater in EG21 than in the CG and EG1 ($p < 0.01$ for both; Figure 4).

Morphometric analysis of the lung parenchyma was performed by determining the mean nuclear area (in pixels). In the CG, the mean nuclear area was 893.13 ± 51.89, which is within normal values. In EG1, polymorphonuclear and mononuclear cellularity started to increase, and the mean nuclear area was 1,373.66 ± 155.43; in EG7, the mean nuclear area reached 2,280.98 ± 744.80 ($p < 0.01$ in the intergroup comparison). However, the mean nuclear area decreased

to 1,251.31 ± 231.75 in EG21, which is suggestive of tissue repair (Figure 5).

Morphometric analysis showed no angiogenesis in the CG, EG1, or EG7. In contrast, in EG21, angiogenesis was detected in 100% of the cases (Figure 5).

DISCUSSION

Our results show that exposure of Wistar rats to emissions from sugar cane burning over different periods of exposure was associated with increased inflammation in tracheal and lung tissues. Focal and diffuse inflammatory polymorphonuclear cell infiltrates were found in the acute phase in the trachea of experimental group rats, especially of EG7 rats. No loss of ciliated epithelium was observed in any of the experimental groups relative to the CG. Tissue fibrosis in the trachea, corresponding to the early stages of the chronic phase, was confirmed in EG21. In the lung parenchyma, alveolar, vascular, and bronchiolar changes were observed in the experimental groups relative to the CG. The time criteria adopted for designating the inflammatory response phases were based on a study of Wistar rats that were administered bleomycin sulfate, in which the inflammatory response was characterized as acute (from day 1 to day 7 after the insult); subacute (from day 7 to day 14 after the insult); and resolving (from day 15 to day 30 after the insult).[17]

An experimental study, in which rats received intratracheally-instilled fine PM, observed lung inflammation characterized by macrophage and

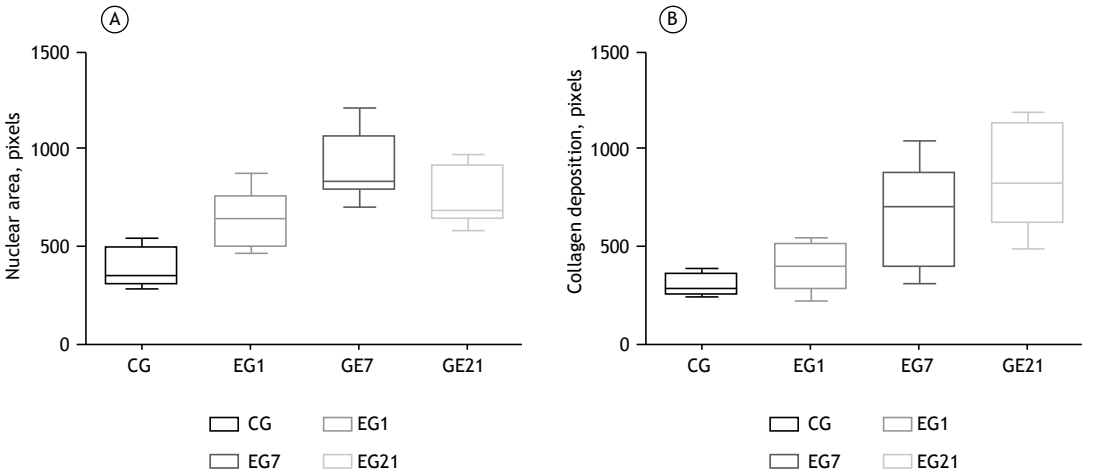

Figure 4. Morphometric analysis of the trachea in the control group (CG) and in the groups exposed to emissions from sugar cane straw burning for 1 day (EG1), for 7 days (EG7), and for 21 days (EG21). In A, kinetics of the inflammatory process as determined by nuclear area analysis. EG7 showed a significant difference relative to the CG ($p < 0.05$). There was a reduction in inflammation in EG21, suggestive of initiation of tissue repair. In B, determination of collagen deposition. Only EG21 showed significant differences relative to the CG and EG1 ($p < 0.01$ for both).

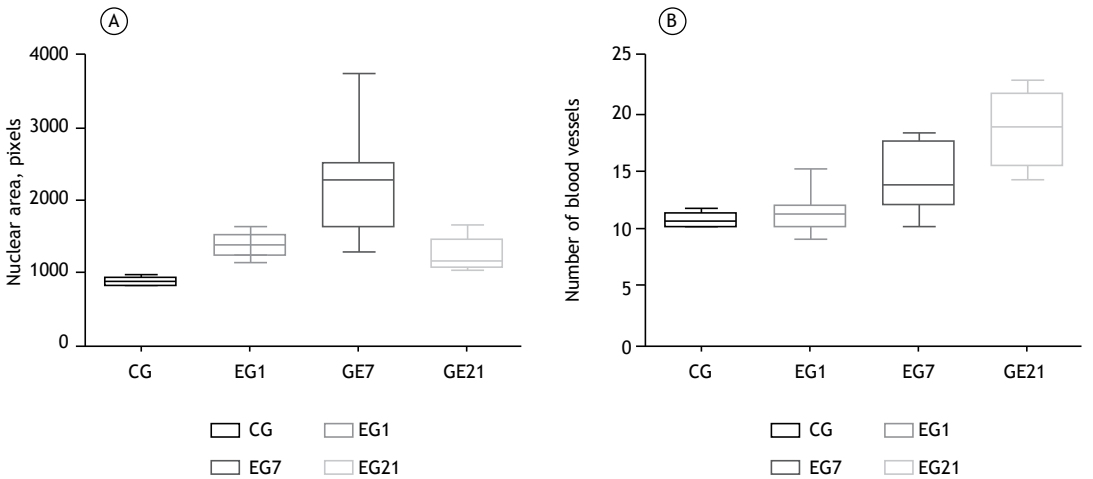

Figure 5. Morphometric analysis of the lung parenchyma in the control group (CG) and in the groups exposed to emissions from sugar cane straw burning for 1 day (EG1), for 7 days (EG7), and for 21 days (EG21). In A, nuclear area analysis showing the presence of an inflammatory infiltrate in all groups. EG7 showed statistically significant differences relative to the CG, EG1, and EG21 ($p < 0.01$ for all). There was a reduction in inflammation in EG21, suggestive of initiation of tissue repair. In B, quantification of the number of blood vessels. There was an increase in EG7, but angiogenesis was confirmed only in EG21 with significant differences relative to the CG and EG1 ($p < 0.001$ for both).

neutrophil infiltrates, demonstrating that cytokines (IL-12 and IFN-γ) play a key role in injury severity[18]; similarly, an experimental rabbit study found an increased recruitment of macrophages and polymorphonuclear cells in the lung parenchyma.[19] In the present study, we found inflammatory changes consisting of polymorphonuclear cells and alveolar macrophages in the lung tissue of rats as early as in EG1.

Tracheal instillation of low doses of PM from sugar cane burning produced changes in the respiratory tract by reducing the thickening of the connective tissue and increasing the production of proinflammatory cytokines and chemokines.[8] In the present study, morphometry confirmed that emissions from sugar cane burning are able to induce significant and progressive necrotic inflammatory processes, even after short periods of exposure. Alveolar macrophages (after phagocytosis), as well as lung epithelial cells, respond to exposure to PM by increasing inflammatory mediator production, which can lead to certain mechanisms, such as leukocyte proliferation and activation, apoptosis, and endothelial repair.[20] These changes are explained by the elements present in smoke; these data confirm our findings, especially in EG7.

It is known that the size of particles emitted from biomass burning has a negative impact on the airways.[21,22] The size of inhaled PM, in terms of varying particle granularity, determines the clinical manifestations in the body. Coarse PM (< 10 μm) is retained in the upper airways and can be removed by ciliary activity; thin PM (< 2.5 μm) and ultrafine particles/nanoparticles (< 0.1 μm) are usually the result of incomplete oxidation of carbon.[22-24] Fine and ultrafine PM have the ability to reach the alveoli and be phagocytosed by alveolar macrophages, having greater deleterious effects, such as changes in lung mechanics, alveolar collapse, and oxidative stress, in rats.[23-26] Chronic exposure to fine particles is strongly associated with higher rates of chronic respiratory disease.[3]

After direct exposure of mice to dung biomass smoke for 7 consecutive days, a significant increase in cellularity, especially in macrophage cellularity, was observed in the lungs.[27] Exposure to emissions from sugar cane burning produced inflammatory infiltrates of varying intensity in the animals of the present study, and, in EG7, there was a more significant inflammatory infiltrate in both tissues of the trachea and lung parenchyma, given that there were areas of more severe inflammation.

Damage to the lung parenchyma after chronic exposure to dung biomass smoke and cigarette smoke includes moderate to marked interstitial inflammation, bronchial and perivascular inflammation, vascular congestion, alveolar destruction, an increase in the number of macrophages, and an increase in vascular wall thickness.[3] In the present study, although the exposure was acute only, it was possible to observe that the experimental groups showed a growing change in alveolar structure (septal loss) relative to the CG, with PM being phagocytosed especially in EG1. Areas suggestive of necrosis were identified especially in EG7 and EG21, and angiogenesis was confirmed in EG21.

Rabbits chronically exposed to emissions from biomass and cigarette burning show perivascular inflammation, peribronchiolar inflammation, parenchymal infiltrate, and fibrosis, with respiratory epithelial proliferation and emphysematous changes.[28] Using picrosirius red staining, we demonstrated that, in EG7 and EG21, there were areas of tracheal tissue collagen deposition, areas of peribronchiolar and vascular collagen deposition, and diffuse areas of lung parenchymal collagen deposition, which suggest that continued exposure can lead to a tissue fibrotic process.

On the basis of morphological criteria, we found that the changes in alveolar structure in EG7 and the rupture of interalveolar septa in EG21 were consistent with the findings of a rat study that showed that 24.6% of the cigarette smoke-exposed animals had increased alveolar spaces relative to controls, which were not exposed.[29]

Therefore, the above data allow us to state that acute exposure to emissions from sugar cane burning is able to induce severe damage to the respiratory system. The components of emissions from sugar cane burning trigger polymorphonuclear cell inflammatory processes in the trachea and also induce inflammatory infiltrates and interstitial and alveolar edema in the lung parenchyma of Wistar rats. Changes in alveolar architecture and angiogenesis are also found.

Further research targeting prolonged exposure and determination of proinflammatory marker levels is needed to demonstrate the potential damage caused by chronic exposure to the components of emissions from sugar cane burning, since workers in sugar cane fields and the neighboring population are exposed to these emissions for long periods of their life.

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Frequency of indeterminate results from an interferon-gamma release assay among HIV-infected individuals

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ABSTRACT

Objective: To evaluate the frequency of and factors associated with indeterminate interferon-gamma release assay (IGRA) results in people living with HIV/AIDS (PLWHA). **Methods:** We tested 81 PLWHA in the central-west region of Brazil, using the tuberculin skin test and an IGRA. Information on sociodemographic and clinical variables was gathered through the use of questionnaires and from medical records. The association of those variables with indeterminate results was analyzed by calculating the adjusted ORs in a multivariate logistic regression model. Concordance was evaluated by determining the kappa statistic. **Results:** Among the 81 patients evaluated, the tuberculin skin test results were positive in 18 (22.2%) of the patients, and the IGRA results were positive in 10 (12.3%), with a kappa of 0.62. The IGRA results were indeterminate in 22 (27.1%) of the patients (95% CI: 17.8-38.1%). The odds of obtaining indeterminate results were significantly higher in smokers (adjusted OR = 6.0; 95% CI: 1.4-26.7) and in samples stored for less than 35 days (adjusted OR = 14.0; 95% CI: 3.1-64.2). Patients with advanced immunosuppression (CD4+ T-cell count < 200 cells/mm^3) were at a higher risk for indeterminate results (OR adjusted for smoking and inadequate duration of sample storage = 4.7; 95% CI: 0.91-24.0), although the difference was not significant. **Conclusions:** The high prevalence of indeterminate results can be a major limitation for the routine use of IGRAs in PLWHA. The need to repeat the test increases its costs and should be taken into account in cost-effectiveness studies. The processing of samples can significantly alter the results.

Keywords: Interferon-gamma release tests; Interferon-gamma; Tuberculosis; HIV; Latent tuberculosis; Tuberculin test.

INTRODUCTION

In people living with HIV/AIDS (PLWHA), the treatment of latent tuberculosis infection (LTBI) is crucial for reducing morbidity and mortality.[1] Therefore, the identification and appropriate treatment of LTBI in PLWHA is a priority. Currently, there are two classes of tests for detecting LTBI[2]: the tuberculin skin test (TST) and interferon-gamma (IFN-γ) release assays (IGRAs). Two commercially available IGRAs have been widely studied: the QuantiFERON-TB Gold In-Tube (QFT-GIT) assay (Cellestis, Carnegie, Australia), and the T-SPOT.TB assay (Oxford Immunotec, Abingdon, UK). IGRAs have replaced or been added to the TST in many high-income countries.[2] However, the World Health Organization does not recommend these tests for detecting LTBI in low- and medium-income countries. The TST and IGRAs both show lower sensitivity in PLWHA, because both evaluate the T-cell response to mycobacterial antigens.[3] Although high rates of indeterminate QFT-GIT results have been reported in countries with high HIV burdens, those rates can vary according to the geographic region and the severity of immunosuppression.[4,5] In the presence of indeterminate results, repeating the test once is recommended.[6]

The recent temporary discontinuation of the most widely used PPD (RT23; Statens Serum Institut, Copenhagen, Denmark) has resulted in market shortage of tuberculin, which has impeded the identification of LTBI in PLWHA in several countries. Replacing the TST with the QFT-GIT assay could be an option, even in low-income countries.

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The objective of the present study was to evaluate the frequency of and factors associated with indeterminate QFT-GIT results in a sample of PLWHA.

METHODS

From January to December of 2011, we conducted a cross-sectional study at the Infectious Disease Clinic of the Federal University of Mato Grosso do Sul. Mato Grosso do Sul is a state with a moderate incidence of tuberculosis (38.8/100,000 population), located in the central-west region of Brazil. The Brazilian National Tuberculosis Guidelines recommend that all PLWHA undergo the TST at least every six months.[7] In this study, we included HIV-infected subjects ≥ 18 years of age, all of whom gave written informed consent for additional QFT-GIT testing. Patients with active tuberculosis were excluded, as were those under treatment for LTBI. The study was approved by the Research Ethics Committee of the Federal University of Mato Grosso do Sul (Protocol no. 1060/2008).

Information was gathered through the use of a questionnaire and from medical records. Each TST was performed using two units of PPD RT23 (Statens Serum Institut) on the volar aspect of the left forearm. After 48-72 h, a trained nurse measured the induration. An induration ≥ 5 mm in diameter was considered indicative of a positive reaction.[7] The QFT-GIT assay was performed in accordance with the manufacturer's protocol. In brief, whole blood samples were collected directly into 1-mL heparinized tubes containing either *Mycobacterium tuberculosis* antigens (early secretory antigenic target 6, culture filtrate protein 10, and TB7.7); dextrose and PHA (positive control); or no antigens (negative control). Tubes were incubated for 24 h at 37°C and centrifuged at 2,000 *g* for 10 min, after which the serum supernatant was harvested. The median time from blood collection to incubation was 144 min (range, 10-294 min). All supernatants were stored at −70°C for up to 8 weeks, until ELISA was performed to quantify the amount of secreted IFN-γ. The assay was run in batches of 24-44 samples of the same lot. Software provided by the manufacturer was used in order to analyze the results. The QFT-GIT result was considered positive if the IFN-γ level after stimulation with *M. tuberculosis* antigens minus the negative control was ≥ 0.35 IU/mL and 25% higher than the IFN-γ concentration in the unstimulated control sample, whereas it was considered negative if the IFN-γ level was < 0.35 IU/mL. The result was considered indeterminate if the IFN-γ production in the unstimulated sample was ≥ 8.0 IU/mL or the PHA minus the IFN-γ concentration in the unstimulated sample was < 0.5 IU/mL. When the first QFT-GIT assay produced an indeterminate result, we did not perform a second assay, the clinical decision being based on the TST.[7] Concordance between the QFT-GIT and TST was assessed using the kappa statistic. Agreement was considered excellent if the kappa was > 0.75, fair if it was 0.4-0.75, and poor if it was < 0.4. For the concordance calculation, only positive and negative results were included. Proportions were compared using the adjusted OR (aOR) and its 95% confidence interval in a multivariate regression model. Analyses were carried out with the SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Eighty-one PLWHA were enrolled in the study. The median age was 41 years (range, 34-48 years); the median CD4+ T-cell count was 422 cells/mm^3 (interquartile range [IQR], 221-646 cells/mm^3). Among the 81 subjects, the TST and QFT-GIT results were positive in 18 (22.2%) and 10 (12.3%), respectively. Indeterminate QFT-GIT results were obtained in 22 (27.1%) of the subjects (95% CI: 17.8-38.1%). The concordance between the two tests (among valid results) was categorized as fair (κ = 0.62; 95% CI: 0.37-0.87), mainly due to a higher number of negative results on the TST (Table 1).

Among the subjects for whom an indeterminate result was obtained, the median CD4+ T-cell count was 329 cells/mm^3 (IQR, 156-575 cells/mm^3), compared with 494 cells/mm^3 (IQR, 235-696 cells/mm^3) among those for whom a valid result was obtained (p = 0.237). The odds of obtaining an indeterminate result were 6.0 times higher if the subject was a smoker, 14.2 times higher if the duration of sample storage was < 35 days, and 4.7 times higher if the subject had advanced immunosuppression (CD4+ T-cell count < 200 cells/mm^3), although the last was not statistically significant, even after adjustment for storage duration and smoking (Table 1).

DISCUSSION

The frequency of indeterminate QFT-GIT results has been reported to range from 0% to 19.8%.[8-12] Many variables have been associated with indeterminate results: HIV infection,[9] advanced immunosuppression,[9] previous BCG vaccination,[10] immunosuppression therapy,[11] underlying diseases,[11] bedridden status,[8] hypoalbuminemia,[8] and active tuberculosis.[13] Technical aspects also result in a significant increase in the proportion of indeterminate results[6,9,11]: manufacturing defects; analytical errors; incubation or processing delay; incorrect tube shaking technique; and inappropriate blood volume. In our study, we found the proportion of indeterminate QFT-GIT results to be higher than that reported in the literature. Different than in previous reports, that proportion was not significantly associated with the CD4+ T-cell count or BCG status, although few of our subjects had CD4+ T-cell counts lower than 200 cells/mm^3, which reduced the power of our analysis. In contrast, smoking and shorter serum storage before processing for ELISA were found to strongly increase the odds of indeterminate results. Smoking can induce immunosuppression through mechanisms other than lowering the CD4+ T-cell count, such as reducing the proliferative response to

Table 1. Factors associated with indeterminate QuantiFERON-TB Gold In-Tube results in 81 HIV-infected patients.

Characteristic	QFT-GIT result			OR (95% CI)	aOR (95% CI)
	Positive n (%)	Negative n (%)	Indeterminate n (%)		
Overall	10 (12)	49 (60)	22 (27)	--	--
Gender					
Female (n = 41)	5 (12)	23 (56)	13 (31)	1.6 (0.50-4.3)	--
Male (n = 40)	5 (12)	26 (65)	9 (22)	1.0 (reference)	
Age group					
42-84 years (n = 40)	7 (17)	23 (57)	10 (25)	0.81 (0.30-2.2)	--
18-41 years (n = 41)	3 (7)	26 (63)	12 (27)	1.0 (reference)	
Using HAART					
No (n = 10)	1 (10)	6 (60)	3 (30)	1.2 (0.28-5.1)	--
Yes (n = 64)	8 (13)	39 (61)	17 (27)	1.0 (reference)	
Unknown (n = 7)	1 (14)	4 (57)	2 (28)		
Smoking					
Yes (n = 51)	8 (15)	24 (47)	19 (37)	5.3 (1.4-20.0)	6.0 (1.4-26.7)
No (n = 30)	2 (16)	25 (83)	3 (10)	1.0 (reference)	
Alcohol abuse (CAGE)					
Yes (n = 3)	1 (33)	1 (33)	1 (33)	1.4 (0.12-15.9)	--
No (n = 76)	9 (12)	46 (62)	21 (27)	1.0 (reference)	
BCG scar					
No (n = 22)	3 (14)	14 (64)	5 (23)	1.2 (0.40-3.9)	
Yes (n = 53)	6 (11)	33 (62)	14 (26)	1.0 (reference)	--
Unknown (n = 6)	1 (16)	2 (33)	3 (50)		
TST					
≥ 5 mm (n = 18)	8 (44)	5 (28)	5 (28)	1.04 (0.32-3.4)	--
< 5 mm (n = 63)	2 (3)	44 (70)	17 (27)	1.0 (reference)	
CD4+ T-cell count					
< 200/mm^3 (n = 13)	1 (8)	5 (39)	7 (54)	4.0 (1.2-13.9)	4.7 (0.91-24.0)
≥ 200/mm^3 (n = 62)	9 (15)	39 (63)	14 (23)	1.0 (reference)	
Unknown (n = 6)	--	5 (84)	1 (16)		
HIV viral load					
Undetectable (n = 44)	10 (23)	29 (66)	10 (23)	1.8 (0.65-4.9)	
≥ 50 copies/mm^3 (n = 62)	11 (34)	16 (50)	11 (34)	1.0 (reference)	--
Unknown (n = 5)	--	4 (80)	1 (20)		
Duration of sample storage					
≤ 35 days (n = 41)	2 (5)	19 (48)	19 (48)	11.5 (3.0-43.3)	14.2 (3.1-64.2)
> 35 days (n = 40)	8 (20)	30 (73)	3 (7)	1.0 (reference)	
Incubation delay					
> 144 min (n = 40)	6 (15)	29 (73)	5 (13)	5.0 (1.6-15.3)	--
≤ 144 min (n = 41)	4 (10)	20 (49)	17 (42)	1.0 (reference)	
Years since HIV/AIDS diagnosis	-				
≥ 7 (n = 39)	6 (15)	23 (59)	10 (26)	0.91 (0.34-2.5)	--
< 7 (n = 40)	4 (10)	25 (63)	11 (28)	1.0 (reference)	
Unknown (n = 2)	--	2 (67)	1 (33)		

QFT-GIT: QuantiFERON-TB Gold In-Tube; aOR: adjusted OR (adjusted for CD4+ T-cell count, smoking, and sample storage duration); HAART: highly active antiretroviral therapy; CAGE: Cut down, Annoyed, Guilty, Eye-opener (questionnaire); and TST: tuberculin skin test.

mitogens.[14] We know of no reports of freezer storage time affecting QFT-GIT results, and we can offer no reasonable explanation for our finding that shorter serum storage increased the odds of indeterminate results. Regardless of the reasons for indeterminate results, a second test is recommended when the first produces such a result, and repeating tests will significantly increase laboratory costs.[5] Despite the small size of our study sample, we do not believe that there was a selection bias.

In summary, we found that a high proportion of QFT-GIT assays produced indeterminate results, which represents a major limitation to the use of such assays in PLWHA in Brazil. This finding has relevant implications for the cost-effectiveness and feasibility of adopting the use of QFT-GIT assays in low and medium-income countries.

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Brazilian guidelines for the diagnosis and treatment of cystic fibrosis

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ABSTRACT

Cystic fibrosis (CF) is an autosomal recessive genetic disorder characterized by dysfunction of the *CFTR* gene. It is a multisystem disease that most often affects White individuals. In recent decades, various advances in the diagnosis and treatment of CF have drastically changed the scenario, resulting in a significant increase in survival and quality of life. In Brazil, the current neonatal screening program for CF has broad coverage, and most of the Brazilian states have referral centers for the follow-up of individuals with the disease. Previously, CF was limited to the pediatric age group. However, an increase in the number of adult CF patients has been observed, because of the greater number of individuals being diagnosed with atypical forms (with milder phenotypic expression) and because of the increase in life expectancy provided by the new treatments. However, there is still great heterogeneity among the different regions of Brazil in terms of the access of CF patients to diagnostic and therapeutic methods. The objective of these guidelines was to aggregate the main scientific evidence to guide the management of these patients. A group of 18 CF specialists devised 82 relevant clinical questions, divided into five **categories:** characteristics of a referral center; diagnosis; treatment of respiratory disease; gastrointestinal and nutritional treatment; and other aspects. Various professionals working in the area of CF in Brazil were invited to answer the questions devised by the coordinators. We used the PubMed database to search the available literature based on keywords, in order to find the best answers to these questions.

Keywords: Cystic fibrosis/diagnosis; Cystic fibrosis/therapy; Cystic fibrosis/complications; Practice guideline.

INTRODUCTION

Cystic fibrosis is an autosomal recessive genetic disorder characterized by dysfunction of the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene, which encodes a protein that regulates chloride transmembrane conductance. It is a multisystem disease that most often affects White individuals. In Brazil, the incidence of cystic fibrosis is estimated to be 1 in 7,576 live births; however, there are regional differences, with higher values being found in the southern states.[1]

In recent decades, various advances in the diagnosis and treatment of cystic fibrosis have drastically changed the scenario of this disease, resulting in a significant increase in survival and a gain in quality of life. In Brazil, the current neonatal screening program for cystic fibrosis has broad coverage, and most of the Brazilian states have referral centers for the follow-up of individuals with the disease. Previously, cystic fibrosis was limited to the pediatric age group. However, an increase in the number of adult patients with cystic fibrosis has been observed, because of the

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*Os autores contribuíram de forma equivalente para o trabalho.
*These authors contributed equivalently to this work.

greater number of individuals being diagnosed with atypical forms (with milder phenotypic expression) and because of the increase in life expectancy provided by the new treatments.[2-4] However, there is still great heterogeneity among the different regions of Brazil in terms of the access of patients with cystic fibrosis to diagnostic and therapeutic methods. The objective of this publication was to aggregate the main scientific evidence to guide the management of patients with cystic fibrosis, this body of evidence being compiled by the main health professionals involved in caring for this disease in Brazil.

METHODS

A group of 18 cystic fibrosis specialists (coordinators) devised 82 relevant clinical questions, divided into five categories: characteristics of a referral center; diagnosis; treatment of respiratory disease; gastrointestinal and nutritional treatment; and other aspects. Various professionals working in the area of cystic fibrosis in Brazil were invited to answer the questions devised by the coordinators of the guidelines.

We used the PubMed database to search the available literature based on keywords, in order to find the best answers to these questions. In addition, manual searches of references in articles or books were performed. The Oxford Centre for Evidence-Based Medicine guidelines were used to classify the level of evidence for the questions regarding the treatment chapters. The guidelines include a classification system for levels of evidence of studies, with levels of evidence ranging from "1" (highest level) to "5" (lowest level). The classification system was simplified in 2011 in order to facilitate its clinical application. Chart 1A (JBP online appendix—http://jornaldepneumologia.com.br/detalhe_anexo.asp?id=51) provides further details on the current Oxford classification system.

A total of 2,352 publications were identified using the keyword search strategy, manual searches, and reference suggestions made by the authors. A total of 243 articles were selected for the present paper.

The first version of the text was written between March and August of 2016. The coordinators of each area were responsible for the validation of the level of evidence classification. In controversial cases, the questions were brought to a consensus meeting of coordinators on September 24, 2016. The final version was reviewed by the national coordinators (the first two authors) and sent to the editor of the JBP in February of 2017.

CHARACTERISTICS OF A REFERRAL CENTER

How important is a referral center in the care of patients with cystic fibrosis?

The complexity of cystic fibrosis and the peculiarities of its treatment result in the need for specialized treatment centers.[5] There is evidence that treatment at specialized referral centers, which have a multidisciplinary team, results in better clinical results, with an impact on prognosis.[6,7]

What is a referral facility and what is a referral center?

A referral center is defined as one that treats at least 50 patients regularly. It should have a structure that meets the needs related to diagnosis, follow-up, and treatment.

A referral facility is one that treats fewer than 50 patients, and it can have a less complex structure. It should be affiliated with a referral center for the purposes of continuing education and of supplementing any needs.[5]

How important is a multidisciplinary team? What would be the composition of such a team?

Given that cystic fibrosis is characterized by chronic multisystem involvement, it requires a multidisciplinary care model.[5] The care provided by a multidisciplinary team enables more comprehensive and effective treatments, resulting in an increased patient life expectancy.[5,8,9] The minimum multidisciplinary team for treating patients with cystic fibrosis should consist of the following professionals: pediatricians (when treatment is provided to children and adolescents); pulmonologists; gastroenterologists; physical therapists; nutritionists; nurses; psychologists; pharmacists; and social workers.

Are there differences between pediatric and adult centers? Are there advantages to planning for transitioning from pediatric to adult care?

Pediatric cystic fibrosis centers are quite different from adult cystic fibrosis centers. Adults have control and autonomy over their care. Pediatric centers need to meet demands that are characteristic of childhood, both in terms of structure and health professionals. Adult centers need resources to treat cases of greater complexity (comorbidities and different and more frequent complications, as well as pregnancy).[10]

Transitioning an adolescent patient into an adult center is challenging, and there is evidence that transition programs optimize the process of transfer to the adult center.[11-15]

What should the referral center infrastructure be like? What are the basic ancillary tests?

Referral centers should have multidisciplinary teams and resources so that they can provide accurate diagnoses and comprehensive care to patients with cystic fibrosis. They should be able to treat all cystic fibrosis complications, or provide referral to treatment, and should work in conjunction with facilities that are closer to the place of residence of the patients.[5,16]

Patients should have 24-h/day access to the center or to emergency facilities affiliated with the center.[16]

Each referral center should have or should ensure access to:

- A laboratory for conducting tests to confirm the diagnosis of cystic fibrosis: sweat testing and/or *CFTR* gene mutation analysis
- A pulmonary function laboratory
- A microbiology laboratory with experience in and resources for identifying typical cystic fibrosis pathogens
- A radiology department with CT
- A clinical pathology laboratory with the capacity to perform routine tests, including hematologic tests, liver and kidney function tests, serology, and determination of proteins, vitamins, and immunoglobulins.

How important is microbiological segregation? How should it be done?

There is ample evidence that pathogen transmission can occur among individuals with cystic fibrosis, especially via droplets and contact. It can involve virulent strains, worsening disease progression. Infection control and prevention measures have been effective in decreasing pathogen transmission. Patient segregation should be instituted inside and outside the hospital setting to prevent cross infection. Cystic fibrosis centers should provide adequate structure and have a clear Infection control and prevention policy, including separate days of treatment for patients or use of different treatment spaces on the basis of patient colonization.[5,17-19]

How important is commitment to care, research, and teaching?

A cystic fibrosis center should be committed to active participation in clinical and translational research, enabling patient participation in clinical trials. Education, research, and contribution to cystic fibrosis registries should be preferably performed by all centers. The various members of the multidisciplinary team should play an active role in research and education. Their work contributes to increasing and disseminating specialized knowledge, which plays a significant role in improving the quality of care.[5]

What are the advantages of cooperation with cystic fibrosis patient/parent associations and with the Brazilian Cystic Fibrosis Study Group?

Cystic fibrosis patient/parent associations aim at defending the interests of this group of individuals, which includes making the disease known and improving diagnosis and treatment, in order to increase survival, improve quality of life, and integrate patients into society.[5] In North America and Europe, some of these associations still play an important role in promoting and funding scientific research and in registering patients.

In Brazil, bringing cystic fibrosis patient/parent associations closer to health professionals working in cystic fibrosis (currently represented by the Brazilian Cystic Fibrosis Study Group) would offer great advantages that could improve the current situation, such as aid in the inclusion of all Brazilian patients in the national registry (Brazilian Cystic Fibrosis Registry) and monitoring of the availability of medications in the various Brazilian states, in addition to the joining of forces to submit to the Federal Government a new (more comprehensive) directive on the care of the cystic fibrosis patient.

DIAGNOSIS

How does one confirm the diagnosis of cystic fibrosis after positive newborn screening?

The cystic fibrosis newborn screening algorithm used in Brazil is based on two determinations of immunoreactive trypsinogen levels, the second of which is performed within 30 days of life. If screening is positive (i.e., two positive determinations), sweat testing is performed to confirm or rule out cystic fibrosis. Sweat chloride concentrations ≥ 60 mmol/L, as measured by quantitative methods, in two samples, confirm the diagnosis. Diagnostic alternatives are detection of two cystic fibrosis-related mutations and CFTR functional tests. Figure 1 shows a flowchart summarizing how infants with positive newborn screening results should be managed.[20,21]

Does a positive or negative newborn screening result confirm or rule out the diagnosis of cystic fibrosis?

No. Newborn screening for cystic fibrosis identifies newborns at risk for the disease, but does not confirm the diagnosis. The rate of false-positive results with the algorithm based on measurement of immunoreactive trypsinogen levels is quite high. Conversely, a negative newborn screening result does not rule out the diagnosis.[22,23]

After confirmation of the diagnosis of cystic fibrosis in patients with positive newborn screening results, when should the patients be referred to a cystic fibrosis referral center?

Immediately after diagnosis, because cystic fibrosis requires early multidisciplinary management in order to maintain normal nutritional status and timely treat respiratory infections.[20,23]

What are the steps involved in sweat testing? How does one ensure the quality of sweat testing?

Chart 2A (JBP online appendix) summarizes the steps that should be followed when performing sweat testing. Table 1 shows the reference values.

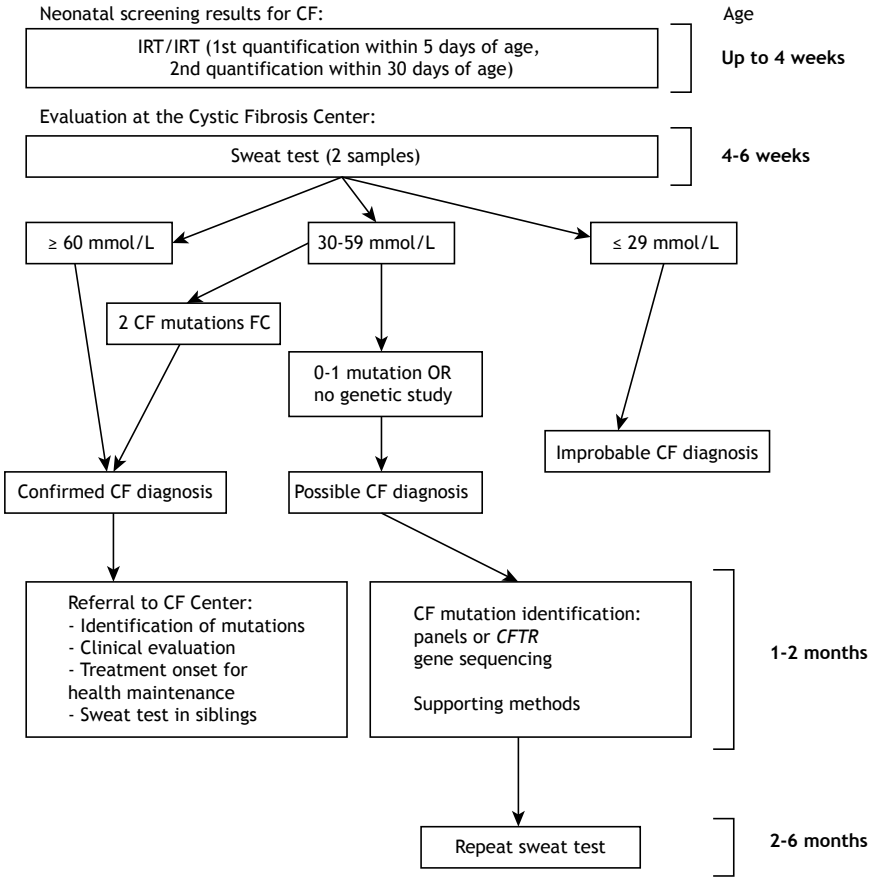

Figure 1. Management of cases with positive neonatal screening for cystic fibrosis. CF: cystic fibrosis; and IRT: immunoreactive trypsinogen. Adapted from Farrel et al.[21]

Table 1. Reference values for sweat test.

Result	Chloride, mmol/L	Electrical conductivity, mmol/L
Normal	< 30	< 60
Intermediate	30-59	60-90
Positive[a]	≥ 60	> 90

[a]Quantitative chloride analysis in sweat should be carried out on a different day in order to confirm the result.

It is recommended that laboratories qualified to perform sweat testing should have internal and external quality control and should perform at least 100 tests per year (at least 10 tests per year per technician). The percentage of insufficient sweat samples should not exceed 5% of the total samples collected.[24-26]

What are the main approved methods of quantitative sweat chloride determination?

Chart 1 describes the main methods of chloride determination, all of which must be validated in each laboratory before use.[24,25]

What is the role of sweat conductivity testing?

Despite the high level of agreement between sweat conductivity results and sweat chloride concentrations, sweat conductivity testing is still considered a screening test.[26] It is recommended that a patient with a sweat conductivity result greater than or equal to 50 mmol/L should undergo quantitative testing. Sweat conductivity testing has the advantages of being easy to use and yielding immediate results.[24,27,28]

What are the minimum criteria for a laboratory to perform CFTR mutation studies?

- Certification by the Brazilian National Health Oversight Agency
- Capability to perform DNA extraction with different methods and from different sample types
- Ability to identify the F508del mutation and other more prevalent mutations
- Availability to perform *CFTR* mutation panel analysis and/or complete *CFTR* sequencing, either in its facilities, or by referral to other laboratories
- Capability to interpret and report pathogenic variants

Should all patients with cystic fibrosis undergo genetic testing? How important is it to undergo genetic testing?

Yes, the identification of mutations in the *CFTR* gene has implications for prognosis and family planning,

allowing the diagnosis of cystic fibrosis (Chart 2). In addition, there are drugs that act on specific mutations (CFTR protein correctors and potentiators), some of which have been approved in various countries, whereas others are in development.[21,29-32]

What mutation panel should be investigated?

The investigation of mutations in the *CFTR* gene is described in Chart 3.[31-35]

When are CFTR functional tests indicated?

CFTR functional tests are indicated when sweat testing and genetic analysis are inconclusive. In essence, these tests assess CFTR protein function by measurement of chloride transport. Currently, nasal potential difference and intestinal current measurements are internationally standardized. Other promising tests, such as assessment of CFTR function by evaporimetry and by sweat gland potential difference measurement, are being studied.[36,37]

TREATMENT OF RESPIRATORY DISEASE

What types of respiratory samples are most appropriate, how are they obtained, and how important are they?

Respiratory secretion samples are essential for follow-up of chronic bacterial infection of the airways in patients with cystic fibrosis, as well as for identification of opportunistic infections and as a follow-up method for therapeutic interventions. Expectorated sputum is the specimen of choice. For children who cannot expectorate, collect oropharyngeal cough swabs (tonsillar region and soft palate), nasopharyngeal aspirates, secretion following inhalation of 5% hypertonic saline solution, or bronchoalveolar lavage fluid. These samples should be delivered to the laboratory immediately or kept under refrigeration for up to 3 h.[38,39]

(Level of evidence: 4)

When should the samples be collected?

The samples should be collected at visits (with a maximum interval of 3 months), during exacerbations, and following treatment to eradicate the infection. Annual screening for mycobacteria and fungi is recommended for patients who cannot expectorate or for those with an unfavorable clinical course.[40]

(Level of evidence: 5)

What are the routine culture methods and media?

Bronchoalveolar lavage fluid specimens must be quantitatively cultured. The recommended culture media for routine microbiological investigation in cystic fibrosis are as follows:

- Blood agar: universal for routine microbiological investigations
- Mannitol agar: selective for *Staphylococcus aureus*
- MacConkey agar: for gram-negative bacilli (including *Pseudomonas aeruginosa*, *Achromobacter* spp., and *Stenotrophomonas* spp.)
- *Burkholderia cepacia* complex-selective agar
- *Chocolate agar for Streptococcus pneumoniae* and *Haemophilus influenzae*
- Sabouraud agar – for fungi, including *Aspergillus* spp. – supplemented with chloramphenicol or gentamicin
- Liquid culture media, depending on the automation available, and a solid medium, such as Lowenstein-Jensen agar. For non-tuberculosis mycobacteria, blood agar and *Burkholderia cepacia* selective agar can also be used provided that these media are incubated for 14 days.[39,41-45]

(Level of evidence: 5)

What are the methods of bacterial identification?

- Phenotypic methods: typical *S. aureus*, *P. aeruginosa*, and *Stenotrophomonas maltophilia* colonies are easily recognized, and few tests are needed.
- Commercial, non-automated phenotypic kits: when associated with typical characteristics, they can be used for the identification of *S. aureus* and some glucose-nonfermenting gram-negative

Chart 1. Methods of quantitative of sweat chloride determination.

Method	Description	Observation
Titration or colorimetry	Chloride concentration is quantified by measuring the absorption of a specific light wavelength. The intensity of the color is directly proportional to the concentration of chloride. The Schales & Schales manual titration method using mercury nitrate is commonly used.	It depends on the experience of the technician in performing the procedure. Possible subjectivity during the analysis.
Coulometry	Analytical chemistry technique that uses an electrolysis reaction to measure changes in current resistance between the electrodes. The chloride concentration is equivalent to the generated current.	It requires a chloridometer.
Selective ion electrode	It converts the activity of a specific ion dissolved in a solution into an electrical potential that is measured by a voltmeter.	Low sensitivity. It is an automatic analyzer that must be validated against the classical methods.

Chart 2. Benefits from the study of *CFTR* gene mutations.

Benefits from the study of *CFTR* gene mutations
1. Patients with an established diagnosis of CF: - indication of mutation-specific therapy - determination of prognosis (genotype-phenotype correlation)
2. Investigation of atypical forms of CF[a]
3. Genetic counseling: - Asymptomatic individuals with no family history of CF, when the spouse has CF or is an asymptomatic carrier of a mutation in the *CFTR* gene (heterozygote) - Asymptomatic individuals when they have first-degree, second-degree, or third-degree relatives with CF in the family
4. Prenatal/preimplantation genetic diagnosis of CF: - Current or future pregnancy, in couples who already have a child with CF - Heterozygous couples if the test cannot be done on a child with CF - Embryos of heterozygous couples When the fetus has a hyperechoic bowel, dilatation of intestinal loops, growth retardation, or overgrowth suggestive of uniparental disomy

CF: cystic fibrosis. [a]Atypical forms of CF: symptoms consistent with CF and intermediate results in the sweat chloride test.

Chart 3. Stepwise molecular analysis for the identification of *CFTR* mutations.

Mutation	Technique	Reason
F508del	Conventional or real-time PCR	Higher prevalence
Research of two mutations already identified in the family	PCR site-directed mutagenesis; RFLP, reverse dot blot hybridization; ARMS; minisequencing or similar technique	Index case in the family
Individual identification of mutations of higher prevalence by targeted panels	Real-time PCR using hybridization probes; commercial mutation arrays and kits	High prevalence; need for limited infrastructure
Mutations not identified in previous tests	Bidirectional sequencing of the *CFTR* gene by Sanger or next-generation sequencing of all exons and flanking exons/introns of the *CFTR* gene, including poly-T variants in intron 8	Identification of less prevalent *CFTR* mutations
Mutations not identified in previous tests	Analysis of large rearrangements in the *CFTR* gene, including deletions, insertions, and duplications, by semiquantitative techniques, such as real-time PCR, MLPA, or quantitative fluorescent techniques (fluorescent multiplex PCR)	Identification of less prevalent *CFTR* mutations

PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; ARMS: amplification refractory mutation system; and MLPA, multiplex ligation-dependent probe amplification.

bacilli, such as *P. aeruginosa*, *S. maltophilia*, and *Achromobacter* spp., but are not suitable for the identification of *B. cepacia* complex, *Burkholderia gladioli*, *Pandoraea* spp., or *Ralstonia* spp.

- Automated methods: they are not recommended for the identification of most glucose-nonfermenting gram-negative bacilli.
- Molecular tests: they are recommended for the characterization of *Achromobacter* spp., *B. cepacia* complex, and the genera *Ralstonia*, *Cupriavidus* and *Pandoraea*.
- Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (MS): it represents a rapid alternative, but has limitations, especially in identifying glucose-nonfermenting gram-negative bacilli.[42,43,46]

(Level of evidence: 5 for all methods, except MALDI-TOF MS for the identification of glucose-nonfermenting gram-negative bacilli—level of evidence: 2)

What is the role of pulmonary function testing in the management of patients with cystic fibrosis?

Spirometry should be performed starting at age 5 years at every clinical visit or at least twice a year. Testing with and without bronchodilators is recommended. Washout techniques, with determination of the lung clearance index, have increasing and promising use in identifying early lung disease.

Studies have shown that FEV_1 is essential for assessing the course and progression of cystic fibrosis, as well as for early detection of acute pulmonary exacerbations, being correlated with quality of life. $FEF_{25-75\%}$ should also be taken into consideration, since it may be altered earlier. Whole-body plethysmography and oscillometry can complement the functional assessment.[9,47-50]

(Level of evidence: 5)

What imaging tests should be performed in patients with cystic fibrosis? How often?

Chest X-ray is the most widely used test in the evaluation of patients with cystic fibrosis and is correlated with pulmonary function testing in detecting disease progression.[51,52]

Chest HRCT is more accurate in the diagnosis and follow-up of lung lesions in individuals of all ages, including children with normal pulmonary function.[53-55] This benefit is questionable in infants, and there are technical obstacles inherent to this age group.[56] Magnetic resonance imaging of the chest has advanced in recent years and may become a future option because it is a radiation-free method.[57]

Although there is no consensus regarding the frequency of imaging tests, an annual chest X-ray is recommended. In addition, it is suggested that, in the presence of clinical, functional, or radiological deterioration, a chest HRCT should be performed. Periodic follow-up with chest HRCT every 2 to 4 years may be indicated on a case-by-case basis. In cases of pulmonary exacerbation in cystic fibrosis, chest X-ray and chest HRCT can be used, always considering the use of the lowest radiation dose possible.[58,59]

(Level of evidence: 2 for chest HRCT in individuals of all ages, except infants) (Level of evidence: 5 for chest X-ray and magnetic resonance imaging)

How important are nebulizers in the treatment of lung disease in cystic fibrosis?

The daily treatment of lung disease in cystic fibrosis includes nebulization of various medications that are key to maintaining lung health, and an inhaler system is essential for all patients with cystic fibrosis.[60-62]

(Level of evidence: 5)

What inhaler system should be used for each type of inhalation therapy in cystic fibrosis?

Matching a substance to be inhaled with the right type of inhaler system is essential for ensuring the efficacy of treatment. Given the great variability of devices, it is recommended that the inhaler systems tested in the clinical trials of the medications should be used.[63,64]

The following types are often used for each therapy[64,65]:

- Ultrasonic nebulizers: hypertonic saline
- Air-jet nebulizers: tobramycin; colistimethate; dornase alfa; and hypertonic saline
- Active vibrating mesh nebulizers: tobramycin; colistimethate; dornase alfa; and aztreonam
- Passive vibrating mesh nebulizers that adjust to the patient's breathing pattern: tobramycin and colistimethate

(Level of evidence: 2)

What care should be given to inhalation therapy and chest physiotherapy devices?

Devices for the treatment of lung disease in cystic fibrosis include nebulizers and equipment used in chest physiotherapy for secretion removal. Bacterial contamination of nebulizers of patients with cystic fibrosis has been described, and educational programs on cleaning and disinfection of these devices have an impact on this situation. Cleaning after each use and daily disinfection by boiling, 70-90% alcohol, isopropyl alcohol, or 3% hydrogen peroxide are recommended.[17,66-69]

(Level of evidence: 3)

What chest physiotherapy techniques are indicated in the treatment of lung disease?

Chest physiotherapy techniques should be performed daily after diagnosis in all patients with cystic fibrosis.[70] Chest physiotherapy has proven clinical benefits when compared with no intervention; however, there is no evidence of the superiority of one technique over the other. Patient preference is an essential factor for adherence to treatment, but the use of devices such as positive expiratory pressure masks and oscillatory positive expiratory pressure devices such as the Flutter®, the Shaker®, and the Acapella® is of great value and gives the patient independence.[71] The use of high-frequency chest wall oscillation devices, despite also giving the patient independence, was found to be inferior to the use of positive expiratory pressure masks in a recent study.[72] Noninvasive ventilation may be used as an adjunct to airway clearance therapy and in patients with advanced disease and hypercapnic respiratory failure.[73-76]

(Level of evidence: 2 for chest physiotherapy)

(Level of evidence: 2 for the superiority of positive expiratory pressure masks vs. high-frequency chest wall oscillation devices)

(Level of evidence: 2 for noninvasive ventilation vs. no noninvasive ventilation as an adjuvant in the treatment of patients with advanced disease and hypercapnia)

What is the role of exercise in cystic fibrosis?

Exercise (aerobic and anaerobic) can aid in functional and postural outcomes, as well as in the self-esteem of patients with cystic fibrosis. An exercise frequency of 3-5 times a week and an exercise duration of 20-30 min are recommended, with benefits being observed from 6 weeks onward. Exercise should be part of the recommendations for patients with cystic fibrosis, including during hospitalizations. Physical activity does not replace chest physiotherapy.[77-82]

(Level of evidence: 2)

What are the indications for the use of dornase alfa and what is its dosing schedule?

Inhaled dornase alfa has proven efficacy in cystic fibrosis as demonstrated by improvement in pulmonary function and quality of life, as well as by reduction in the number of respiratory exacerbations.[83-89] It is recommended starting at age 6 years in patients with lung disease at any stage.[83,87,90] The recommended dose is 2.5 mg once daily, with an appropriate nebulizer. Alternate-day administration may be considered in stable patients,[91,92] and twice-daily administration may be considered in patients with severe disease.[102]

Inhaled dornase alfa can be used at any time, at least 30 min before chest physiotherapy.[93,94]

(Level of evidence: 1)

When should dornase alfa be used in children under 6 years of age?

The use of dornase alfa should be considered in younger patients with persistent respiratory symptoms or with evidence of early lung disease (bronchiectasis, for example).[40,95-97]

(Level of evidence: 2)

What is the role of hypertonic saline and mannitol? What are their recommended concentrations?

Hypertonic saline solution and mannitol are mucokinetic substances. They function as moisturizers on the airway surface, as osmotic agents, changing the rheological properties of mucus.

Twice-daily administration of 7% hypertonic saline solution reduces the number of respiratory exacerbations and produces improvement in pulmonary function and quality of life. Long-term studies are needed to determine whether there is sustained improvement.[87,98-100]

Mannitol is available as dry-powder for inhalation (400 mg twice daily). Its use is associated with reduced nebulizer treatment time, clinical improvement, and pulmonary function improvement.[101-103] The use of mannitol is safe and well tolerated but should be preceded by the use of inhaled bronchodilators, given that they can act as irritating substances. Both are complementary approaches to dornase alfa therapy.

(Level of evidence: 1 for hypertonic saline and for mannitol)

What should *P. aeruginosa* eradication therapy be like?

Eradication therapy in cases of first acquisition of *P. aeruginosa* or early infection with *P. aeruginosa* aims to eradicate the bacterium and delay chronic infection. There are various therapeutic strategies, none being superior to the other. The most widely recommended strategy is to use inhaled tobramycin (300 mg) twice daily for 28 days.[104-107] Sodium colistimethate (1,000,000 to 2,000,000 IU, twice daily) is an alternative with consistent results and should be associated with oral ciprofloxacin for 2-3 weeks.

Inhalation therapy may be extended for 2-3 months. Intravenous antibiotic therapy for 2 weeks may be an option in selected cases and should always be followed by inhaled antibiotic therapy. Successful eradication is defined as negative bacterial culture results over a 1-year period after treatment completion. Eradication therapy, in addition to having significant clinical benefits, may be cost-effective.[103-107]

(Level of evidence: 1)

What should therapy for eradicating *B. cepacia* complex strains be like?

The *B. cepacia* complex consists of a group of more than 80 closely related species,[108,109] *B. multivorans* and *B. cenocepacia* being the predominant species infecting people with cystic fibrosis.[110]

Clinical manifestations in cystic fibrosis range from no symptoms to severe conditions with rapid clinical deterioration and fulminant progression to necrotizing pneumonia, respiratory failure, and sepsis (cepacia syndrome).[110] Treatment of *B. cepacia* complex is difficult because of intrinsic resistance of these organisms to most antimicrobial agents available. It is therefore recommended that, whenever possible, antibiogram-guided combination therapy be used. There is no available evidence assessing the efficacy of its eradication, nor are there recommendations for inhalation therapy for chronic infection.[110,111]

(Level of evidence: 4)

What should therapy for eradicating methicillin-resistant *S. aureus* be like?

Chronic infection with methicillin-resistant *S. aureus* is associated with worse clinical outcomes in patients with cystic fibrosis.[112] There have been reports of methicillin-resistant *S. aureus* eradication therapies using combinations of oral, topical, and inhaled drugs, such as sulfamethoxazole/trimethoprim, rifampin, fusidic acid, and chlorhexidine, in addition to vancomycin. Linezolid may be considered, but on the basis of less evidence.[113] Shorter treatment protocols (< 3 weeks) appear to be as effective as longer ones, as well as being less likely to result in intolerance and adverse effects. Combination therapy appears to have a greater likelihood of success than does monotherapy.[114,115]

There is still no clear evidence of the benefits of eradication of methicillin-resistant *S. aureus* in patients with cystic fibrosis.[113,114,116] There is also no evidence to recommend inhaled antibiotic therapy for chronic infection with this pathogen.

(Level of evidence: 4)

What are the recommendations for chronic use of inhaled antibiotics in cystic fibrosis?

Table 2 shows the inhaled antibiotics that are used for suppression of chronic infection with *P. aeruginosa*.[23,117,118] The regular use of inhaled antibiotics delays deterioration of pulmonary function in patients chronically infected with *P. aeruginosa*.[23,87,117-119] Chart 4 presents the Leeds criteria, which classify respiratory infection with *P. aeruginosa* in patients with cystic fibrosis on the basis of respiratory secretion culture results obtained in the last 12 months.[120]

Inhaled tobramycin is the most studied antibiotic,[119,121,122] and its use is recommended after age 6 years in patients with chronic infection with *P. aeruginosa*, regardless of disease severity, in alternating cycles of 28-days-on and 28-days-off therapy. Sodium colistimethate and aztreonam are

Table 2. Treatment with inhaled antibiotics in accordance with a European consensus.[118]

Inhaled antibiotic	Dose[a]	Trade name
Aztreonam	75 mg (3 times/day)	Cayston
Colistimethate sodium*	< 2 years of age: 0.5 million IU 2-10 years of age: 1 million IU > 10 years of age: 2 million IU	Colistin/Colomycin/Promixin
Colistimethate sodium[b] (dry powder inhaler)	1 capsule	Colobreathe
Tobramycin	> 6 years of age: 300 mg	Bramitob/Tobi
Tobramycin (dry powder inhaler)	> 6 years of age: 112 mg (4 capsules of 28 mg)	Zoteon

[a]Twice a day, except where otherwise indicated. [b]That dose has been used in various European cystic fibrosis centers. When using I-neb® (Phillips Respironics) device, the dose should be reduced.

Chart 4. Leeds criteria for the classification of respiratory infection by *Pseudomonas aeruginosa* in patients with cystic fibrosis.

Classification	Definition
Chronic infection	> 50% positive Pa culture results in the last 12 months
intermittent infection	≤ 50% positive Pa culture results in the last 12 months
Cured of Pa infection	Previous positive Pa culture results; only negative PA culture results in the last 12 months
Never infected	All of Pa culture results have always been negative

Pa: *Pseudomonas aeruginosa*. Adapted from Lee et al.[120]

other options.[23,87,123,124] Tobramycin inhalation powder has been used and shown to have equivalent efficacy to tobramycin inhalation solution, being associated with reduced treatment administration time and not requiring the use of nebulizers.[125]

The recommendation of using suppression therapy in alternating months is aimed at preventing the development of bacterial resistance. In cases that are more severe, however, continued use of therapy or switching antimicrobial agents may be recommended.[124]

It is advisable that the first inhalations be performed under supervision to allow for assessment of occurrence of drug-induced bronchoconstriction (wheezing, dyspnea, and chest tightness). Bronchodilator use is recommended, followed by bronchial hygiene via chest physiotherapy and, finally, antibiotic use in order to ensure greater medication deposition.[87,119,126,127]

(Level of evidence: 1)

What are the indications for the use of azithromycin in patients with cystic fibrosis and how should azithromycin be used?

The use of oral azithromycin 3 times a week in cystic fibrosis patients over 5 years of age who are chronically colonized with *P. aeruginosa* results in improvement in pulmonary function and reduction in the number of exacerbations.[119,127-133]

(Level of evidence: 1)

In patients who were not colonized with *P. aeruginosa* and had an FEV_1 > 50% of the predicted value, azithromycin was found to reduce exacerbations by 50%, although with no improvement in pulmonary function.[134]

(Level of evidence: 1)

The continued use of azithromycin is recommended, despite the lack of long-term assessment studies. Initial use for at least 6 months is suggested for assessment of response to therapy.[135,136] Side effects, such as epigastric pain, electrocardiographic changes, ototoxicity, and nontuberculous mycobacterial infection, should be monitored.

(Level of evidence: 1)

The use of azithromycin (250 mg for body weight < 40 kg and 500 mg for body weight > 40 kg; 3 times a week) is recommended in patients chronically colonized with *P. aeruginosa* who are over 5 years of age, as well as in those who are not colonized with *P. aeruginosa* and have frequent pulmonary exacerbations. Sputum sample collection for investigation of the presence of nontuberculous mycobacteria is recommended before initiation of azithromycin.[132,134]

(Level of evidence: 2)

Given the possibility of a drug interaction between azithromycin and aminoglycosides, combined azithromycin and inhaled tobramycin use should be reassessed especially in patients with frequent exacerbations despite optimal treatment.[137]

(Level of evidence: 3)

How does one recognize an acute pulmonary exacerbation?

Acute pulmonary exacerbations are characterized by clinical findings of increased cough, changes in secretion appearance, fever, abnormalities on pulmonary auscultation, decreased FEV_1, decreased saturation, radiological abnormalities, and weight loss.[23]

(Level of evidence: 5)

What therapy is indicated for acute pulmonary exacerbations?

For mild exacerbations (without hypoxemia or significant respiratory distress), use oral antimicrobial

agents, on the basis of the last respiratory secretion culture result. For severe exacerbations or in cases of intolerance to oral medications, intravenous therapy (usually in hospital) is recommended,[139] but the choice of medications depends on previous respiratory secretion culture results and on patient history.[23]

Antibiotic pharmacokinetics is different in individuals with cystic fibrosis, and dosage regimens should be adjusted[139] (Table 3). For *P. aeruginosa*, the combination of two or more antibiotics (usually a beta-lactam and an aminoglycoside) is recommended.

Treatment time for an acute pulmonary exacerbation depends on clinical response, with the recommendation being 8 to 14 days. Patients with more severe disease may benefit from longer antimicrobial therapy.[138,140-142]

In addition to antibiotic therapy, the treatment of exacerbations requires the participation of a multidisciplinary team, because there is often need for oxygen supplementation, use of long-term intravenous devices, intensified chest physiotherapy, and a different nutritional approach.[138,143,144]

(Level of evidence: 5)

How does one assess response to treatment?

One should observe clinical parameters, such as respiratory symptoms, fever, and weight gain, as well as improvement in pulmonary function with a view to it returning to its baseline levels. Despite intensive treatment, approximately 25% of the patients who have an acute pulmonary exacerbation requiring intravenous therapy fail to recover completely to pre-exacerbation levels of pulmonary function,[23,138-142] emphasizing the need for maintenance therapies to prevent acute pulmonary exacerbations.

(Level of evidence: 5)

When and how should oxygen therapy be used in patients with cystic fibrosis?

In hypoxemic patients, continuous oxygen supplementation is associated with increased exercise tolerance and mild improvement in sleep and school/work attendance, but does not result in increased survival.

Table 3. Antimicrobial agents commonly used against acute pulmonary exacerbations in cystic fibrosis patients.[a]

Bacterium	Antimicrobial agent	Dose, mg/kg/day	Intervals and route
Staphylococcus aureus	Cephalexin	50-100 (max, 4 g/day)	6/6 h p.o.
	Cefadroxil	30 (max, 4 g/day)	12/12 h p.o.
	Cefuroxime	20-30 (max, 1,5 g/day)	12/12 h p.o.
	Clarithromycin	15 (max, 1 g/day)	12/12 h p.o.
	Clindamycin	30-40 (max, 2,4 g/day)	6/6 h or 8/8 h i.v.
	Amoxicillin + Clavulanic acid	50[b] (max. 1,5 g/day)	8/8 h or 12/12 h p.o.
	Sulfamethoxazole/trimethoprim	40[c] (max, 1,6 g/day)	12/12 h p.o.
	Oxacillin	200 (max, 8 g/day)	6/6 h i.v.
	Vancomycin[d]	40-60 (max, 8 g/day)	6/6 h i.v.
	Teicoplanin[d]	10 (max, 400 mg/day)	24/24 h i.v. or i.m.
	Linezolid[d]	20 (max, 1,2 g/day)	12/12 h p.o. or i.v.
	Tigecycline[d]	2 (max, 100 mg/day)	12/12 h i.v.
Haemophilus influenzae	Amoxicillin + Clavulanic acid	50[b] (max, 1,5 g/day)	8/8 h or 12/12 h p.o.
	Cefuroxime	20-30 (max, 1,5 g/day)	12/12 h p.o.
	Cefaclor	40 (max, 1 g/day)	8/8 h p.o.
Pseudomonas aeruginosa	Ciprofloxacin	30-50 (max, 1,5 g/day)	12/12 h p.o.
		30 (max, 1,2 g/day)	8/8 h i.v.
	Amikacin	20-30 (max, 1,5 g/day)	24/24 h i.v.
	Tobramycin	10 (max, 660 mg/day)	24/24 h i.v.
	Ceftazidime	150 (max, 9 g/day)	8/8 h i.v.
	Cefepime[e]	150 (max, 6 g/day)	8/8 h i.v.
	Piperacillin + tazobactam[e]	300 (max, 18 g/day)	6/6 h or 8/8 h i.v.
	Meropenem[e]	120 (max, 6 g/day)	8/8 h i.v.
	Aztreonam	50 (max, 6 g/day)	8/8 h i.v.
Stenotrophomonas maltophilia[f]	Sulfamethoxazole/trimethoprim	40[c] (max, 1,6g/day)	12/12 h p.o.
	Chloramphenicol	60 a 80 (max, 4 g/day)	6/6 h p.o. or i.v.
	Levofloxacin	10 (max, 750 mg/day)	< 5 years o f age: 12/12 h > 5 years of age: 24/24 h
Burkholderia cepacia complex[f,g]	Sulfamethoxazole/trimethoprim	40[c] (max, 1,6 g/day)	12/12 h p.o.
		100[c] (max, 2,4 g/day)	6/6 h i.v. (severe cases)
	Meropenem	120 (max, 6 g/day)	8/8 h i.v.
	Chloramphenicol	60 a 80 (max, 4 g/day)	6/6 h p.o. or i.v.
	Doxycycline	1-2 (max, 200 mg/day)	12/12 h p.o.

Max: maximum. [a]It is recommended to control the serum level of drugs whose laboratory tests are available (e.g.: aminoglycosides and vancomycin).[b]Amoxicillin dose. [c]Sulfamethoxazole dose. [d]They should only be used against methicillin-resistant *Staphylococcus aureus*. [e]Also effective against methicillin-susceptible *S. aureus*. [f]Lack of standardization regarding the level of efficacy of the antimicrobial agents. [g]Usually resistant to many antimicrobial agents.

Oxygen therapy may be indicated on a case-by-case basis when SpO_2 is below 90%, for relieving dyspnea, delaying the development of *cor pulmonale*, and improving the aforementioned outcomes. A PaO_2 < 55 mmHg or an SpO_2 < 88% is an indication for oxygen therapy, regardless of symptoms. The preferred route of administration is via a nasal cannula, at the lowest flow possible to maintain SpO_2 above 90%. Intermittent use may be necessary during acute pulmonary exacerbations.[145,146]

(Level of evidence: 5)

How does one diagnose and treat pneumothorax in patients with cystic fibrosis?

Pneumothorax manifests as dyspnea and/or sudden-onset chest pain. Extensive pneumothorax requires hospitalization and chest drainage, the only indication for pleurodesis being recurrence. Noninvasive ventilation and chest physiotherapy should be performed only in patients who received drainage.

Small pneumothorax should be drained only if there is clinical instability.[23,147]

(Level of evidence: 5 for the non-recommendation of antibiotics)

(Level of evidence: 5 for the non-discontinuation of inhaled medications)

How does one classify and treat hemoptysis in patients with cystic fibrosis?

The management of hemoptysis depends on its volume. Bleeding ≥ 5 mL requires considering treatment with antibiotics for pulmonary exacerbation.[23,147] Bleeding ≥ 240 mL/day or > 100 mL/day for several days requires specialized treatment, and, when there is evidence of clinical instability, bronchoscopic treatment or bronchial artery embolization is indicated.[23,147] Surgical intervention can be performed in the acute phase only in refractory cases.

(Level of evidence: 2)

(Level of evidence: 5 for surgical intervention)

When are invasive and noninvasive ventilation indicated in cystic fibrosis?

The use of invasive ventilation in patients with severe disease is controversial and is associated with low survival rates, especially when the indication is respiratory infection. Invasive ventilation should be considered in cases of respiratory failure due to an acute, correctable precipitating factor (massive hemoptysis, pneumothorax, and during postoperative periods).

Noninvasive ventilation may be used as an adjuvant in the treatment of exacerbations and may be indicated in patients with daytime hypercapnia and sleep disorders. The use of noninvasive ventilation has been reported to be associated with increased exercise tolerance, improved quality of life and survival, and reduced decline in pulmonary function. Its use as a resource in chest physiotherapy provides benefits regarding dyspnea, muscle fatigue, and oxygenation.[73-75]

(Level of evidence: 2 for noninvasive ventilation)

(Level of evidence: 5 for invasive ventilation)

How does one diagnose and treat allergic bronchopulmonary aspergillosis?

Allergic bronchopulmonary aspergillosis is a common complication in cystic fibrosis. Annual measurement of total IgE is recommended as a screening strategy. The diagnostic criteria for allergic bronchopulmonary aspergillosis are presented in Chart 5.[124,148] Treatment is with oral prednisone with or without antifungal agents (Chart 6).[118,149-155]

(Level of evidence: 5 for diagnosis and treatment)

What is the approach to patients with positive sputum for Aspergillus spp.?

The presence of *Aspergillus* spp. in sputum usually does not mean disease.[156] If there is clinical worsening or a lack of response to antimicrobial therapy, one should investigate for allergic bronchopulmonary aspergillosis and consider fungal bronchitis.[157]

(Level of evidence: 5)

What are the existing CFTR-modulating therapies, for which types of mutations have they been used, and what effects have been observed?

Potentiators increase the function of the CFTR protein that is expressed at the plasma membrane (class III, IV, and V mutations), and correctors correct defects of the protein that is not expressed at the cell membrane (class I and II mutations).[158-161]

Ivacaftor is a potentiator that was initially studied in patients carrying the G551D mutation (a class III mutation). Its use had relevant effects resulting in a reduction in sweat chloride levels, improvement in FEV_1, and weight gain, as well as in a reduction in the number of exacerbations and improvement in quality of life. Its use was subsequently approved for other class III mutations and R117H.[162-164]

Among corrector drugs, a drug for class I mutations (ataluren) showed slight effects on pulmonary function and on the number of exacerbations in a phase 3 trial, only for patients who did not use inhaled tobramycin.[165]

For the most prevalent class II mutation worldwide, F508del, the use of ivacaftor (a potentiator) in combination with lumacaftor (a corrector) was shown to produce a reduction in the number of exacerbations and a slight improvement in FEV_1 and quality of life for homozygous patients, with no significant effects being observed for heterozygous patients.[166]

(Level of evidence: 1 for ivacaftor in patients carrying a class III mutation [G551D])

(Level of evidence: 3 for ataluren in patients not exposed to tobramycin)

(Level of evidence: 2 for ivacaftor/lumacaftor in patients carrying a class II mutation [F508del])

Is there an indication for the use of ibuprofen in patients with cystic fibrosis?

The use of ibuprofen appears to delay the decline in pulmonary function and result in nutritional improvement, especially in children. Studies recommend doses between 20 and 30 mg/kg twice daily (maximum: 1,600 mg), in addition to monitoring of adverse events (discontinue use of ibuprofen when using aminoglycosides) and serum levels (50-100 mg/mL). Low doses are associated with a paradoxical increase in inflammation. Given the high rate of adverse events associated with ibuprofen and the difficulty in monitoring the serum level of the drug, its routine use is not recommended. The benefits of ibuprofen in patients with advanced disease are unknown.[167-174]

(Level of evidence: 2)

What is the role of inhaled and systemic corticosteroids in cystic fibrosis?

There is no scientific evidence supporting the routine use of inhaled corticosteroids in cystic fibrosis; they can be used in patients with cystic fibrosis and asthma. It is recommended that, whenever possible, spirometry be performed to confirm the benefits of their use.[175] The chronic use of oral corticosteroids is also not recommended because of the risk of significant adverse effects, such as increased risk of diabetes and growth retardation. The effects of their short-term use and of their use during pulmonary exacerbations have yet to be elucidated.[176]

(Level of evidence: 5 for not using oral corticosteroids chronically)

(Level of evidence: 5 for using inhaled corticosteroids)

What are the indications for the use of bronchodilators in cystic fibrosis?

Bronchodilators have been shown to provide benefits only in patients with confirmed bronchial hyperresponsiveness or evidence of asthma; in the latter case, bronchodilators should be used in combination with an inhaled corticosteroid. In this group of patients, an increase in pulmonary function was observed in the short and long term. Long-acting beta-agonists improved pulmonary function in the short term, with inconsistent long-lasting results, being therefore indicated only for individuals with confirmed asthma.[177] Regarding long-acting anticholinergics, tiotropium has recently been shown to be well tolerated, although the gain in pulmonary function was not statistically significantly different when compared with placebo.[178]

(Level of evidence: 5 for beta-agonists in patients with cystic fibrosis and asthma)

(Level of evidence: 5 for tiotropium)

How does one diagnose and treat nontuberculous mycobacterial infections?

There has been an increase in the incidence of nontuberculous mycobacterial infections in cystic fibrosis patients, with this incidence rising with advancing age. It is associated with progressive clinical deterioration, and differentiating between colonization and infection is essential, this differentiation being based on clinical, microbiological, and radiological criteria.[179]

In patients who can spontaneously expectorate, mycobacterial cultures should be performed at least annually. The most commonly identified species are *M. avium-intracellulare* complex, *M. chelonae*, and *M. abscessus.*[180]

Treatment of the infection with at least three antibiotics, usually including a macrolide, is recommended. The antimicrobial regimen should be tailored to the nontuberculous mycobacterial species, following guideline recommendations.[179,180]

(Level of evidence: 5)

GASTROINTESTINAL AND NUTRITIONAL TREATMENT

How to suspect, diagnose, and manage meconium ileus?

Meconium ileum is the first clinical manifestation in patients with cystic fibrosis, in 15-20% of cases. Ileal obstruction by a plug of meconium and thick mucus may arise in intrauterine life with polyhydramnios, meconial peritonitis, and ileal distension, evidenced in prenatal ultrasonography. It is manifested by the absence of stool elimination in the first 48 h of life, accompanied by abdominal distension and vomiting (acute obstructive abdomen).

Clinical treatment includes hyperosmolar enemas, use of a nasogastric tube, hydration, and control of electrolytes. Complex cases (atresia, microcolon, necrosis, or perforation) should be treated surgically using minimally invasive techniques with ileostomy and reanastomosis in a timely manner.

(Level of evidence: 5)

How should electrolyte disturbances be prevented?

Salt loss from sweat and the large body surface pose a risk for dehydration and electrolyte disturbances in infants with cystic fibrosis, even without apparent loss. Signs, such as apathy or irritability, tachypnea, and prostration, may indicate dehydration, hyponatremia, hypokalemia, and hypochloremia, which are potentially life-threatening. Newborns and infants receiving breast milk or infant formulas should be supplemented with sodium chloride at a dose of 2.5-3.0 mEq/kg/day.[23,182,183]

(Level of evidence: 5)

When should exocrine pancreatic insufficiency be clinically suspected?

We should suspect it in the presence of steatorrhea, chronic diarrhea, low weight gain, and signs of

Chart 5. Diagnostic criteria for allergic bronchopulmonary aspergillosis.

Classic disease
• Acute or subacute clinical deterioration (cough, wheezing, exercise intolerance, exercise-induced asthma, decreased lung function, and increased sputum) not attributable to another etiology • Total serum IgE level > 1,000 IU/mL (2,400 ng/mL) unless the patient is receiving systemic corticosteroids (if so, retest after discontinuation of treatment) • Immediate skin reactivity to *Aspergillus* spp. (prick test > 3 mm in diameter with surrounding erythema while the patient is not being treated with systemic antihistamines) or presence of serum IgE antibody against *A. fumigatus* • Precipitating antibodies against *A. fumigatus* or serum IgG antibodies against *A. fumigatus* New or recent abnormalities on chest X-rays (infiltrates or mucoid impaction) or on CT scans (bronchiectasis) that do not improve with antibiotics and chest physiotherapy
Minimal diagnostic criteria
• Acute or subacute clinical deterioration (cough, wheezing, exercise intolerance, exercise-induced asthma, decreased lung function, and increased sputum) not attributable to another etiology • Total serum IgE level > 500 IU/mL (1,200 ng/mL). If allergic bronchopulmonary aspergillosis is suspected and total serum IgE level is 200-500 IU/mL; repeating the test at 1-3 months is recommended. If the patient is taking steroids, repeat the test when the steroid treatment is discontinued • Immediate skin reactivity to *Aspergillus* spp. (prick test > 3 mm in diameter with surrounding erythema while the patient is not being treated with systemic antihistamines) or presence of serum IgE antibody against *A. fumigatus* • One of the following: (a) precipitins for *A. fumigatus* or in vitro demonstration of IgG antibodies against *A. fumigatus*; (b) new or recent abnormalities on chest X-rays (infiltrates or mucoid impaction) or on CT scans (bronchiectasis) that do not improve with antibiotics and chest physiotherapy

Chart 6. Allergic bronchopulmonary aspergillosis treatment.

Allergic bronchopulmonary aspergillosis treatment
Prednisone: initial dose of 0.5-2.0 mg/kg/day; maximum, 60 mg/day, for 1-2 weeks Reduce to alternate days, gradually decrease the dose and withdraw it in 2-3 months
Itraconazole: 5 mg/kg/day; maximum, 400 mg/day (every 12 h if dose > 200 mg), for 3-6 months
Voriconazole: 4 mg/kg (12/12 h); maximum, 400 mg/day, for 3-6 months
Alternative treatments in cases of unsatisfactory response Pulse therapy Omalizumabe Inhaled amphotericin B

hypovitaminosis. The infant may also present with edema, hypoalbuminemia, and anemia. Indirect signs are observed through the characteristics of the stool, such as oiliness, foul smell, and diarrhea.[184]

(Level of evidence: 5)

How do we confirm the diagnosis of exocrine pancreatic insufficiency?

In clinical practice, the best method for confirming exocrine pancreatic insufficiency is the quantification of fecal elastase. Values < 200 µg/g of feces confirm exocrine pancreatic insufficiency (sensitivity, 86-100%).[185] Quantitative determination of fecal fat by the Van de Kamer method is considered the gold standard for the diagnosis of steatorrhea, but its use is limited by technical difficulties.[185]

(Level of evidence: 4)

How should pancreatic sufficiency be followed?

The fecal elastase test is simple and reliable in patients older than two weeks of age in the absence of liquid feces. Patients with pancreatic insufficiency should be monitored annually during childhood and during periods of growth failure, weight loss, or chronic diarrhea. The semiquantitative assessment of fat in stool (steatocrit) has relative value during the follow-up of patients, and the qualitative evaluation of fecal fats (Sudan III) has only a screening value for fecal fat loss.

(Level of evidence: 5)

How should enzyme replacement therapy be performed?

The need for replacement of pancreatic enzymes varies greatly and should be evaluated individually, relating clinical symptoms to the diet of each patient. The initial doses (Table 4) and their eventual subsequent increase should be guided by the improvement/resolution of the symptoms of malabsorption.

Enzyme capsules should be swallowed whole and taken at the beginning of or during meals. Infants can ingest the granules mixed with milk or mashed fruit. Doses above 10,000 IU lipase/kg/day should be avoided, but they may be necessary in childhood, especially during accelerated growth phases.[186]

(Level of evidence: 1)

How should the response to enzyme replacement therapy be evaluated?

The determination of the adequacy of enzyme replacement therapy is clinical: nutritional status,

signs and symptoms of malabsorption, and patient's weight gain plot should be verified. Inappropriate doses of pancreatic enzymes may result in abdominal pain, constipation, or diarrhea. Stool pattern and stool characteristics (oily, foul-smelling, floating, diarrheal, grayish, or yellowish) may indicate inadequacy of enzyme replacement therapy.[23,24]

(Level of evidence: 5)

When should distal bowel obstruction syndrome be suspected and treated?

If there is incomplete obstruction, intermittent abdominal pain, nausea, and palpable masses in the lower right quadrant are noted, whereas in cases of complete obstruction, bilious vomiting and abdominal distension (acute obstructive abdomen) appear. The use of oral hydration and laxatives (such as polyethylene glycol) are indicated in cases of incomplete obstruction. In more severe cases, venous hydration, use of tubes, and use of enemas with polyethylene glycol or meglumine diatrizoate + sodium diatrizoate solution (Gastrografin®; Bracco Diagnostics, Canada) are indicated. Surgical treatment should be considered in cases of severe obstruction or in the presence of perforation.[187,188]

(Level of evidence: 4)

Are there other common clinical gastrointestinal conditions in cystic fibrosis?

Approximately 30% of the patients have gastroesophageal reflux disease, and 40% have intestinal constipation. Recurrent acute pancreatitis is more common in patients with pancreatic insufficiency (10%), and rectal prolapse occurs in about 20% of the patients, especially those between 1-2 years of age. Patients with rectal prolapse and recurrent acute pancreatitis should be investigated for cystic fibrosis. The approach and treatment of all of these pathologies do not differ from those in patients without cystic fibrosis.[23]

(Level of evidence: 4)

How should hepatic and biliary disease be monitored and managed?

The frequency of hepatic and biliary tract manifestations is shown in Table 5. Multilobular cirrhosis associated with hepatic insufficiency is rare,[189] but bile sludge and lithiasis in the biliary tract are common and generally asymptomatic.[190,191] Patient monitoring includes clinical evaluation at all visits, biochemical tests (liver enzymes and prothrombin time), and annual abdominal ultrasonography. Gastrointestinal endoscopy may be requested to investigate cases of gastrointestinal bleeding or suspected esophageal and gastric varices. Liver biopsy is rarely indicated. Patients with hepatic impairment should undergo quantification of alpha fetoprotein annually, due to the risk of hepatocellular carcinoma.[189]

The treatment of liver disease in patients with cystic fibrosis aims to improve bile flow, viscosity, and composition. Ursodeoxycholic acid at the dose of 15-20 mg/kg/day (2-3 doses) is recommended, but its use is controversial in the medical literature. There is no indication of treatment in the case of hepatic steatosis.[190,192] In cases of advanced liver disease, liver transplantation may be indicated.

(Level of evidence: 5)

How should the nutritional status of patients with cystic fibrosis be monitored?

There is a strong association between pulmonary function and nutritional status. Periodic monitoring is necessary, especially regarding anthropometry, pulmonary function, gastrointestinal function, quality and quantity of food ingested, body composition, and biochemical evaluation.

Patients are more vulnerable to malnutrition during periods of rapid growth, and special attention should be paid to the first 12 months after the diagnosis, the first year of life, and the peripuberal period.[193] The parameters and periodicity for monitoring are shown in Chart 7.[194]

(Level of evidence: 5)

What reference data should be used?

The growth curves used in Brazil are those by the World Health Organization (2006-2007),[195,196] and anthropometric data must be obtained and recorded in every medical visit (Chart 8).

(Level of evidence: 5)

How to define nutritional deficiencies?

In children and adolescents, height-for-age, weight-for-age, weight-for-height and body mass index (BMI)-for-age Z-scores with results < −2 reveal anthropometric deficiencies. It is suggested to associate the anthropometric evaluation with the growth rate and the target height. For adults, the recommended BMI is ≥ 22 kg/m^2 for women and ≥ 23 kg/m^2 for men. Additional body composition assessments should include skinfold thickness and arm circumference

Table 4. Recommended initial doses for pancreatic enzyme replacement therapy.[a]

Dose	Infants, per 120 mL of formula or breast milk	< 4 years of age, U/kg per meal	> 4 years of age, U/kg per meal
Initial	2.000 U	1.000 U	500 U
Maximum per meal	4.000 U	2.500 U	2.500 U
Snacks	---	½ dose	½ dose

[a]Maximum daily dose: 10.000 U/kg.

measurements, as well as bioimpedance, to help determine optimal nutritional status.[197]

(Level of evidence: 5)

What are the main strategies for the prevention and treatment of nutritional disorders in cystic fibrosis patients?

The prevention of nutritional disorders presupposes the ingestion of a hypercaloric and high protein diet, vitamin supplementation, enzyme replacement therapy, and control of cystic fibrosis-related infections/exacerbations/other comorbidities. Treatment involves behavioral therapy, use of nutritional supplements, and the use of enteral diet via a nasoenteral tube in an acute phase and via gastrostomy for prolonged use.[198-201]

(Level of evidence: 5)

What factors should be evaluated in the growth failure?

It is recommended to evaluate the intake of macronutrients and micronutrients, as well as to control malabsorption and infections/exacerbations. In addition, comorbidities, such as electrolyte disturbances, gastroesophageal reflux disease, bacterial overgrowth, diabetes, or behavioral appetite disorders should be evaluated. Less frequent causes of growth failure include lactose intolerance, celiac disease, food allergy, and inflammatory bowel disease.[193,202]

(Level of evidence: 5)

Table 5. Frequency of hepatic and biliary tract manifestations in patients with cystic fibrosis.

Organ	Approximate proportion, %
Liver	
Increased liver enzymes	10-35
Hepatic steatosis	20-60
Focal biliary cirrhosis	11-70
Multilobular biliary cirrhosis	5-15
Neonatal cholestasis	< 2
Bile duct stenosis	< 2
Sclerosing cholangitis	< 1
Cholangiocarcinoma	rare
Gallbladder	
Cholelithiasis and cholecystitis	10-30
Microvesicules	24-50

Adapted from Debray et al.[189]

What are the options for nutritional therapy?

All of the patients should receive dietary advice. Behavioral therapy may be helpful for children between 3-12 years of age. Energy intake of 110-200% of recommended values for age and sex, with 35-40% of the energy supplied by lipids is recommended, as well as is vitamin supplementation, according to the needs of the patients. The use of dietary supplements and/or increased caloric density of the diet are indicated for patients showing weight loss or weight gain failure for 2-6 months, according to the age bracket. Enteral nutritional support by means of tubes is reserved for more severe cases and for short periods of time. Gastrostomy is indicated for long-term nutritional therapy. Parenteral nutrition is an exceptional measure, indicated for patients whose digestive tract cannot be used (during postoperative period or in the presence of critical illness) or in cases of short bowel syndrome.[193,202] Figure 2 shows the algorithm for the management of patients with low weight or inadequate weight gain.

(Level of evidence: 5)

What are the requirements for vitamin supplementation in cystic fibrosis patients?

Patients with cystic fibrosis are at high risk of developing fat-soluble vitamin deficiency due to exocrine pancreatic insufficiency. The recommended doses vary widely (Table 6 and Table 1A—online appendix).[193,202]

Chart 7. Nutritional parameters and suggested monitoring frequency in patients with cystic fibrosis.

Parameter	Frequency
Anthropometry	Every 3 month
Cephalic perimeter	Every 3 month
Weigh, height (length)	Every 3 month
Arm circumference and triceps skinfold thickness	Annually
Food intake	Every medical visit
Food recall	Every medical visit
Strategies to increase calorie intake	Every medical visit
Use of oral supplements	Every medical visit
Enteral nutritional therapy	Every medical visit
Detrimental behaviors (e.g., skipping meals, long meals, refusal to eat, and food neophobia)	Every medical visit
Biochemical testing	Annually
Complete blood workup	Annually
Iron	Annually
Vitamin A (retinol)	Annually
Vitamin D (25-hydroxyvitamin D)	Annually
Vitamin E (alpha-tocopherol)	Annually
Vitamin K (prothrombin time and RNI)	Annually

RNI: recommended nutrient intake. Adapted from Stallings et al.[194]

Fat-soluble vitamins are better absorbed when given in combination with a meal and pancreatic enzymes.

(Level of evidence: 2 for vitamin E)

(Level of evidence: 5 for vitamin A)

(Level of evidence: 3 for vitamin D)

(Level of evidence: 2 for vitamin K)

OTHER ASPECTS

When and how should diabetes be investigated in patients with cystic fibrosis?

Approximately 20% of the adolescents and 40% of the adults develop cystic fibrosis-related diabetes, resulting in worsening of nutrition, worsening of pulmonary function, and increase in morbidity and mortality rates, even in its asymptomatic phase.[208] Every cystic fibrosis patient older than 10 years of age should undergo the oral glucose tolerance test for the determination of blood glucose levels after fasting for 8 h and 2 h after the ingestion of 1.75 g/kg of glucose (maximum, 75 g).[209-213] The oral glucose tolerance test should be performed preferably when the patient is clinically stable.

The test is also recommended for patients with unexplained clinical worsening, prior to transplantation, in use of systemic corticosteroids, and before and during gestation, as well as in patients receiving enteral nutrition as nutritional support.

Blood glucose levels for the diagnosis of cystic fibrosis-related diabetes are similar to those for non-cystic fibrosis-related diabetes (Table 7).

(Level of evidence: 2)

What is the current recommended treatment for cystic fibrosis-related diabetes?

Cystic fibrosis-related diabetes should be treated with insulin.[208-210] Mean insulin doses range from 0.38 to 0.58 IU/kg/day,[214] distributed between slow-acting basal insulin and long-acting or ultralong-acting basal insulin at meals. Calories and carbohydrates should not be restricted, but complex carbohydrates and foods with low glycemic index should be favored and distributed in smaller portions and shorter intervals (2-3 h). Patients with changes in glucose levels during exacerbations might benefit from intermittent insulin administration. There is no definite consensus regarding the treatment of glucose intolerance.

Chart 8. Anthropometric indices recommended by the World Health Organization and adopted by the Brazilian Ministry of Health for the evaluation of the nutritional status of children and adolescents.

Age bracket	Children up to 5 years old	Children between 5 and < 10 years old	10-19 years old
Anthropometric indices	Weight for age	Weight for age	-
	Weight for height	-	-
	BMI for age	BMI for age	BMI for age
	Height for age	Height for age	Height for age

BMI: body mass index.

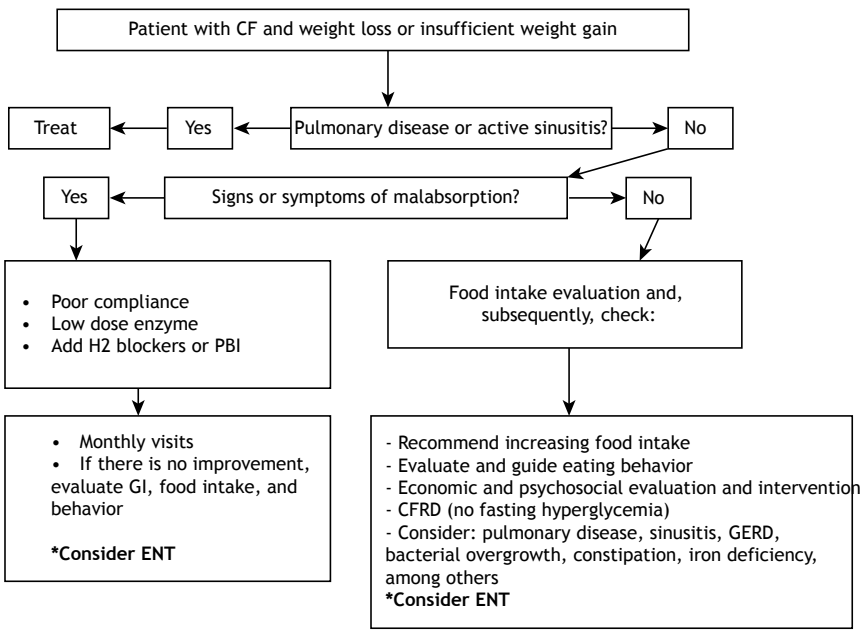

Figure 2. Algorithm for patients with low weight or insufficient weight gain. CF: cystic fibrosis; PBI: proton pump inhibitor; GI: gastrointestinal; ENT: enteral nutrition therapy; CFRD: cystic fibrosis-related diabetes; and GERD: gastroesophageal reflux disease. Adapted from Sinaasappel et al.[202]

(Level of evidence: 2 for insulin treatment)

(Level of evidence: 3 for recommendations regarding calories and carbohydrates)

When and how should osteopenia/osteoporosis be investigated in cystic fibrosis patients?

Low bone mineral density is common in cystic fibrosis patients, and it might occur since childhood. Bone densitometry is the gold standard test for diagnosing osteopenia/osteoporosis and should be performed in patients between 8-10 years of age. In patients younger than 20 years of age, the sites for that assessment are the total body and lumbar spine, whereas, in those aged 20 years or more, the sites are the hip and lumbar spine. The results should be adjusted for gender, age, and ethnicity, and they should be expressed as a Z-score for patients < 50 years of age and as a T-score for patients > 50 years of age and menopausal women. Bone densitometry should be repeated every 1-5 years, depending on the clinical classification of the findings.[23,215]

(Level of evidence: 4 for body sites for bone densitometry)

(Level of evidence: 5 for confirming the need for bone densitometry)

What is the recommended treatment for osteoporosis/osteopenia in cystic fibrosis patients?

In order to prevent bone mass loss, it is recommended to maintain an adequate nutritional status, perform low-impact physical exercises, and avoid the use of inhaled or oral corticosteroids.[23,215]

(Level of evidence: 5)

If the diagnosis of osteopenia is confirmed (Z-score between −1.0 and −2.5), vitamin D, vitamin K, and calcium supplementation should be initiated.[216]

(Level of evidence: 2)

If the diagnosis of osteoporosis is confirmed (Z-score < −2.5), prescribe bisphosphonates: alendronate v.o. (70 mg/week or 10 mg/day); risedronate v.o. (35 mg/week or 5 mg/day); pamidronate i.v. (0.5-1.0 mg/kg/day for 3 days every 3 months); or zoledronic acid i.v. (0.025-0.05 mg/kg/day in a single dose every 6 months).[213,217]

(Level of evidence: 1 for bisphosphonates)

When should the use of long-term venous access be considered and what are the options?

The evaluation of the need for using a long-stay intravenous device is based on the expected length of therapy, characteristics of the medications, such as pH (<5 or > 9), osmolarity (> 600 mOsmol/L), and

Table 6. Doses for fat-soluble vitamin supplementation in patients with cystic fibrosis.

Age	Individual daily vitamin supplementation			
	Vitamin A, IU (μg)	Vitamin E, mg	Vitamin K, mg	Vitamin D, IU
0-12 months	1,500 (510)	40-50	0,3-0,5	400-500
1-3 years	5,000 (1,700)	80-150	0,3-0,5	800-1,000
4-8 years	5,000-10,000 (1,700-3,400)	100-200	0,3-0,5	800-1,000
> 8 years	10,000 (3,400)	200-400	0,3-1,0	800-2,000
Adults	10,000 (3,400)	200-400	2,5-5,0[a]	800-2,000

[a]mg/week.

Table 7. Screening and diagnostic criteria for cystic fibrosis-related diabetes and interpretation of blood serum glucose results by means of the oral glucose tolerance test.

OGTT, mg/dl	Interpretation	Fasting BSG	BSG-2 h	BSG-1 h
• Healthy patients > 10 years of age	Glucose tolerance	< 126	< 140	
• Prior to transplantation	Glucose intolerance	< 126	140-199	
• Pregnancy scheduling	CFRD	≥ 126	≥ 200	
• During pregnancy	Indeterminate	< 126	< 140	≥ 200
Monitorização de glicemia de jejum e GPP de 2 h				
• During hospitalization	DRFC	GP de jejum ≥ 126 mg/dl		
• Outpatient setting				
1. Pulmonary exacerbation, treated with i.v. antibiotic therapy or systemic glucocorticosteroids		GPP ≥ 200 mg/dl (persistente por 48 h)		
2. Monthly, during and after nocturnal enteral feeding		≥ 200 mg/dl durante ou após a dieta		
Glycated hemoglobin	DRFC	≥ 6,5% (< 6,5% não exclui)		
Random blood glucose testing	DRFC	Glicemia ao acaso ≥ 200 mg/dl + poliúria e polidipsia		

OGTT: oral glucose tolerance test; BSG: blood serum glucose; BSG-2h: blood serum glucose 2 h after glucose intake during OGTT, GP-1h: blood serum glucose 2 h after glucose intake during OGTT; CFRD: cystic fibrosis-related diabetes; and PBG: postprandial blood glucose.
Adapted from Sermet-Gaudelus et al.[213]

the irritant capacity of such medications, as well as the durability of the intravenous device, the clinical condition of the patient, and the possibility of associated complications (Figure 3).[218]

Options for long-term venous access devices include central peripherally inserted central catheters, central venous catheters (Intracath®, Becton Dickinson, Sandy, UT, USA), tunneled catheters (e.g., Hickman type), and totally implantable catheters (PORT-A-CATH®, Smiths Medical, Minneapolis, MN, USA). In a preserved venous network, the first option is the central peripherally inserted central catheter valve technology, which allows its intermittent use.[218]

(Level of evidence: 4 for venous access)

When and how should sinus disease be approached in cystic fibrosis patients?

Sinonasal manifestations are common in patients with cystic fibrosis, especially nasal obstruction due to nasal polyposis and chronic rhinosinusitis. The extent of sinonasal disease may not correlate with the symptoms.

The patient should have routine otorhinolaryngological evaluation, since sinus disease may be related to pulmonary exacerbations. Imaging examinations are indicated only for surgical planning or investigation of complicated cases.[219]

Treatment of sinonasal disease in cystic fibrosis patients consists of anti-inflammatory drugs, antibiotics, topical medications, and surgery.[219,220]

A study with the use of nasal dornase alfa in post-nasal endoscopic surgery patients showed benefits. However, the effectiveness depends on the surgical dilation of the paranasal sinus ostia to allow the medication to reach the sinus mucosa.[219,221-223]

In relation to nasal topical corticosteroids, studies have shown positive effects on both the improvement of nasal symptoms and the reduction of polyps.[224,225]

Surgical treatment should be considered in the persistence of nasal obstruction even after clinical treatment, in cases of anatomical obstruction, when there is a relationship with pulmonary exacerbations, in cases of lung transplantation, or in patients whose symptoms affect their quality of life.[219]

No studies on the use of mucokinetic drugs are available, and the recommendations are extrapolated from patients without cystic fibrosis. It is advocated that 7% hypertonic saline solution would be more adequate due to its mucokinetic effect in cystic fibrosis patients, but the use of 3% saline solution is more widespread.

(Level of evidence: 2 for dornase alfa)

(Level of evidence: 3 for surgical treatment)

(Level of evidence: 5 for further recommendations)

When should lung transplantation be indicated and when should the patient be referred for it?

Lung transplantation should be considered in patients with cystic fibrosis whose predicted life expectancy < 50% in 2 years and who have functional class III or IV according to the New York Heart Association. Although there is no clear indicator of a 2-year survival, a decrease in FEV_1 < 30% is related to a 2-year mortality of approximately 40% in males and 55% in females. Because the mean time on the

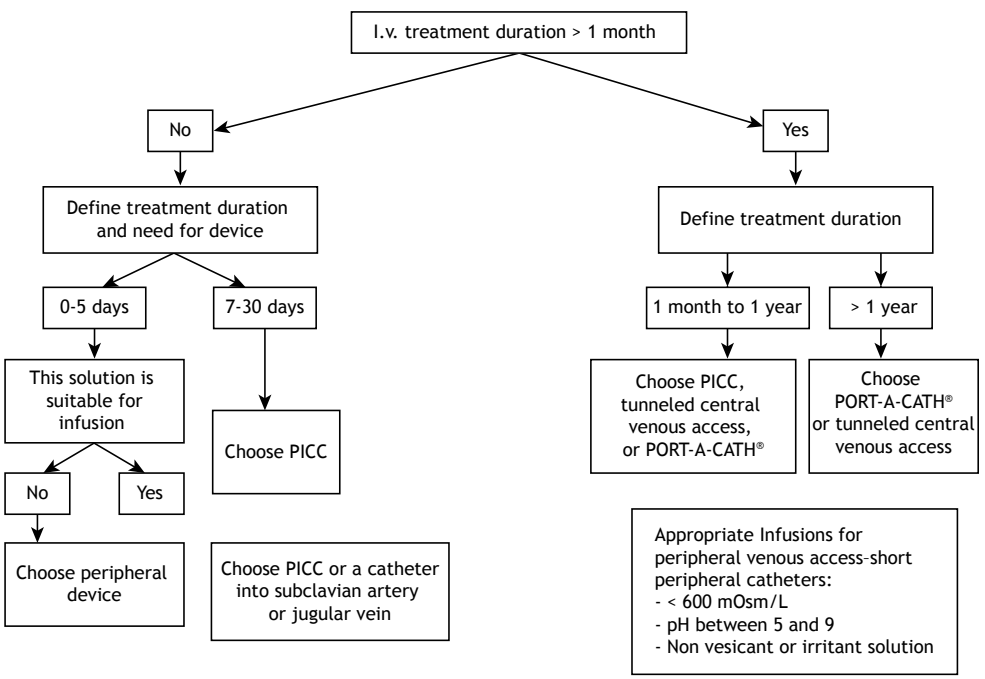

Figure 3. Selection of long-term endovenous device. PICC: peripherally inserted central catheter. Adapted from Santolim et al.[218]

waiting list for lung transplantation is approximately 2 years, adult patients with cystic fibrosis should be referred for lung transplantation under the following conditions: FEV_1 < 30%; six-minute walk test distance < 400 m; clinical or functional worsening, especially in females; hypoxemia or hypercapnia (PaO_2 < 60 mmHg and $PaCO_2$ > 50 mmHg); and pulmonary artery systolic pressure > 35 mmHg. Patients with episodes of pneumothorax or hemoptysis should be referred early. Regarding pediatric patients, long-term results are less consistent, and, although the referral criteria are similar to those abovementioned, the indication should be individualized, taking into account the availability and expertise of the transplant team.[23,226-228]

(Level of evidence: 5)

How should palliative care be in patients with cystic fibrosis and advanced lung disease?

Open and frank dialogue about the progression of the disease should be promoted early on, and palliative care should be provided by the staff responsible for the patient. The team must be trained and qualified regarding the basic principles of analgesia and sedation and be able to treat symptoms, such as pain, nausea, anxiety, and dyspnea.

Oftentimes, palliative care is instituted with the remainder of the active treatment. The desire of the patient and his/her family members, not only in general terms, but also in terms of investment in situations of emergency and end-of-life, should be known by the whole team.

(Level of evidence: 5)

What are the recommendations regarding the use of contraceptive methods in patients with cystic fibrosis?

Female patients with cystic fibrosis should be advised of the contraceptive methods available (hormonal methods, intrauterine devices, barrier methods, and sterilization).[230] The efficacy of these methods is similar to that for the general population, except for the lower activity of hormonal contraceptives with the use of the new drugs (ivacaftor and lumacaftor).[231] Male patients, despite the fact that almost all are infertile, should be advised of the risks of sexually transmitted diseases. Although there is evidence of greater severity in the use of oral contraceptives in females, supposedly related to hormonal issues, their use does not seem to influence the evolution of cystic fibrosis.[232] Genetic counseling should be offered to all patients and their families, facilitating the prevention of cystic fibrosis in the affected families.

(Level of evidence: 5 for indication of contraceptives)

(Level of evidence: 5 for genetic counseling)

How to approach pregnancy in cystic fibrosis patients?

The pregnant woman with cystic fibrosis must be closely followed by the multidisciplinary team and by an obstetrician specializing in high-risk pregnancy. Oral glucose tolerance test and ultrasonography should be performed quarterly, as well as nutritional and pulmonary function monitoring.

Respiratory exacerbations should be treated aggressively. Most drugs used to treat cystic fibrosis do not compromise the fetus. Whenever possible, vaginal delivery should be performed with epidural anesthesia.[233-236]

(Level of evidence: 5 for vaginal delivery)

What is the best way to approach infertility in cystic fibrosis patients?

Infertility or subfertility in both sexes usually accompanies cystic fibrosis. Female infertility appears to be related to the thickening of cervical mucus, whereas male infertility is related to congenital and bilateral absence of the vas deferens.[237] Sperm counts should be offered to every patient who wants to know his fertility level. Referral centers should provide access to various specialists, including gynecologists, urologists, geneticists, and human reproduction specialists, to guide couples and patients on investigation strategies and infertility treatments.

(Level of evidence: 5)

What is the importance of treatment compliance in cystic fibrosis?

The therapies recommended for the treatment of cystic fibrosis, despite their proven efficacy in survival, cause burden on patients, interfere with their quality of life, and impair their compliance with the treatment due to the complexity of the therapeutic regimens.

Strategies to overcome barriers and appropriate psychosocial interventions to improve compliance should be implemented by professionals from specialized centers. Open communication and discussion might help identify the key barriers, addressing the problems inherent to each family unit. These actions are essential, since adequate compliance with the actions inherent to the disease is related to relevant clinical benefits.[239-242]

(Level of evidence: 5)

What is the relevance of anxiety and depression in the management of cystic fibrosis patients?

The prevalence of anxiety and depression among patients with cystic fibrosis is extremely high, especially in women. High rates are also found in the parents of such patients. The referral center must be prepared to identify, support, and treat the patients and their family members. The multidisciplinary team should be attentive in order to identify these comorbidities, and an annual screening using specific questionnaires or structured conversations is suggested. In the face of suspected anxiety or depression, a trained professional can confirm the diagnosis and allow psychological or medication interventions.[243]

(Level of evidence: 5)

FINAL CONSIDERATIONS

The scenario of cystic fibrosis in Brazil and worldwide has undergone drastic changes, due to the incorporation of new technologies for the diagnosis and treatment of the disease. In this context, the life expectancy of the patients has increased significantly, which will bring about the need for changes in the performance of health care professionals and the incorporation of new therapeutic resources.

Patients with cystic fibrosis have complex needs for the management of their disease, requiring specialized care that involves a multidisciplinary team, as well as an adequate health care structure and access to advanced medical resources.

The present Brazilian guidelines were prepared in partnership with several Brazilian medical societies and received contributions from several Brazilian professionals involved in the care of patients with cystic fibrosis, aiming at the homogenization of diagnosis and treatment of the disease nationwide.

CONFLICT OF INTEREST

All of the authors have stated their conflicts of interest (Chart 3A—online appendix).

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The names listed here (in alphabetical order) answered the questions related to the categories of the present guidelines and take part in the Brazilian Guidelines for the Diagnosis and Treatment of Cystic Fibrosis Work Group:

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A storm of stones in the lungs: an uncommon sequela of varicella pneumonia

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A 29-year-old female patient, never smoker, restorer by profession, presented with slight malaise and the flu that lasted for a few days. An X-ray of the chest showed various nodules of varying sizes in random distribution and with high density in both lungs, similar to calcifications (Figure 1A). The laboratory test results were unremarkable. Pulmonary function tests and blood gases were normal: FEV_1 = 3.23 L (97% of predicted); FVC = 3.81 L (98% of predicted); DLCO = 98%; pO_2 = 97 mmHg; and pCO_2 = 39 mmHg. An HRCT of the chest was performed to clarify the chest X-ray findings, showing that the totality of nodules was calcified, but there were no calcified lymph nodes (axial HRCT scan with mediastinal window; Figure 1B). The HRCT scans also showed numerous small bilateral nodules—sharply defined and randomly distributed in both lungs—but no interstitial thickening or any other pathologic findings (Figures 1C and 1D). Parathyroid function, autoantibodies, and quantiFERON-TB (Cellestis, Ltd., Carnegie, Australia) testing was negative, and blood calcium levels were normal. The patient confirmed a severe varicella infection in childhood (at age 4 years), and antibody testing for the varicella-zoster virus showed positive results (IgG = 348 mIU/mL and IgM = 0.34 mIU/mL). Varicella (chickenpox) is a contagious viral disease transmitted by respiratory droplets. The development of multiple, small, diffuse nodular calcifications in both lungs with noncalcified lymph nodes is an uncommon sequela of varicella pneumonia.

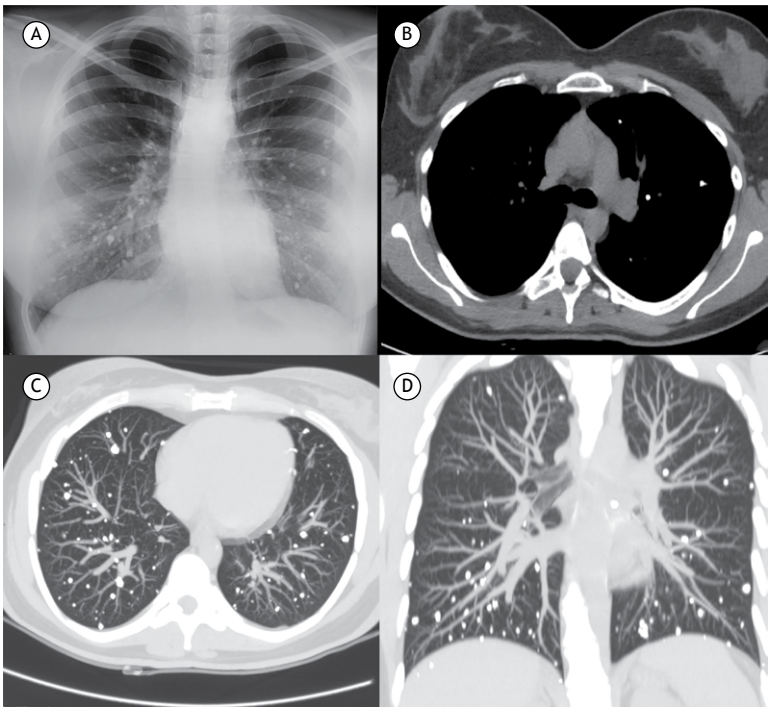

Figure 1. In A, anteroposterior chest X-ray showing innumerable, coarse and punctate micronodules with high calcific density throughout both lungs; in B, axial HRCT scan (mediastinal window) showing no mediastinal calcified lymph nodes. Axial (in C) and coronal (in D) HRCT scans of the chest (thickness of maximum intensity projection: 14 mm and 30 mm, respectively) showing scattered, randomly distributed calcified nodules in both lungs, with no calcified mediastinal lymph nodes, suggestive of healed varicella pneumonia in the appropriate clinical setting.

RECOMMENDED READING

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Edital de Seleção

Brasília, 08 de maio de 2017

Foi aprovada uma alteração no Regulamento do Jornal Brasileiro de Pneumologia para a criação do cargo de Vice-Editor. O Vice-Editor será eleito sempre na metade do mandato do Editor-Chefe para auxiliá-lo na condução editorial do jornal. Ao final de dois anos, o Vice-Editor assume a posição de Editor-Chefe, com mandato pleno, de quatro anos. Com essa mudança, visa-se aperfeiçoar o processo de transição na condução do jornal, garantindo familiaridade com todos os processos a ela inerentes.

No período entre 15 de maio e 30 de julho de 2017 estarão abertas as inscrições para candidatos a posição de Vice-Editor do Jornal Brasileiro de Pneumologia com atuação no biênio 2017-2018, o qual assumirá a posição de Editor-Chefe em 2019. Os interessados ao posto deverão ter experiência prévia na editoração de periódicos de circulação internacional e enviar à administração da SBPT, em Brasília, suas propostas de gestão e curriculum vitae na plataforma Lattes. As propostas dos candidatos deverão abranger o campo administrativo, científico e orçamentário, e deverão ser apresentadas em relação aos dois anos como Vice-Editor e aos quatro anos previstos para a duração do futuro mandato como Editor-Chefe. Os candidatos deverão conhecer as normas relativas à seleção do Vice-Editor e o funcionamento do Jornal Brasileiro de Pneumologia, explícitas em seu regulamento, o qual poderá ser obtido por meio de contato com a secretaria do JBP em Brasília.

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For further clarification, please contact the Journal Secretary by e-mail or by telephone.

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Within this context, the *Jornal Brasileiro de Pneumologia* adheres to the definition of a clinical trial as described by the WHO, which can be summarized as "any study that prospectively assigns human beings to be submitted to one or more interventions with the objective of evaluation the effects that those interventions have on health-related outcomes. Such interventions include the administration of drugs, cells and other biological products, as well as surgical procedures, radiological techniques, the use of devices, behavioral therapy, changes in treatment processes, preventive care, etc

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Original articles: For original articles, the text (excluding the title page, abstracts, references, tables, figures and figure legends) should consist of 2000 to 3000 words. Tables and figures should be limited to a total of five. The number of references should not exceed 30. Original articles should be divided into the following sections: Introduction, Methods, Results, Discussion, Acknowledgments, and References. The Methods section should include a statement attesting to the fact the study has been approved by the ethics in human research committee or the ethics in animal research committee of the governing institution. There should also be a section describing the statistical analysis employed, with the respective references. In the Methods and Results sections, subheadings may be used, provided that they are limited to a reasonable number. Subheadings may not be used in the Introduction or Discussion.

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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.

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Official Publications

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Electronic publications

6. Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Homepages/URLs

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Other situations:

In other situations not mentioned in these author instructions, authors should follow the recommendations given by the International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2004. Available at http://www.icmje.org/.

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NACIONAIS

XX Congresso da Sociedade Brasileira de Cirurgia Torácica
Data: 03 a 06 de maio de 2017
Local: Windsor Barra – Rio de Janeiro/RJ
Organização: Método Eventos
Informações: Beatriz Lemgruber
(21) 25485141

ATS/ALAT & SBPT Critical Care Meeting Special Topics in Multidisciplinary Critical Care: Acute Respiratory Failure and Mechanical Ventilation
Data: 13 a 15 de julho de 2017
Local: Centro de Convenções Rebouças, São Paulo/SP
Informações: 0800616218 ou eventos@sbpt.org.br

V Curso Nacional de Circulação Pulmonar
Data: 01 e 02 de setembro
Local: São Paulo – SP

INTERNACIONAIS

ATS 2017
Data: 19-24 de Maio de 2017
Local: Washington, D.C/USA
Informações: www.thoracic.org

SEPAR 2017
Data: 2-5 de junho de 2017
Local: Madrid Marriott Auditorium Hotel & Conference Center, Madrid/Espanha
Informações: www.separ.es

ERS 2017
Data: 09-13 de Setembro de 2017
Local: Milão, Itália
Informações: www.ersnet.org

CHEST 2017
Data: 28/10 a 01 de novembro de 2017
Local: Toronto/Canadá
Informações: www.chestnet.org

REGIONAIS

XX Congresso da Sociedade Brasileira de Cirurgia Torácica
Data: 03 a 06 de maio
Local: Rio de Janeiro – RJ

9º Congresso do Centro-Oeste de Pneumologia e Tisiologia
Data: 08 a 10 de junho de 2017
Local: Cuiabá - MT
Informações: a definir

Espiro 2017
10 de junho
Salvador – BA

VIII Congresso Gaúcho de Pneumologia e II Congresso Gaúcho de Pneumologia Pediátrica
Data: 29 de junho a 01 de julho de 2017
Local: Centro de Eventos do Hotel Plaza São Rafael
Informações: www.sptrs.org.br - sptrs.secretaria@gmail.com - (51)3384-2889

IX Congresso Mineiro de Pneumologia e Cirurgia de Torácica
IV Congresso Mineiro de Pneumologia Pediátrica
Data: 29 de junho a 01 de Julho de 2017
Local: Associação Médica de Minas Gerais - Belo Horizonte – MG
Informações: Sociedade Mineira de Pneumologia e Cirurgia Torácica – 3213-3197 Renata Miranda
smpct@smpct.org.br
www.smpct.org.br

XVI Congresso de Pneumologia e Tisiologia do Estado do Rio de Janeiro
Data: 27 a 30 de setembro
Local: Rio de Janeiro – RJ

O ESTADO DE GOIÁS RECEBERÁ UMA ILUSTRE VISITA:

O principal congresso brasileiro de pneumologia e tisiologia.

A SBPT convida você a agregar novos conhecimentos através de uma grade científica cuidadosamente elaborada, que vai abranger a maioria das doenças do sistema respiratório junto com um renomado time de congressistas estrangeiros e nacionais. Será uma oportunidade única para você levar mais conhecimento para dentro do seu consultório e para seus pacientes, e também conhecer as belezas do Estado de Goiás, do dia 4 a 8 de agosto de 2018!

Realização:

SOCIEDADE BRASILEIRA DE PNEUMOLOGIA E TISIOLOGIA · 1937 ·

SOCIEDADE GOIANA DE PNEUMOLOGIA E TISIOLOGIA

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XXXIX Congresso Brasileiro de Pneumologia e Tisiologia
e XV Congresso Brasileiro de Endoscopia Respiratória

CENTRO DE CONVENÇÕES DE GOIÂNIA/GO • DE 4 A 8 DE AGOSTO DE 2018.