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HIGHLIGHT

Recommendations for the pharmacological treatment of COPD

Mechanical ventilation weaning

Chest CT findings in patients with dysphagia

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JBP and bibliometric indices

Rogério Souza[1,2]

The process of publishing a scientific journal has complexities that go well beyond the choice of manuscripts, although this process alone has intrinsic peculiarities. Initially, it is necessary to consider the context surrounding the journal.[1] The JBP is the leading journal in the field of respiratory medicine in Latin America, a fact that has recently been confirmed with the release of the 2016 bibliometric indices. We achieved an impact factor of 1.496, according to the Thomson Reuters index, and, according to the Scopus database, which uses the same methodology, we achieved an index of 1.609. These are the highest values ever achieved by our Journal and place us in the second quartile of the respiratory medicine journals. In addition, if we observe other indicators, we can infer that the trend is toward growth. For instance, international collaboration has grown consistently in recent years, increasing from 8.5% in 2013 to 16.9% in 2016, which demonstrates the improved representativeness of the JBP.

It is important to emphasize the concept that the indices used for the evaluation of the various scientific publications are not the sole determinant of the relevance of such publications and, sometimes, even create additional complicating factors.[2] We need to maintain our commitment to increasing our visibility without losing focus on the formative character that our Journal has, particularly in Brazil. However, the metric by which the national publications are evaluated in the Brazilian graduate system does not take that into account, giving importance only to the impact factor and making large research groups less interested in the national publications. This is a problem that needs to be addressed directly if we want to further increase the editorial relevance of the JBP.

Over the past two years, we have been able to balance all that. The profile of the most often cited articles includes review of topics that are most prevalent[3,4] and original articles addressing prevalent topics or rarer conditions.[5,6] However, it should also be considered that the JBP is the official organ of the Brazilian Thoracic Association, and, therefore, all related fields should be covered, regardless of the citation potential of each one of them, since it is well known that smaller or still incipient fields are less likely to be cited over the time period used in the bibliometric indices. All of these aspects should be considered together in analyzing the relevance of the JBP in the respiratory medicine setting.

For such discussions to become increasingly present in the JBP, the participation of the associate editors in editorial decisions has been most relevant. They are the ones mainly responsible for the growth of the Journal and the consolidation of our indices. For this to be even more long-lasting, the position of Vice Editor of the JBP was created. It is the Vice Editor's responsibility to participate in the most significant editorial decisions, together with the Editor-in-Chief, for a period of two years, after which he will take on the editorial leadership for the customary period of four years. The creation of this new position was aimed at enabling smoother transitions, allowing changes in editorial policies in a context known to all parties involved. The Vice Editor selection process was disseminated through our media and will be completed in July of 2017, and the results should be known by the time the September/October issue of the JBP comes out.

While on one hand the decentralization of editorial policies is underway, several barriers have yet to be overcome. As a result of the increased visibility of the JBP, there has been a significant increase in the number of submissions. While such an increase is desirable, because it reflects our representativeness, it carries with it an even greater demand for reviewers. We have had the unequivocal collaboration of a large number of colleagues, who, almost anonymously, have contributed significantly with their critical and analytical thinking and their insight. There is a need for greater recognition to be given to these colleagues, to whom the entire editorial board expresses its eternal gratitude. The Brazilian Thoracic Association has studied alternatives for achieving this objective. This is not a characteristic of ours alone; the major international journals are discussing how to give better recognition to their reviewers and, at the same time, attract more people to this position, a position that is key to the routine of any journal known for excellence, such as ours is. Critical analysis of scientific studies needs to be made part of the daily life of pulmonologists in training. In the long term, the result of this process will be better education of researchers and faculty. An increased critical mass of reviewers and potential editors will be a very beneficial secondary effect of this process.

All in all, we have much to celebrate from the growth of the JBP, but we still have numerous challenges ahead, both known and unknown. To overcome all of them, the participation of the JBP's readership is essential. Therefore, here is an invitation: give your opinions, ideas, criticisms, and suggestions! This will allow the JBP to reflect the concerns of those for whom it is intended.

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The difficult task of searching for tools that help predict mechanical ventilator weaning success

Bruno do Valle Pinheiro[1]

Mechanical ventilation (MV) is one of the most common supportive measures employed in ICU and is fundamental in maintaining life under certain conditions.[1] However, MV can be associated with serious complications, such as pneumonia, tracheobronchitis, critical illness neuropathy and myopathy, delirium, barotrauma, and MV-induced lung injury, making its interruption desirable once the patient is able to breathe spontaneously in a safe manner and without need of a tracheal cannula.[2] This process of disconnecting the patient from the ventilator is designated weaning.

Weaning remains one of the great challenges of MV, especially because it is impossible to predict, with the desired accuracy, whether extubation will be successful or whether reintubation will be necessary. The rates of patients who undergo unscheduled extubation and are successfully weaned range from 25% to 75%; these data show that exaggerated conservatism may delay MV weaning in some cases. However, the mean rates of reintubation after elective extubation remain between 10% and 12%, regardless of the indices used to in order to predict weaning success.[4] Nevertheless, these are mean values and certainly vary depending on the complexity of MV weaning: it can be simple — patients extubated after a first spontaneous breathing trial (SBT) — difficult — patients who fail on the first SBT and require up to three SBTs or up to 7 days after the first weaning trial — or prolonged — patients requiring more than three SBTs or more than 7 days after the first weaning trial.

Among the causes of weaning failure, especially in difficult and prolonged cases, it is worth noting cardiac dysfunction, associated or not with fluid overload. When the patient spontaneously breathe without the help of positive pressure of the ventilatory support, either during a T-piece trial or after extubation, the negative intrathoracic pressure during inhalation promotes an increase in venous return, with a consequent increase in the preload of the right and left ventricles, as well as a decrease in the left ventricular ejection pressure gradient, causing an increase in left ventricular afterload. At the same time, right after spontaneous breathing is initiated, there may be an increase in adrenergic tone, with increased levels of catecholamines and increases in left ventricular preloads and afterloads. These changes altogether increase oxygen consumption by the myocardium and may even generate ischemia in patients with previous coronary disease. Another possible consequence is the inability of the heart to deal with the increases in preload and afterload, resulting in increased filling pressures and pulmonary congestion. Pulmonary congestion increases the work of breathing and may be responsible for MV weaning failure.[6]

Given the importance of cardiac dysfunction and hypervolemia in weaning failure, it is expected that the identification of these conditions can be useful in the evaluation of these patients. In this sense, Antonio et al.,[7] in the current issue of the JBP, evaluated whether the presence of signs of pulmonary congestion on chest X-rays correlated with SBT failure. To that end, the authors evaluated patients older than 18 years of age undergoing MV for more than 24 h, depending on their clinical or surgical conditions. The patients were evaluated daily and were considered eligible for weaning if the cause of their respiratory failure improved and if they had good level of consciousness, adequate gas exchange, absence of respiratory acidosis, hemodynamic stability, and a rapid shallow breathing rate ≤ 105 breaths/min/L. In such cases, a T-tube was placed for 30-120 min, and the following signs of failure were observed: RR > 30 breaths/min; arterial oxyhemoglobin saturation < 90%; use of accessory muscles; HR > 140 bpm; systolic blood pressure < 90 mmHg or < 20% of basal levels; and altered level of consciousness. The presence of any of these findings indicated SBT failure, whereas the absence of all of the signs meant SBT success, and extubation was carried out. A radiologist, blinded to the SBT result, evaluated the chest X-ray performed within 24 h prior to the trial and used a radiological score, described by Shochat et al.,[8] in order to assess pulmonary congestion.

The authors evaluated 170 patients, the majority of whom had simple weaning — 78.3% were extubated on first attempt, and the duration of MV before weaning was 4 days (interquartile range [IQR]: 2-4 days) among those who had SBT success and 6 days (IQR: 4-11 days) among those who had SBT failure. The radiological score was not able to discriminate SBT results; the scores were similar between the patients showing SBT success or SBT failure (median = 3 days; IQR: 2-4 days) in both groups. ROC curve analysis revealed no cut-off point that accurately discriminated between SBT success and SBT failure. The results led the authors to conclude correctly that there is no indication to perform chest X-rays in order to evaluate pulmonary congestion as an additional tool to recommend the use of SBT in patients who meet the commonly accepted criteria to start the trial.

In some respects, this negative result could already be expected. The vast majority of patients had simple weaning; therefore, failure rates were low. Failure can occur due to various causes, cardiovascular failure being only one of them. In addition, among the patients studied in that cohort, less than half had systolic or diastolic

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dysfunction, which would be risk factors for weaning failure due to cardiovascular disease or hypervolemia. However, this negative result does not rule out the possibility that the evaluation of cardiac dysfunction or hypervolemia may be useful as a predictor of weaning success. In this sense, at least two points deserve to be discussed. The first point is whether such an assessment is necessary before SBT is performed in each and every patient. Performing additional evaluations in patients with a low probability of failure can be only a delaying factor in extubation, increasing the chances of MV complications. Therefore, it would be interesting to study a population at a greater risk of failure, even with an increased risk of cardiovascular failure or hypervolemia. Some criteria that could define this population would be the classification of weaning as difficult or prolonged, history of heart disease, or other risk factors, such as advanced age. The second point is whether a chest X-ray is the ideal tool for this sort of investigation or whether other options have higher yields. Among these options, some studies have demonstrated the usefulness of echocardiography and B-type natriuretic peptide quantification in identifying patients who fail SBT due to heart disease.[9,10]

In summary, another study showed the ineffectiveness of an isolated parameter in predicting SBT success or SBT failure; in this case, a radiological score for pulmonary congestion. Although the parameter itself might be inadequate, it should be considered that the result might have been due to the population studied, which consisted of patients who had simple weaning, with a low probability of weaning failure. Increasing the number of predictors is not only unnecessary but can lead to delayed extubation, as the authors have properly discussed.

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Thickening of the tracheal wall

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

A 63-year-old female patient presented with a 1-year history of recurrent polyarthritis and a 3-month history of dry cough. Her laboratory test results were normal. Physical examination revealed deformity in both ears, with inflammatory signs. A chest CT showed diffuse thickening of the walls of the trachea and main bronchi (Figure 1). Her lung parenchyma was normal.

Diffuse thickening of the tracheal wall has a large number of possible etiologies—amyloidosis; relapsing polychondritis (RP); tracheopathia osteochondroplastica (TPO); infections, such as tuberculosis, paracoccidioidomycosis, and rhinoscleroma; granulomatosis with polyangiitis; sarcoidosis; lymphomas; etc. Some imaging features can be useful in narrowing the differential diagnosis, such as the presence of calcifications, and define whether the entire tracheal circumference is affected or whether the lesion spares the posterior membranous wall, affecting only the cartilaginous portion. In the case presented here, two CT features are of note: the wall thickening has calcifications in its entire longitudinal extension; and the posterior membranous portion of the tracheal wall is spared.

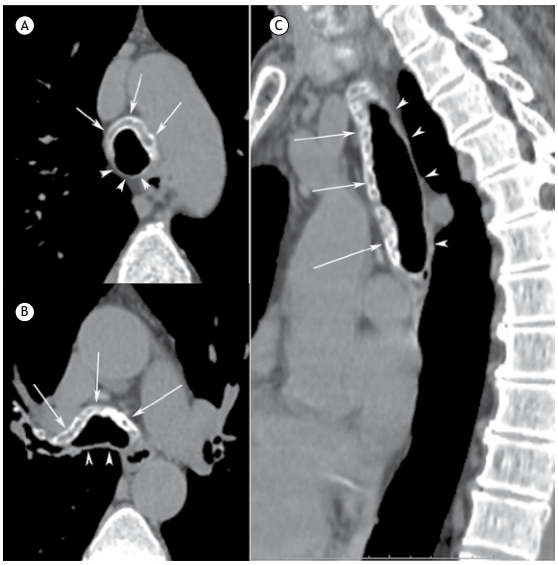

Figure 1. Axial CT slices (in A and B) and coronal CT reconstruction (in C) showing diffuse thickening of the anterior wall of the trachea and main bronchi, with calcifications (arrows). Note that the posterior wall (arrowheads) is spared.

Tracheal wall calcifications can be observed in healthy patients, being related to senility. However, calcifications associated with wall thickening can be seen in amyloidosis, TPO, and RP. In amyloidosis, involvement is circumferential, also affecting the posterior membranous wall. Therefore, in the case presented here, the differential diagnosis is restricted to two diseases: TPO and RP.

TPO is a disease of unknown etiology, characterized by the formation of small, usually calcified submucosal nodules protruding into the tracheal lumen. The disease restricts itself to the tracheobronchial tree. It may be asymptomatic, or it may result in cough, dyspnea, wheezing, or, occasionally, hemoptysis.

RP is characterized by recurrent, potentially severe episodes of inflammation of cartilaginous tissues, including the cartilage of the ear, nose, peripheral joints, and tracheobronchial tree. Airway symptoms include progressive dyspnea, cough, stridor, and hoarseness, which are due to destruction and fibrosis of the cartilaginous rings of the larynx and trachea, leading to luminal collapse, and also to airway narrowing caused by inflammation and cicatricial fibrosis.

Our patient had, in addition to characteristic tracheobronchial changes on chest CT, a seronegative arthropathy and auricular chondritis. On the basis of these elements, a diagnosis of RP was made. In most cases, biopsy is not necessary for diagnostic confirmation.

RECOMMENDED READING

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Prognostic studies for health care decision making

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

PRACTICAL SCENARIO

A multicenter retrospective cohort study was conducted to develop and validate a prognostic model to predict 1-year mortality among adult patients receiving at least 14 uninterrupted days of mechanical ventilation. Likely prognostic variables were chosen, *a priori*, based on published literature and clinical judgment (10 variables). During the development phase of the study, the prognostic variables were included in a logistic regression model to evaluate how well each variable predicted 1-year mortality by calculating discrimination (ability to correctly classify patients into those who did and did not die) using ROC curves and area under the curve (AUC). The authors found that 5 of the 10 variables maximized the prognostic capability of the model for 1-year mortality (age, platelet count, vasopressor use, hemodialysis, no trauma diagnosis) showing very good discrimination (AUC = 0.80; 95% CI: 0.76-0.83). For the validation phase, the authors used the β-coefficient values estimated for each variable in the development cohort logistic regression model to predict 1-year mortality in a new cohort of patients and showed that discrimination was also very good (AUC = 0.78; 95% CI: 0.72-0.83), thus showing that the 5-variable model was valid. Then the authors created a clinical prediction rule, a point system used to easily calculate the probability of 1-year mortality for each patient, based on the strength of association of each variable (β-coefficient) with mortality in the development model. All β-coefficients were assigned 1 point except for the category "age ≥ 65 years," which was assigned 2 points. Lastly, the authors validated this point system by showing that, as the number of points increased, the probability of 1-year mortality increased.[1]

WHY PROGNOSTIC STUDIES ARE USEFUL

The overall goal of prognostic research for clinical settings is to help clinicians, patients, and families make informed health-care decisions based on information available on each patient in the present to predict outcomes in the future. In our example, identifying patients at high risk of dying within 1 year justifies clinicians' recommendation for closer outpatient-monitoring after discharge. Additionally, it helps patients and family think about appropriate end-of-life decisions for those at very high risk of dying, as well as to identify individualized interventions to prevent future hospitalizations due to respiratory failure.

HOW TO DEVELOP A CLINICAL PREDICTION RULE

The process involves designing a retrospective or prospective cohort study that measures prognostic variables among participants at study baseline (entry), that follows them during a pre-specified time and that assesses whether they develop the outcome or not. Using data from a subset of the participants, called the development cohort, a logistic regression model with the outcome (in our example, 1-year mortality) as the dependent variable and plausible predictive variables as independent variables is built and the AUC is calculated (Figure 1). In a second step, the mathematical equation (β-coefficients) from the development model is tested in another subgroup of similar patients, called the validation cohort. The clinical prediction rule is built by assigning points to each predictive variable based on their strength of association with the outcome.[2]

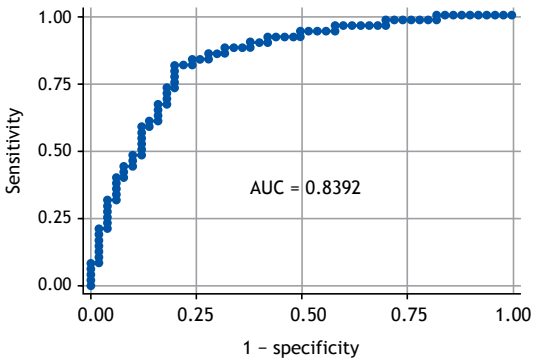

Figure 1. The ROC curve is used to quantify model discrimination by plotting the true positive rate (sensitivity) against the false positive rate (1 – specificity) for different possible cut-off values of a prognostic model. The greater the area under the curve (AUC), the better the model discriminates the subjects with the outcome from those without it. This figure was created with fictitious data.

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Usefulness of radiological signs of pulmonary congestion in predicting failed spontaneous breathing trials

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Study carried out at Hospital Moinhos de Vento, Porto Alegre (RS) Brasil.

ABSTRACT

Objective: Inspiratory fall in intrathoracic pressure during a spontaneous breathing trial (SBT) may precipitate cardiac dysfunction and acute pulmonary edema. We aimed to determine the relationship between radiological signs of pulmonary congestion prior to an SBT and weaning outcomes. **Methods:** This was a post hoc analysis of a prospective cohort study involving patients in an adult medical-surgical ICU. All enrolled individuals met the eligibility criteria for liberation from mechanical ventilation. Tracheostomized subjects were excluded. The primary endpoint was SBT failure, defined as the inability to tolerate a T-piece trial for 30-120 min. An attending radiologist applied a radiological score on interpretation of digital chest X-rays performed before the SBT. **Results:** A total of 170 T-piece trials were carried out; SBT failure occurred in 28 trials (16.4%), and 133 subjects (78.3%) were extubated at first attempt. Radiological scores were similar between SBT-failure and SBT-success groups (median [interquartile range] = 3 [2-4] points vs. 3 [2-4] points; p = 0.15), which, according to the score criteria, represented interstitial lung congestion. The analysis of ROC curves demonstrated poor accuracy (area under the curve = 0.58) of chest x-rays findings of congestion prior to the SBT for discriminating between SBT failure and SBT success. No correlation was found between fluid balance in the 48 h preceding the SBT and radiological score results ($\rho = -0.13$). **Conclusions:** Radiological findings of pulmonary congestion should not delay SBT indication, given that they did not predict weaning failure in the medical-surgical critically ill population.

(ClinicalTrials.gov identifier: NCT02022839 [http://www.clinicaltrials.gov/])

Keywords: Radiography; Pulmonary edema; Ventilator weaning.

INTRODUCTION

Weaning from mechanical ventilation (MV) is a gradual process that involves withdrawing the patient from the ventilator and removing the endotracheal tube. The weaning process can account for as much as 42% of the total duration of MV.[1-3] MV is associated with significant complications that are time-dependent in nature, prolonged intubation resulting in an increased incidence of complications, such as ventilator-associated pneumonia and increased mortality.[4,5] However, impetuous attempts at weaning from MV are also hazardous. A failed attempt at extubation is associated with an 8-fold increase in the odds ratio for nosocomial pneumonia and a 6-to-12-fold increase in mortality risk.[6] Therefore, the clinical challenge is to balance aggressiveness against safety.

Large clinical trials conducted in the 1990s showed that clinicians frequently miss opportunities to wean patients from MV. The fact that most patients (75%) are extubated on the same day on which the weaning process is initiated suggests that the process can be initiated earlier, misconceptions and "slow" weaning procedures accounting for delayed weaning.[7,8]

Weaning-induced cardiac dysfunction is recognized as an important cause of weaning failure.[9] During a spontaneous breathing trial (SBT), an abrupt drop in intrathoracic pressure during inhalation tends to increase the systemic venous return pressure gradient and to decrease the left ventricular (LV) ejection pressure gradient, thus resulting in increased LV filling pressure. A marked increase in the work of breathing can result in increased cardiac work and myocardial oxygen demand.[9,10]

Chest X-rays (CXRs) are commonly used in order to detect pulmonary edema. Radiographic signs that suggest accumulation of fluid in the lung interstitium or alveolar space include vascular redistribution, septal lines (Kerley's A and B lines), interlobular septal thickening, peribronchial cuffing, bilateral opacities ("bat wing" pattern), air bronchogram, and pleural effusion. In patients with pulmonary edema due to heart failure, the heart is commonly enlarged.[11,12] Some experts recommend that CXRs be routinely taken before an SBT in order to confirm "disease reversal", discard fluid overload, and define eligibility.[2,13-15] However, these criteria have been neither defined nor prospectively evaluated in a randomized controlled trial. In addition, CXR accuracy is significantly limited by acquisition techniques and clinical issues that override standardization procedures, especially in the ICU.[11,12]

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Shochat et al.[16] developed a radiographic score (RS) to evaluate lung fluid content in individuals with acute heart failure following acute myocardial infarction. In that prospective single-center study, the novel RS was found to be able to assess lung edema severity and its changes over time, as well as correlating significantly with patient clinical status.

In a recent study, our research group showed loss of lung aeration during the weaning process, as estimated by bedside lung ultrasound; however, the presence of interstitial syndrome before initiation of weaning from MV failed to distinguish between individuals in whom weaning was successful and those in whom weaning failed.[17] We assumed that CXR findings of lung edema also lack predictive power to discriminate between weaning success and weaning failure; therefore, radiological signs of pulmonary congestion should not delay the decision to initiate the weaning process. The objective of the present study was to assess prospectively whether radiological signs of pulmonary congestion prior to an SBT correlated with weaning outcomes in a heterogeneous group of mechanically ventilated patients.

METHODS

Between January of 2011 and March of 2013, nonconsecutive patients over 18 years of age and undergoing invasive MV for at least 24 h were selected from among those treated at a semiclosed medical-surgical ICU in a private hospital, with 24-h intensivists. Patients with a tracheostomy were excluded. The local research ethics committee approved the study and waived the requirement for informed consent. The present study was a post hoc analysis of a prospective cohort study designed to investigate the potential role of lung ultrasound in predicting weaning outcomes.

Patients were assessed daily for eligibility to weaning according to the following parameters: clinical improvement of the underlying condition that led to acute respiratory failure; alertness and ability to communicate; adequate gas exchange, as indicated by a PaO_2 of at least 60 mmHg and an $FiO_2 < 0.40$; no significant respiratory acidosis (i.e., pH > 7.3); rapid shallow breathing index ≤ 105 breaths/min/L; and vasoactive drugs at low and stable doses (norepinephrine doses < 0.12 μg/kg/min or equivalent dopamine doses).

Attending physicians ordered digital CXRs on a heterogeneous pattern. Confirmation of disease resolution is a typical reason for the prescription of CXRs in our center, notably during MV. Anteroposterior CXR views were performed with the patients in the semi-upright position. For every ready-to-wean subject, a sole attending blinded radiologist was asked to interpret the most recent CXR available, usually obtained in the preceding 1-24 h, in accordance with the RS suggested by Shochat et al.[16] Then, the staff team, blinded to the CXR findings, coordinated ventilator discontinuation by means of a T-piece trial.

Each selected radiological sign of lung congestion was ascribed a predetermined value (Table 1), based on the sum of the RS sign scores: greater increases in lung fluid content represented higher RS scores, reflecting fluid accumulation. However, one single adjustment had to be made in one of the RS parameters: cardiothoracic ratio ≥ 60% was considered abnormal given that patients were in the semi-upright position during image acquisition.[18] Examples of CXRs findings of lung edema are presented in Figures 1A and 1B.

The primary outcome in this post hoc analysis was SBT failure, defined as the inability to tolerate a T-piece trial for 30-120 min, subjects not being extubated in this case. SBT was interrupted if the subject developed signs of respiratory discomfort (RR > 35 breaths/min; arterial oxyhemoglobin saturation < 90%; use of accessory respiratory muscles or paradoxical thoracoabdominal ventilation); tachycardia (HR > 140 bpm); hemodynamic instability (systolic blood pressure < 90 mmHg or 20% over basal levels); or change in mental status (drowsiness, coma, or anxiety). There were no secondary endpoints in the present study.

Demographic data, including age, gender, and race, as well as comorbidities, severity of illness at the time of ICU admission, reason for MV initiation, physiological weaning predictors, and fluid balance (total inputs minus total outputs) 48 h before the SBT were recorded. The presence of diastolic or systolic LV dysfunction (the latter condition being defined as an ejection fraction < 45%) was documented based on a formal echocardiogram report dated up to six months prior to admission. A diagnosis of COPD was based on history, physical examination, CXR, and previous pulmonary function tests, if available.

Shochat et al.[16] found a mean raise of 4.8 points in the RS of individuals who developed overt acute heart failure during hospitalization, whose mean baseline values were 0.6. Hence, our final sample of 170 subjects available for the analysis of the primary outcome had a 99% power to detect the same difference between SBT-success and SBT-failure groups, at a two-sided alpha level of 0.05.

The results were expressed as mean ± SD, median (interquartile range [IQR]), and proportions, as appropriate. The normal distribution of the various parameters was investigated by the distribution of data and using the Kolmogorov-Smirnov test. We used the Student's t-test or the Mann-Whitney U test to compare continuous variables, and the chi-square test or Fisher's exact test to compare proportions, as appropriate. A ROC curve was generated based on predictive RS results and SBT outcomes. Spearman's correlation coefficient was determined in order to correlate fluid balance and RS results. The analyses were performed with the use of the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

We obtained complete data for 170 weaning procedures. Overall, SBT failure occurred in 28

(16.4%). Table 2 shows the baseline characteristics of the cohort according to the outcome. Patients who were successfully extubated had been intubated for a shorter duration than had those who were not (median duration of MV: 4 days vs. 6 days; p = 0.003). In our cohort, 133 patients (78.3%) were extubated at first attempt. Sepsis of any source was the main reason for MV initiation, in approximately 40% of all individuals in both groups. Approximately 11% of the individuals were intubated owing to congestive heart failure, and the same amount had a pre-existing diagnosis of systolic LV dysfunction.

Table 1. Radiological score parameters and values.[a]

Parameter	Value
Redistribution of lung vessels	
No	0
Yes	1
Width of the cardiac silhouette > 60%	
No	0
Yes	1
Peribronchial cuffing	
No	0
Yes	1
New pleural effusion	
No	0
Unilateral	1
Bilateral	2
Kerley's A, B, or C lines	
None	0
Uncertain	1
Definite	2
Lung opacity	
None	0
Lung opacity	1
Ground-glass opacity	2
"Bat wing" pattern	3

Based on Shochat et al.[16] [a]Severity of pulmonary edema was determined as follows: normal chest X-ray, 0-1 points; interstitial lung congestion, 2-4 points; and mild, moderate, and severe alveolar edema, respectively, 5-6 points, 7-8 points, and 9-10 points, respectively.

The RS results were similar between SBT-failure and SBT-success groups (median = 3 [IQR: 2-4] vs. 3 [IQR: 2-4]; p = 0.15), which corresponded to interstitial lung congestion. The analysis of the ROC curve showed that the RS prior to a T-piece trial had poor accuracy in discriminating between SBT failure and SBT success (area under the curve = 0.58; p = 0.2; Figure 2). There was no correlation between fluid balance 48 h prior to the SBT and RS results (ρ= −0.13; p = 0.1).

DISCUSSION

In a heterogeneous cohort of mechanically ventilated patients who were candidates for a SBT, we found no association between radiological signs of pulmonary congestion indicated by the RS and SBT outcomes. Our study suggests that incorporating radiological estimations of lung edema as a readiness criterion for weaning from MV potentially retards it, as long as interstitial pulmonary congestion was observed on SBTs. To the extent of our knowledge, this is the first report encompassing such a topic.

The rationale behind delaying an SBT due to radiological signs of pulmonary congestion might be the belief that MV patients could not succeed in a T-piece trial unless they were "dry" again, given that cardiorespiratory interactions under negative pressure promote increases in both LV preload and afterload. However, a myriad of changes in respiratory mechanics and in the cardiovascular system related to weaning failure is not evident until clinical manifestations of distress appear, which promptly demand interruption of the trial or reintubation.[1] Fluid balance cannot predict SBT outcomes in a slightly larger, mixed medical-surgical

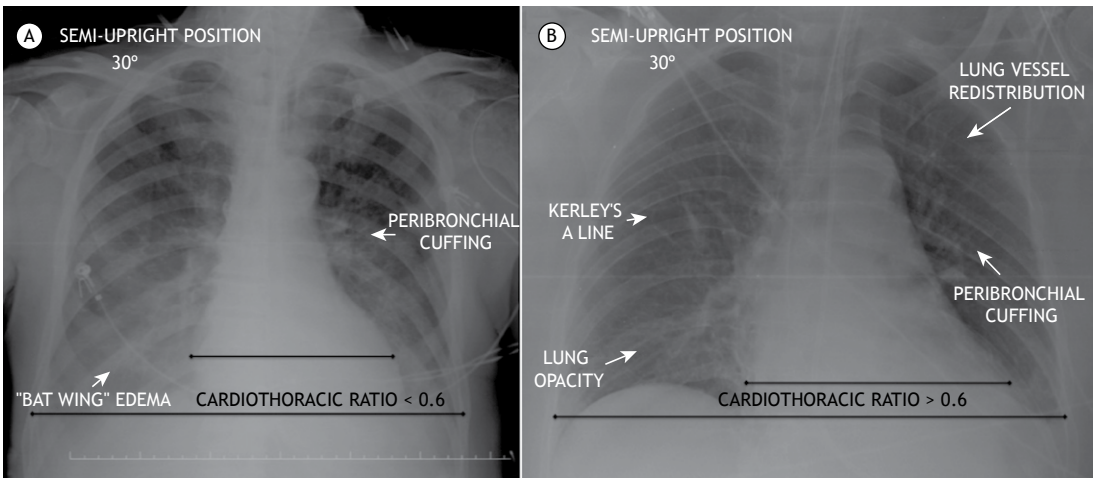


Figure 1. In A, a chest X-ray of a 68-year-old female patient shows peribronchial cuffing and opacity in a "bat wing" pattern, revealing edema, compounding a radiological score of 4 points, characterized as interstitial lung congestion.[16] In B, a chest X-ray of a 57-year-old male patient shows a cardiothoracic ratio > 60%, peribronchial cuffing, lung vessel redistribution, Kerley's A line, and lung opacity, resulting in a score of 5 points, characterized as mild alveolar edema.[16]

Table 2. Characteristics of the study cohort (N = 170).[a]

Characteristic	Groups		p
	SBT success (n = 142)	SBT failure (n = 28)	
Age, years	76 (66-84)	67 (52-80)	0.15
Female gender	62 (43.7)	13 (46.4)	0.79
APACHE II score	21 ± 6.9	23 ± 7.8	0.16
SOFA score	5 (3-9)	5 (2-10)	0.50
BMI, kg/m^2	25 (23-28)	25 (23-29)	0.97
RSBI, f/V_T	53 (41-75)	52 (36-71)	0.94
MV duration, days	4 (2-6)	6 (4-11)	0.003
Fluid balance 48 h prior to the SBT, mL	1,219 ± 2,912	1,838 ± 1,896	0.48
Comorbidities			
COPD	14 (9.9)	5 (17.9)	0.32
EF < 45%	15 (10.6)	4 (14.3)	0.52
LV diastolic dysfunction	55 (38.7)	8 (28.6)	0.30
Ischemic coronary disease	28 (19.7)	4 (14.3)	0.50
RRT	23 (16.2)	7 (25.0)	0.28
Presence of ascites	3 (2.1)	2 (7.1)	0.19
Reason for MV			
Respiratory sepsis	25 (17.6)	6 (21.4)	0.63
Nonrespiratory sepsis	32 (22.5)	5 (17.9)	0.58
CHF	18 (12.7)	1 (3.6)	0.16
Coma	29 (20.4)	4 (14.3)	0.45
Postoperative ARF	7 (4.9)	2 (7.1)	0.63
COPD/asthma	2 (1.4)	2 (7.1)	0.13
Pulmonary embolism	6 (4.2)	1 (3.6)	1.00
ARDS	10 (7.0)	4 (14.3)	0.25
Simple weaning	108 (76.1)	25 (89.3)	0.27
Vasopressor infusion during T-piece trial	27 (19.0)	4 (14.3)	0.55
Vasodilator infusion during T-piece trial	11 (7.7)	2 (7.1)	1.00

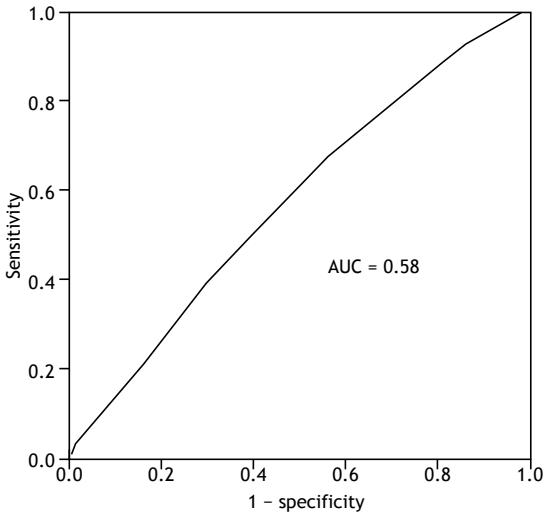
SBT: spontaneous breathing trial; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; BMI: body mass index; RSBI: rapid shallow breathing index; f/V_T: ratio of RR to tidal volume; MV: mechanical ventilation; EF: ejection fraction; LV: left ventricular; RRT: renal replacement therapy; CHF: congestive heart failure; and ARF: acute respiratory failure. [a]Data are presented as median (interquartile range), mean ± SD, or n (%).

ICU population either, perhaps being more relevant for COPD patients, as we published previously.[19] An observational study involving 100 patients immediately before a T-piece trial demonstrated that baseline levels of brain natriuretic peptide—a surrogate marker of congestive heart failure—were moderately elevated exclusively in SBT-failure individuals, who eventually failed owing to cardiac dysfunction.[20] Moreover, overtreatment based on isolated CXR interpretations might be harmful in terms of weaning readiness.[10]

An interobserver agreement study examined the extent to which medical intensivists and a radiologist could agree on whether a CXR revealed diffuse bilateral infiltrates for the diagnosis of ARDS or not and concluded that intensivists without formal consensus training can achieve moderate levels of agreement.[21] Accordingly, in real clinical practice, an expert radiological opinion is not immediately available, and delaying the weaning process based upon poor interpretations of CXRs might be even more questionable. Since the physicians in our study were not aware of the most recent CXR results, we were unable to prove that hypothesis.[24]

A systematic review[22] highlighted the safety of abandoning routine CXRs in favor of a more restrictive approach. Arguments for adopting a restrictive approach included varying interpretations of CXRs depending on clinician and patient factors, low incidence of clinically unsuspected abnormalities, potential harm arising from unnecessary treatment of minor or false-positive findings, costs, radiation exposure and adverse events arising from the repositioning of the patient to obtain CXRs.[23] Likewise, the importance of negative CXR findings for workflow, efficiency, and clinical decision-making might be overestimated. A study collecting the opinions of experienced ICU physicians regarding the appropriateness of performing routine CXRs in various situations encountered in adult ICUs showed there was no consensus regarding the usefulness of obtaining a routine CXR prior to extubation.[24]

It should be pointed out that our study consisted of a relatively small number of patients and absolute number of failure events, with a high prevalence of elderly patients and a low prevalence of systolic LV dysfunction. Nonetheless, our sample had the same



	SBT sucess	SBT failure
Radiological Score	3 (2-4)	3 (2-4)

Figure 2. A ROC curve of the ability of the radiological score to predict spontaneous breathing trial failure. The area under the curve (AUC) is 0.58 (p = 0.2), revealing poor accuracy.

expected pre-test probability of SBT failure as the ordinary medical-surgical ICU population. Our original study focused on lung ultrasound assessment of ready-to-wean subjects. Since CXR results were part of a secondary analysis, we did not standardize the moment of CXR acquisition, so not all exams were performed immediately before the SBT but rather within a period of 24 h prior to the trial. At the beginning of our research, the limited number of experts on bedside lung ultrasound, as well as lack of any research funding, forced us to close enrollment on weekends.

Other limitations include the observational design, with all its intrinsic methodological flaws, and the absence of high scores of radiological signs of lung edema on the RS, which might imply lesser overall severity in this cohort of patients or reflect the pointlessness in requiring CXRs to advance the weaning process. Our ready-to-wean population showed modest median values on the RS. In the original Shochat et al. paper,[16] an RS of 4 or more represented overt acute heart failure in 95% of the patients reaching this level. Hence, it seems unlikely that an individual presenting with a high RS score should be eligible for an SBT.

We decided on SBT failure as the major outcome since we aimed at predicting the earliest time that a patient might resume spontaneous breathing. Moreover, the exact reason for extubation failure often escapes identification. Reintubation is usually performed because of an apparently new episode of respiratory distress, which may be related to primary respiratory failure, congestive heart failure, aspiration, ineffective cough causing accumulation of airway mucus, or upper airway obstruction. Other reasons for reintubation include the onset of a new episode of sepsis, surgical complications, acute coronary syndrome, and neurological impairment.[1]

The RS presented by Shochat et al.[16] was chosen by virtue of its comprehensive analysis of dynamic changes, its good correlation with severity of lung edema, the utilization of lung impedance as the gold-standard method, and the sensitivity for the detection of subtle radiological signs of pulmonary congestion. Currently, that RS is the only method available that proposes a quantitative assessment of CXRs in terms of lung fluid content. In that cohort,[16] high intraobserver (κ = 0.86; p = 0.0001) and interobserver correlations (κ = 0.82; p = 0.0001) were found regarding RS interpretation. However, its main drawbacks are the lack of assessment in the ICU population—although it included patients admitted to a coronary care unit—its single-center design, and the absence of large-scale validation. Therefore, for the sake of generalizability of our findings, the RS must be further studied.

In conclusion, since the radiological signs of pulmonary congestion demonstrated by the RS were unable to predict SBT failure in this medical-surgical critically ill population, we inferred that specific CXR reports on signs of pulmonary congestion are insufficient to preclude hemodynamically stable, sufficiently oxygenated patients from performing an SBT.

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Laryngotracheobronchial papillomatosis: chest CT findings

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ABSTRACT

To evaluate the findings on chest CTs in 16 patients (8 men and 8 women) with laryngotracheobronchial papillomatosis. **Methods:** This was a retrospective study involving patients ranging from 2 to 72 years of age. The evaluation of the CT scans was independently performed by two observers, and discordant results were resolved by consensus. The inclusion criteria were presence of abnormalities on the CT scans, and the diagnosis was confirmed by anatomopathological examination of the papillomatous lesions. **Results:** The most common symptoms were hoarseness, cough, dyspnea, and recurrent respiratory infections. The major CT findings were nodular formations in the trachea, solid or cavitated nodules in the lung parenchyma, air trapping, masses, and consolidation. Nodular formations in the trachea were observed in 14 patients (87.5%). Only 2 patients had lesions in lung parenchyma without tracheal involvement. Only 1 patient had no pulmonary dissemination of the disease, showing airway involvement only. Solid and cavitated lung nodules were observed in 14 patients (87.5%) and 13 (81.2%), respectively. Masses were observed in 6 patients (37.5%); air trapping, in 3 (18.7%); consolidation in 3 (18.7%); and pleural effusion, in 1 (6.3%). Pulmonary involvement was bilateral in all cases. **Conclusions:** The most common tomography findings were nodular formations in the trachea, as well as solid or cavitated nodules and masses in the lung parenchyma. Malignant transformation of the lesions was observed in 5 cases.

Keywords: Papilloma; Tomography, X-ray computed; Lung diseases.

INTRODUCTION

Laryngotracheobronchial papillomatosis (LTBP) is a disease caused by HPV, characterized by the appearance of papillomas in any part of the aerodigestive tract.[1-5] Although LTBP affects the larynx more commonly, the central airway can be involved in less than 5% of cases, and distal dissemination to the lung parenchyma occurs in about 1% of cases.[2,4,6,7] The disease has a higher incidence in children and is the most common benign laryngeal neoplasia in this age group.[4,6-9] It is assumed that the infection is more commonly acquired during birth, during the passage through the birth canal in mothers infected by the virus. Adults may also present LTBP, in whom the contamination by the virus is usually related to sexual contact.[1,3,4,10,11] Although a presumptive diagnosis can be made based on the history and clinical-radiological findings, the final diagnosis is made by histopathological analysis of the laryngeal or tracheal lesions, collected by bronchoscopy.[4] The course of the disease is unpredictable, ranging from spontaneous remission to aggressive disease with pulmonary dissemination and the need for multiple surgical procedures to maintain airway patency.[5]

The objective of the present study was to evaluate the CT scans of 16 patients with LTBP in order to identify the most common tomography findings. In addition, some clinical and epidemiological aspects of the disease have been reported.

METHODS

This was a retrospective study involving 16 patients with LTBP and their CT scans of the chest. These scans were randomly collected through personal contacts with radiologists, originating from eight different institutions, located in five Brazilian states and in Canada. The diagnosis of LTBP was confirmed by the association of clinical, radiological, and histopathological data.

The CTs of the chest, due to the multiple institutions involved, were performed in different scanners, and, in all cases, using the high resolution technique. Ten-millimeter HRCT scans were taken using fine axial sections, 1-2 mm in thickness, from the lung apices to the bases during inspiration, with the patient in the supine position, a high spatial resolution filter being used for image reconstruction. In some cases, iodinated contrast

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medium was injected intravenously. The images were obtained and reconstructed in a matrix of 512 × 512, window openings ranging from 1,000 to 1,500 HU, and levels between −650 and −750 HU. The images were digitized and photographed for the evaluation of the lung fields. Scans were also performed using a mediastinal window with a width between 350 and 400 HU and a center between 40 and 60 HU for the evaluation of the mediastinum.

The evaluation of the HRCT scans was independently performed by two observers, and discordant results were resolved by consensus. Regarding the pattern of the findings, air trapping was defined as reduced attenuation of the lung parenchyma, evidenced mainly by a lower density than usual and absence of reduced lung volume; consolidation was defined as increased attenuation of the lung parenchyma that prevented the visualization of vessels and external contours of the bronchial walls; cavitation was defined as gas-filled spaces, with or without air-fluid level, within a nodule, mass, or pulmonary consolidation; mass was defined as any expansive pulmonary, pleural, mediastinal, or chest wall lesion presenting density of soft, fatty, or bony tissue greater than 3 cm in diameter, regardless of its contours or the heterogeneity of its contents; and nodule was defined as a focal opacity that is rounded, or at least partially delineated, smaller than 3 cm in diameter, and generally presenting soft tissue or calcified tissue density. The criteria for defining these findings are those reported in the Fleischner Society glossary of terms,[12] and the terminology used is that suggested in the terminology consensus by the Department of Imaging of the Brazilian Thoracic Association.[13] The scans were also evaluated for lesions in the central airways, pleural effusion, or any other associated pulmonary or extrapulmonary abnormalities.

RESULTS

Clinical and epidemiological characteristics

Sixteen patients with LTBP were evaluated, 8 (50%) being male and 8 female (50%). Regarding the age group, our sample ranged from 2 to 72 years (mean = 25.7 years; median = 15.0 years, interquartile range [IQR]: 6-42 years). Regarding clinical symptoms, hoarseness was reported in 8 patients (50.0%); cough, in 7 patients (43.7%); and dyspnea, in 6 patients (37.5%). Recurrent pneumonias were also reported in 6 patients (37.5%). Of the 16 patients, 5 (31.2%) developed malignancy (squamous cell carcinoma), all being female, with ages ranging from 7 to 72 years. All of the patients presented weight loss at the time of diagnosis. Four patients underwent tracheostomy during the course of the disease, 2 being male (6 and 11 years of age) and two, female (2 and 5 years of age).

Tomography findings

The major tomography patterns were nodular lesions in the trachea and solid or cavitated nodules in the lung parenchyma. Other less prevalent findings were mass, consolidation, air trapping, and pleural effusion (Figures 1, 2 and 3). In relation to the lower airways, tracheal involvement was found in 14 patients, whereas main bronchus involvement was found in only 4 patients. The CT images revealed that this involvement of the lower airways was represented by nodular thickening of the trachea and of the main bronchi and by nodular lesions of the walls. Solid nodules in the lung parenchyma were found in 14 patients (87.5%), and cavitated nodules were found in 13 patients (81.2%). Masses were observed in 6 patients (37.5%); air trapping, in 3 (18.7%); and pleural effusion, in only 1 (6.2%). Only 1 patient presented no pulmonary dissemination of the disease, showing airway involvement only. The 6 patients who presented masses on the CT images were submitted to pulmonary biopsy, and squamous cell carcinoma was diagnosed in 4 of these patients. One of the patients who presented consolidation was also later diagnosed as having malignant degeneration. Pulmonary involvement was bilateral in all cases.

DISCUSSION

LTBP has a characteristic bimodal distribution, affecting children and young adults.[1,14] The juvenile form of the disease begins before the age of 20 years and is most often diagnosed before the age of 5.[3,15,16] The adult form begins after the age of 20, being more common in males in the third or fourth decades of life.[3,4,9,17,18] Orlamd et al.,[19] studying 224 patients, found that 174 (77.7%) had the juvenile form of the disease, whereas 50 (22.3%) had the adult form. Among the children in that study, 81% were male. In adults, males also prevailed, comprising 62% of the cases. In our sample, the age of the patients ranged from 2 to 72 years (mean = 25.7 years; median = 15 years; IQR: 6-42 years), 8 (50%) being male and 8 (50%), female. Nine patients developed LTBP up to 20 years of age, presenting the juvenile form of the disease. Although the other 7 patients were older than 20 years of age, they can not be said to have the adult form of the disease, since the ages corresponded to the time of CT scanning and not necessarily to the time of the onset of the disease.

The estimated incidence of LTBP is approximately 4:100,000 in children and 2:100,000 in adults.[1,3,14,15] The rates vary according to some factors, such as the age at the onset of the disease, the country studied, and the socioeconomic status of the patients.[1] The incidence is higher in places with lower socioeconomic level, due to the higher prevalence of HPV infection.[5] The most common clinical manifestations are hoarseness, cough, stridor, dyspnea and recurrent infections. Abdulrazak et al.[21] reported that all of the 31 patients in their study showed hoarseness as a symptom, followed by dyspnea in 9 patients (29%). In our sample, the most common symptom was also hoarseness, in 8 patients (50.0%); followed by cough, in 7 (43.7%); dyspnea and recurrent pneumonias, both in 6 (37.5%); and weight loss, in 5 (31.2%). The 5 patients who complained of weight loss were

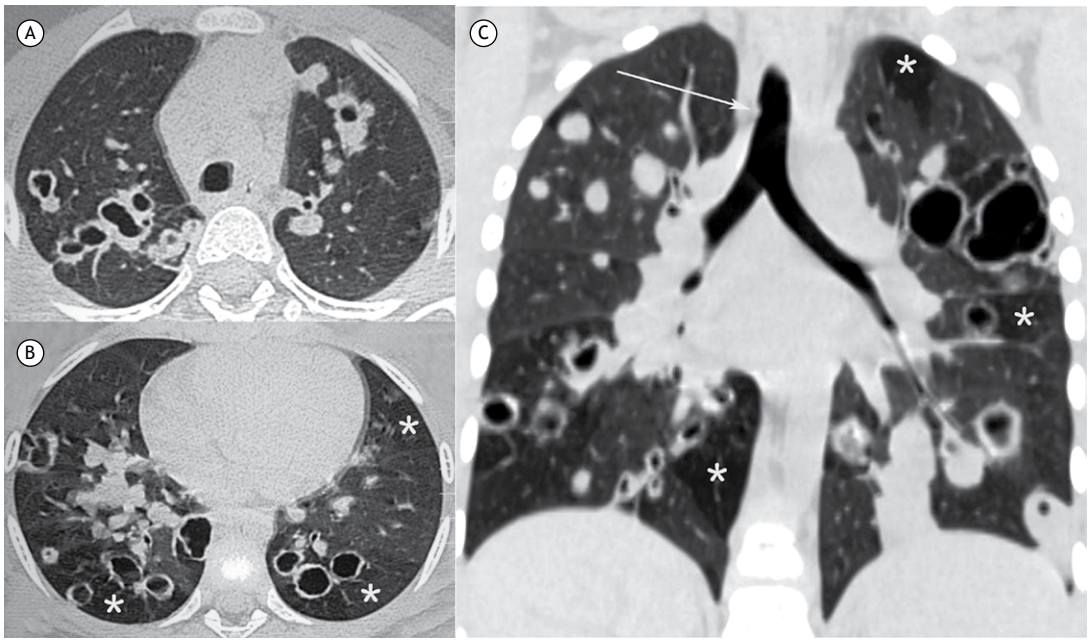

Figure 1. Male patient, 6 years old. Axial CT scans at the level of the upper (in A) and lower lobes (in B), as well as a coronal CT scan of the lungs (in C), showing nodulation in the trachea (white arrow), sparse areas of air trapping in both lungs (white asterisks), and bilateral parenchymal nodules of varying sizes (some solid or cavitated) disseminated in the lungs.

subsequently diagnosed with malignant lesions by biopsy. Tracheostomy may be necessary when there is a serious risk of airway obstruction by papillomatous lesions. In the literature, it is estimated that the need for tracheostomy varies from 13% to 21% in juvenile papillomatosis cases and from 4% to 6% in adult papillomatosis cases. In our study, there were 4 children who needed tracheostomy throughout the course of the disease.

LTBP has the potential to become malignant, especially as squamous cell carcinoma of the lung.[3,4,16,22] The estimated malignancy rate of LTBP is approximately 3-7% in adults and less than 1% in children.[17] In our sample, 5 cases (31.3%) progressed to malignancy, all of which in the form of squamous cell carcinoma of the lung. These 5 patients were female, 4 of whom were adults, ranging from 32 to 72 years of age, and 1 was a child (7 years of age).

Chest CT is the imaging method of choice for the identification and characterization of tracheobronchial polypoid lesions and for the recognition of small nodules during the pulmonary dissemination phase. Chest x-rays may eventually demonstrate solid or cavitated lung nodules; however, tracheal or bronchial lesions are difficult to be identified by this method. Focal or diffuse nodular narrowing, as well as nodular, pedunculated, or sessile polypoid lesions, are generally found in the trachea and the main bronchi, whereas nodules of varying sizes, usually multiple and well circumscribed, are observed in the lung parenchyma. The nodules may be solid or cavitated, with thin or moderately thick walls (2-3 mm or more). Most nodules are small and homogeneous when discovered early, but they can develop large air cavities as they grow and become confluent.[4,7,15,23,24] When there are superimposed infections or airway obstruction, there may be cavitated nodules containing air-fluid level/debris, consolidations, atelectasis due to airway obstruction, air trapping, and bronchiectasis.[24-27]

In our sample, 15 patients had lesions in the lung parenchyma, and only 1 of these showed airway lesions only, with no pulmonary dissemination. Nodular formations in the trachea were observed in 14 patients (87.5%), and parietal nodular formations were also observed in the main bronchi in 4. Solid nodules in the lung parenchyma were found in 14 patients (87.5%), and cavitated nodules, in 13 (81.2%). These nodules had irregular internal contours and walls of varying thicknesses. The lesions were multilobulated and confluent in 8 (50.0%) and 8 patients, respectively. Air trapping was observed in 3 patients (18.7%), and pleural effusion, in only 1 (6.2%). An association with mass was found in 6 patients (37.5%), and consolidation, in 3 (18.7%). Five patients were subsequently diagnosed with squamous cell carcinoma.

Our study had some limitations. The study was retrospective and observational. The analysis of some cases was transversal, without any evaluation of the evolution of and possible complications due to LTBP. The techniques used for CT scanning varied according to the protocol of each institution involved in the research. However, we believe that this variation had no impact on the results. Despite these limitations, we found no case series in the literature that focused on the tomography findings of as many LTBP cases as in our study.

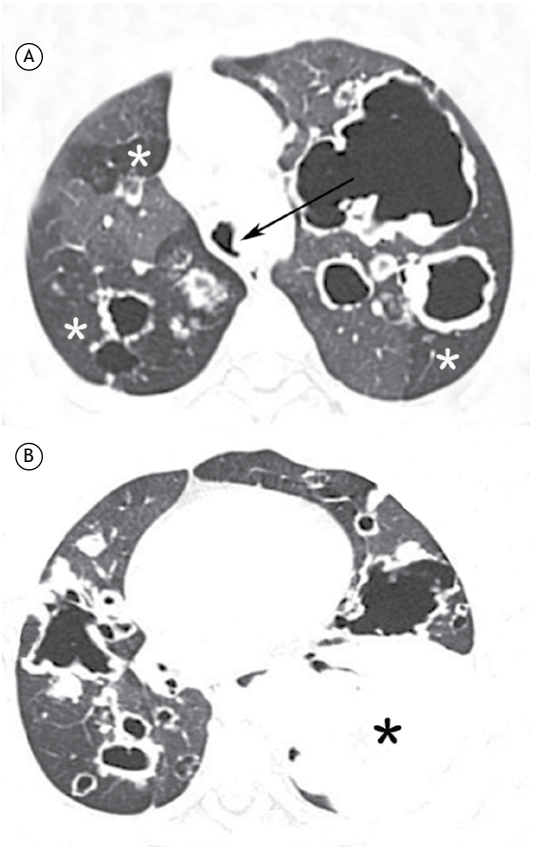

Figure 2. Male patient, 4 years old. Axial CT scans (lung window) above (in A) and below (in B) the bronchial bifurcation. In both scans, there are areas of air trapping (white asterisks) and multiple diffuse solid and cavitated nodules in the lungs. In A, there is an irregular narrowing of the tracheal lumen due to polypoid formations (arrow). In B, there is also a mass in the lower lobe of the left lung (black asterisk). The histopathological study of the mass revealed malignant transformation (squamous cell carcinoma).

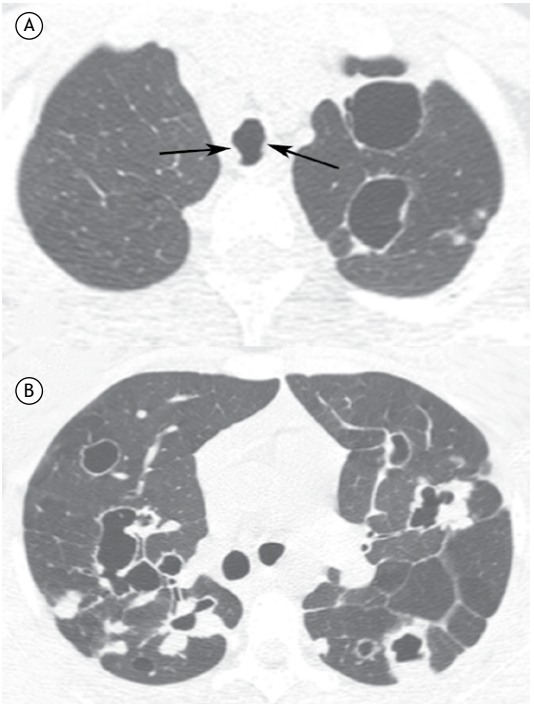

Figure 3. Axial CT scans at the level of the upper lobes (in A) and below the bronchial bifurcation (in B), showing solid and cavitated nodules in both lungs, with thick or thin walls. Nodular formations are also observed in the walls of the trachea (arrows).

In conclusion, the most common tomography findings were nodular formations in the trachea, solid or cavitated nodules in the lung parenchyma, masses, consolidations, and air trapping. Cavitated nodules had irregular borders and walls of varying thicknesses. Most were multilobulated and confluent. Malignant transformation of the lesions was observed in 5 cases, all of which were female.

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Translation and cultural adaptation of a specific instrument for measuring asthma control and asthma status: the Asthma Control and Communication Instrument

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ABSTRACT

Objective: To translate the Asthma Control and Communication Instrument (ACCI) to Portuguese and adapt it for use in Brazil. **Methods:** The ACCI was translated to Portuguese and adapted for use in Brazil in accordance with internationally accepted guidelines. The protocol included the following steps: permission and rights of use granted by the original author; translation of the ACCI from English to Portuguese; reconciliation; back-translation; review and harmonization of the back-translation; approval from the original author; review of the Portuguese version of the ACCI by an expert panel; cognitive debriefing (the clarity, understandability, and acceptability of the translated version being tested in a sample of the target population); and reconciliation and preparation of the final version. **Results:** During the cognitive debriefing process, 41 asthma patients meeting the inclusion criteria completed the ACCI and evaluated the clarity of the questions/statements. The clarity index for all ACCI items was > 0.9, meaning that all items were considered to be clear. **Conclusions:** The ACCI was successfully translated to Portuguese and culturally adapted for use in Brazil, the translated version maintaining the psychometric properties of the original version. The ACCI can be used in clinical practice because it is easy to understand and easily applied.

Keywords: Asthma/classification; Asthma/prevention & control; Surveys and questionnaires.

INTRODUCTION

In its latest report, the Global Initiative for Asthma[1] defined asthma as "a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation".

The 2013 Brazilian National Ministry of Health and Brazilian Institute of Geography and Statistics National Health Survey showed that asthma affects 6.4 million Brazilians over 18 years of age.[2] The prevalence of asthma was found to be 39% higher in females than in males, approximately 3.9 million females and 2.4 million males having reported a diagnosis of asthma. The National Health Survey was the first study to assess the occurrence of asthma in adults in Brazil. The World Health Organization estimates that 300 million children and adults worldwide have asthma.[3] Asthma accounts for a significant number of hospitalizations in Brazil. Between January and November of 2014, there were 105,500 hospitalizations for asthma, which cost 57.2 million Brazilian reals to the public health care system, according to data from the Brazilian Unified Health Care System Hospital Information Service.[4]

The goal of asthma treatment is to control the disease,[1,5,6] asthma control being defined as the extent to which the manifestations of asthma are reduced or removed by treatment. Asthma control can be divided into two domains: current impairment and future risk.[1] The domain of current impairment includes symptoms, use of rescue medication, physical activity, and lung function. The domain of future risk includes accelerated loss of lung function over time, exacerbations, and treatment side effects.[1,7]

In recent years, several studies[8-13] have highlighted the importance of standardizing the assessment of asthma control. As a result, several instruments have been validated and culturally adapted for use in Brazil, including the Asthma Control Test,[12] the Asthma Control Questionnaire,[11] and the Asthma Control Scoring System.[13,14] However, none of the aforementioned instruments was developed specifically for or validated for use in racially diverse populations of asthma patients,

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as is the case in Brazil.[8] This is important in countries such as Brazil because certain colloquial terms might differ among regions within the same country,[15] as well as among immigrants from different countries.[16] Therefore, a questionnaire should be used only in the population for which it has been developed and validated.[17] This bias is of vital importance if the objective of a given epidemiological study is to compare different locations and cultures.[15]

With the objective of assessing asthma control and communication, Patino et al.[8] developed the Asthma Control and Communication Instrument (ACCI). The ACCI is a 12-item self-report questionnaire for asthma patients over 12 years of age. It takes 5-7 minutes to complete. The ACCI has four domains of assessment of asthma activity: acute care, also known as ''risk''; bother; control; and direction of symptoms. In addition, it has one domain for assessment of patient adherence to medication and one domain designed to improve physician-patient communication (one open-ended question). The response choices to questions are sequentially color coded from green (best) to yellow, orange, and red (worst). The ACCI control domain is the only multi-item component of the questionnaire that is scored by the physician, according to patient responses.

The ACCI provides three alternative scoring formats that can be used on the basis of physician preference. The first method, designated categories, classifies patients into four categories ranging from mild-intermittent to severe-persistent, the former indicating better asthma status and the latter indicating poorer asthma status. Consistent with asthma guidelines,[1] the control category is assigned by the most severe response among the five ACCI control items. Patients with intermittent symptoms are considered to be "controlled", whereas those with persistent symptoms are considered to be "uncontrolled". The second method, designated sum score, uses a summation of the five ACCI control items individually coded from 0 to 4 (the exception being the attack item, which is coded from 0 to 3). The sum score ranges from 0 (best) to 19 (worst). The third method, designated problem index, dichotomously rates each item as a control problem (yes or no), the values of which are then summed to provide a problem index ranging from 0 (no control problems) to 5 (five control problems).

Because of its characteristics, the ACCI is a promising clinical tool for measuring asthma control during routine health care and for research; however, in order to be used in Brazil, the ACCI had to be translated to Portuguese and culturally adapted for use in the country. Translation and cultural adaptation are needed in order to preserve the essential features of the original instrument (which was developed for ethnically diverse populations and therefore addresses social and cultural diversity) and prevent misunderstandings arising from literal translations. Therefore, the objective of the present study was to translate the ACCI[8] to Portuguese and adapt it for use in Brazil.

METHODS

This was a methodological study aimed at translating the ACCI to Portuguese and adapting it for use in Brazil, the ACCI being an instrument specifically designed to measure asthma control and communication.[8] The study was approved by the Human Research Ethics Committee of the Federal University of Santa Catarina, located in the city of Florianópolis, Brazil, and was conducted in accordance with established ethical principles. Consent was obtained from the first author of the original instrument, who participated in the validation process.

The ACCI was translated to Portuguese and adapted for use in Brazil in accordance with the guidelines established by Mapi and those used in other studies.[15,16,18,19] Figure 1 illustrates the steps involved in the process.

The process of translation and cultural adaptation of a questionnaire involves determining the acceptability, understandability, and clarity of the translated version in a sample of the target population; this step of the process is designated cognitive debriefing.[16-19] A total of 41 asthma patients participated in the cognitive debriefing process in the present study. Participants were consecutively recruited from among patients routinely followed at the Pulmonology Outpatient Clinic of the Federal University of Santa Catarina University Hospital or at a private respiratory medicine clinic, both of which are located in the city of Florianópolis, Brazil. All of the patients who met the inclusion criteria and gave written informed consent participated in the study. The inclusion criteria were as follows: being in the 18- to 70-year age bracket; having asthma (i.e., having had episodes of wheezing, chest tightness, and dyspnea in the previous year); having a diagnosis of asthma objectively confirmed by reversible airflow limitation (a > 15% increase in FEV_1 after inhalation of a short-acting bronchodilator, with an FEV_1 of < 70% of predicted or an FEV_1/FVC ratio of < 70%) or airway hyperresponsiveness, as detected by methacholine challenge testing—the provocative concentration of methacholine causing a 20% drop in FEV_1 being < 8 mg/mL—with an FEV_1 > 70% of predicted; currently receiving pharmacological treatment; having been clinically stable for at least one month, independently of the presence of atopy; and being a nonsmoker or having been a former smoker for more than 1 year, with a smoking history of < 10 pack-years. The exclusion criteria were as follows: having other known lung diseases (including chronic bronchitis, COPD, and pneumonia); having severe disease affecting systems other than the respiratory system; and having any psychiatric or cognitive disorder that could confound the results.

Given that the present study does not permit a statistical analysis, the data are reported as absolute numbers and proportions, as means and standard deviations, or as medians and interquartile ranges. Statistical analysis was used in order to determine the demographic and clinical characteristics of the participants.

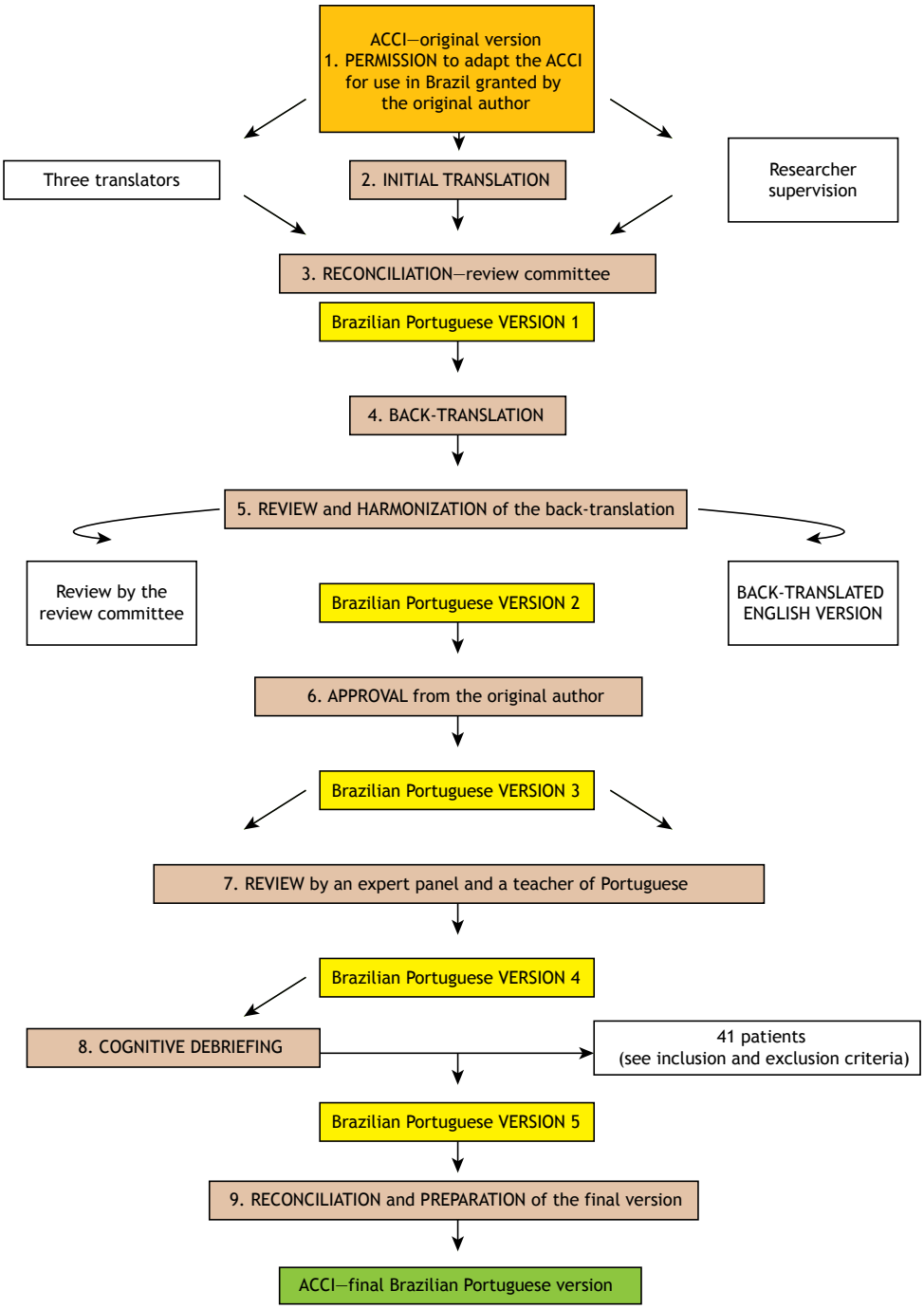

Figure 1. Summary of the process of cross-cultural adaptation of the Asthma Control and Communication Instrument (ACCI) for use in Brazil.

Cultural adaptation of the ACCI was done in accordance with internationally accepted guidelines,[16-19] and the protocol included the following steps (Figure 1):

- preparation—permission to translate the ACCI to Portuguese and adapt it for use in Brazil obtained from the first author of the original version
- translation of the ACCI from English to Portuguese by three translators fluent in English (all three translations having been performed independently)
- reconciliation—analysis and comparison of the three versions by a review committee comprising experts in the area, resulting in the first Brazilian Portuguese version of the ACCI (version 1)
- back-translation—literal translation of version 1 to English by a teacher of English (a native speaker of English fluent in Portuguese)

- review and harmonization of the back-translation—review of the back-translation to English, resulting in the second Brazilian Portuguese version of the ACCI (version 2)
- analysis of version 2 by the original author, the third Brazilian Portuguese version of the ACCI (version 3) being arrived at after the corrections and suggestions made by the original author
- review of version 3 by three bilingual pulmonologists, the fourth Brazilian Portuguese version of the ACCI (version 4) being arrived at
- cognitive debriefing—the clarity, understandability, and acceptability of version 4 being tested in a sample of the target population (41 asthma patients selected during routine outpatient visits, meeting the inclusion criteria, and giving written informed consent)
- analysis of the comments made by participants, resulting in the fifth Brazilian Portuguese version of the ACCI (version 5), which included the necessary corrections and adaptations
- reconciliation and preparation of the final version by the review committee

The objective of cognitive debriefing was to identify problematic questions and find solutions to make them easier to understand. To that end, 41 asthma patients were interviewed. Participants were consecutively scheduled for a single visit to the study site. At that visit, the study was explained in detail and those who agreed to participate in the study gave written informed consent. In addition, sociodemographic and specific data were collected, all of which are shown in Table 1. The questionnaire was administered to each participant by the principal investigator. Participants were told that they need not worry about the accuracy of their responses; rather, they should report what they understood, the difficulties posed by each question or statement, and the acceptability of the instrument.

In the reconciliation step of the process, the review committee and the expert panel met in order to produce the final Brazilian Portuguese version of the ACCI, reviewing each item, discussing the findings of the cognitive debriefing process, and making the relevant changes. The final version of the ACCI for use in Brazil was thus arrived at.

Table 1. Patients participating in the cognitive debriefing process (n = 41), by demographic and specific characteristics.[a]

Characteristic	Result
Age, years[b]	39 (19-86)
Female gender	20 (48.8)
Level of education	
Elementary school	5 (12.2)
High school	14 (34.2)
College	22 (53.6)
Health insurance	
Public	21 (51.2)
Private	19 (48.8)

[a]Values expressed as n (%), except where otherwise indicated. [b]Value expressed as median (minimum-maximum).

RESULTS

Of the 41 asthma patients who participated in the cognitive debriefing process, 20 (48.8%) were female. Patient age ranged from 19 years to 86 years. Most participants had a college degree (Table 1).

During the reconciliation, back-translation, review, and harmonization steps of the process of cultural adaptation of the ACCI, discrepancies among the individual translations (done by pulmonologists) were discussed and standardized by the review committee. In version 1, the phrase "*injeção de corticoide*" was added to question 5. The review committee made no changes to the back-translation of version 1, version 2 being identical to version 1. The first author of the original version approved the back-translation but raised a few questions regarding version 2: the pertinence of the phrase "*um pouco incomodado(a)*" in question 2 was discussed, and a decision was made to replace it with the phrase "*um tanto incomodado(a)*". The remaining questions raised by the original author were discussed by the review committee and did not result in changes in the text, which remained the same in version 3 and was sent to other pulmonologists for evaluation. After having discussed the comments made by those pulmonologists, the review committee prepared version 4 of the ACCI, which was sent to a teacher of Portuguese for correction. Analysis of the data collected during the cognitive debriefing process showed that there was no need to change version 4, given that the clarity index for all ACCI items was > 0.9.

The final Brazilian Portuguese version of the ACCI incorporated changes made by the review committee because, although the ACCI was well understood (as assessed by the clarity index), a question regarding the use of corticosteroids (question 5) was often misunderstood by participants. Some of the interviewees thought that using daily inhaled corticosteroids was the same as using prednisone, whereas, in reality, daily inhaled corticosteroids and prednisone are different medications. Therefore, the review committee decided to add the sentence "(*Essa pergunta não se refere a sua bombinha de uso diário*)" to question 5 in order to avoid misunderstandings.

DISCUSSION

In the present study, a careful methodology was used in order to translate the ACCI and adapt it for use in Brazil.[15,16,18-20] We decided to translate and adapt the ACCI rather than develop a new questionnaire because the ACCI, unlike other existing instruments,[10,11] is the only instrument that was specifically developed and validated to facilitate user understanding.

The process of translation and cultural adaptation of a given questionnaire is complex but indispensable for its correct use in the target population. In addition, in the particular case of the ACCI, the translated version had to preserve the essential features of the original instrument, which was developed for ethnically diverse populations and therefore addresses social and cultural

diversity.[8] In Brazil, this is particularly important because the Brazilian population is heterogeneous and uses a variety of regional terms, some of which might be unknown to individuals from other regions of the country[15] or to immigrants from other countries.[16] Therefore, a questionnaire should be used only in the population for which it has been developed and validated,[17] making it possible to compare different locations and cultures in an epidemiological study.[15,20]

The Brazilian Portuguese version of the ACCI, which was arrived at in the present study, is technically and semantically equivalent to the original version. It includes terms that are commonly used in Brazil, such as the phrase "*injeção de corticoide*" (in question 5), which was included because corticosteroid injection is a prednisone treatment protocol that is used in the country. In addition, the statement "(*Essa pergunta não se refere a sua bombinha de uso diário*") was added to question 5 because users of inhaled corticosteroids commonly mistake prednisone for an inhaled corticosteroid.

Several studies have demonstrated the need for standardizing the assessment of asthma status,[1,8,9,21] standardized assessment playing a major role in asthma control. As a result, several instruments assessing asthma status have been translated to Portuguese and adapted for use in Brazil, including the Asthma Control Questionnaire[11] and the Asthma Control Scoring System.[13,21] The ACCI is an important instrument because it was developed for ethnically diverse populations; it is a self-report questionnaire; and it takes only 5-7 min to complete. In addition, the response choices are sequentially color coded to quantify asthma control, thus facilitating patient understanding of asthma severity and subsequent physician management.[8] Finally, the open-ended question allows patients to write down anything else that they consider important regarding their asthma, thus covering topics that are not covered by the remaining questions.[8]

The ACCI is an instrument that is quick and easy to implement in clinical practice because it is a self-report questionnaire designed to be completed immediately before a medical visit and because it allows physicians to focus on key aspects of disease history. In addition, the ACCI educates patients because it directs their attention to the most common signs and symptoms and allows them to recognize their severity, given that patients who do not perceive or do not recognize the severity of their symptoms are at a higher risk of exacerbations.[22] The ACCI assesses different aspects of asthma control and takes into account the various symptoms of the disease, avoiding specific physician questions regarding each of the multiple manifestations of asthma and improving asthma care.

The ACCI addresses issues that are not addressed by other instruments and, by including questions that are more personal, such as those aimed at determining the level of asthma control and patient discomfort, allows physicians to identify the discomfort threshold in their patients and, consequently, know them better. This is important because the literature shows that a superficial assessment can result in patients with poorly controlled asthma being classified as having well-controlled asthma[23] and, consequently, receiving inappropriate treatment. This in turn can result in increased morbidity or excessive medication use and, consequently, unnecessarily increased costs.[24]

The open-ended item on the ACCI allows asthma patients to reflect on their signs and symptoms and provides physicians with an opportunity to focus on patient concerns, which are not necessarily addressed by other instruments. Therefore, the ACCI allows physicians to provide holistic care to asthma patients, as well as providing an opportunity to improve the physician-patient relationship.

Items 7 through 11 on the ACCI refer to the two weeks preceding the medical visit and follow the established international standard for questions regarding asthma symptoms.[5] However, patient responses are more accurately classified by the ACCI than by other instruments because the ACCI provides more alternatives to be chosen from. In addition, the ACCI allows determination of the level of asthma control in accordance with the former and current Global Initiative for Asthma classifications.[5]

The ACCI was successfully translated to Portuguese and adapted for use in Brazil in accordance with international criteria.[16,19] The Brazilian Portuguese version of the instrument is shown in Appendix 1 (available online at http://jornaldepneumologia.com.br/detalhe_anexo.asp?id=53). The ACCI for use in Brazil is an instrument that maintains the psychometric properties of the original questionnaire, therefore allowing comparisons of data from different countries.

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High-resolution computed tomography findings of pulmonary tuberculosis in lung transplant recipients

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ABSTRACT

Objective: Respiratory infections constitute a major cause of morbidity and mortality in solid organ transplant recipients. The incidence of pulmonary tuberculosis is high among such patients. On imaging, tuberculosis has various presentations. Greater understanding of those presentations could reduce the impact of the disease by facilitating early diagnosis. Therefore, we attempted to describe the HRCT patterns of pulmonary tuberculosis in lung transplant recipients. **Methods:** From two hospitals in southern Brazil, we collected the following data on lung transplant recipients who developed pulmonary tuberculosis: gender; age; symptoms; the lung disease that led to transplantation; HRCT pattern; distribution of findings; time from transplantation to pulmonary tuberculosis; and mortality rate. The HRCT findings were classified as miliary nodules; cavitation and centrilobular nodules with a tree-in-bud pattern; ground-glass attenuation with consolidation; mediastinal lymph node enlargement; or pleural effusion. **Results:** We evaluated 402 lung transplant recipients, 19 of whom developed pulmonary tuberculosis after transplantation. Among those 19 patients, the most common HRCT patterns were ground-glass attenuation with consolidation (in 42%); cavitation and centrilobular nodules with a tree-in-bud pattern (in 31.5%); and mediastinal lymph node enlargement (in 15.7%). Among the patients with cavitation and centrilobular nodules with a tree-in-bud pattern, the distribution was within the upper lobes in 66.6%. No pleural effusion was observed. Despite treatment, one-year mortality was 47.3%. **Conclusions:** The predominant HRCT pattern was ground-glass attenuation with consolidation, followed by cavitation and centrilobular nodules with a tree-in-bud pattern. These findings are similar to those reported for immunocompetent patients with pulmonary tuberculosis and considerably different from those reported for AIDS patients with the same disease.

Keywords: Lung transplantation; Diagnostic imaging; Mycobacterium infections; Thoracic diseases; Tomography, X-Ray computed/methods; Tuberculosis, pulmonary.

INTRODUCTION

Lung transplantation has become an established technique for the treatment of end-stage lung disease in adults, and the number of procedures performed each year has grown, as has the number of transplantation centers.[1,2] However, respiratory infection continues to be one of the major concerns in solid organ transplant recipients, clearly constituting a major cause of morbidity and mortality in that population.[2]

Tuberculosis is a common infectious disease among humans. In 2014, 9.6 million people worldwide developed tuberculosis and 1.5 million of those people died, 95% of all tuberculosis-related deaths occurring in low- or middle-income countries.[3] Solid organ transplant patients are more susceptible to tuberculosis infection than are individuals in the general population, the incidence being 20-74 times greater in the former group and the lungs being the most common site of infection.[4,5]

Pulmonary tuberculosis is diagnosed on the basis of direct examination (sputum smear microscopy), culture for *Mycobacterium tuberculosis*, and radiological findings suggestive of the disease.[6] Therefore, the interpretation of imaging findings consistent with tuberculosis is key for early diagnosis and treatment.

Chest CT is one of the main modalities used in cases of clinical suspicion of pulmonary tuberculosis, especially when initial X-rays are normal or when the individual is immunosuppressed, as is the case in AIDS patients and transplant recipients. Some studies have shown that CT is superior to chest X-ray in the initial evaluation of tuberculosis patients.[7,8] Tuberculosis can have a variety of presentations on CT.[9]

Some authors have previously studied pulmonary tuberculosis in transplant recipients.[10-13] However, there have been no studies focusing on CT patterns of pulmonary tuberculosis in lung transplant patients. Therefore, the

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present study aimed to determine the presentations of pulmonary tuberculosis seen on HRCT scans of lung transplant recipients.

METHODS

This was a descriptive study in which we reviewed data related to 402 lung transplant recipients who underwent transplantation at one of two hospitals in southern Brazil between January of 1990 and August of 2015. This study was approved by the local institutional review board and by the Research Ethics Committee of Plataforma Brasil (Protocol no. 512.215). The inclusion criteria were testing positive for *M. tuberculosis* in sputum culture, testing positive for *M. tuberculosis* in culture from BAL fluid or a lung biopsy sample, and having had an HRCT scan performed after diagnosis. Based on a review of clinical and laboratory data, we excluded patients diagnosed with mycosis or concomitant viral infections potentially affecting the lungs, including cytomegalovirus infections. We collected data regarding the following: gender; age; symptoms; the lung disease that led to transplantation; HRCT lung pattern; HRCT lung distribution pattern; time from transplantation to pulmonary tuberculosis; and mortality rate.

All HRCT scans were acquired in a 64-slice multidetector scanner (LightSpeed VCT; GE Healthcare, Waukesha, WI, USA), with the following parameters: tube voltage, 120 kVp; tube current, 250 mAs; rotation time, 0.8 s; and pitch, 1.375. The technical parameters included inspiratory volumetric acquisition with 1 mm collimation in 1-mm increments using a high-spatial-frequency reconstruction algorithm. Images were obtained with mediastinal window settings (width, 350 to 450 HU; level, 20 to 40 HU) and parenchymal window settings (width, 1200 to 1600 HU; level, −500 to −700 HU), and reconstructions were performed in the axial and coronal planes.

Two chest radiologists, with more than 10 years of experience and both blinded to the clinical status of the patients, independently assessed the HRCT scans in random order. After the two radiologists had conducted their independent analyses, they reviewed the images together with a third chest radiologist (with > 30 years of experience) in order to reach a final consensus decision. For each patient, reviewers identified one predominant CT pattern, according to the criteria set forth in the Fleischner Society's Glossary of Terms.[14] The HRCT findings were categorized as follows: miliary nodules; cavitation and centrilobular nodules with a tree-in-bud pattern; ground-glass attenuation with consolidation; mediastinal lymph node enlargement; or pleural effusion.

A nodule was defined as a rounded or irregular, ill- or well-defined opacity with a diameter ≤ 3 cm.[14] Mediastinal and hilar lymph nodes varied in size from sub-CT resolution to 10 mm. Mediastinal lymph node enlargement was defined as mediastinal lymph nodes > 10 mm in diameter on their short-axis, as demonstrated by Cascade et al.[15] Cavities were defined as gas-filled spaces, presenting as lucencies or areas of low-attenuation within pulmonary consolidations, masses, or nodules. The tree-in-bud pattern refers to centrilobular branching structures that resemble a budding tree. Ground-glass opacities were defined as hazy areas of increased attenuation, with no obscuration of the underlying vessels.[14] Consolidation was defined as homogeneous opacification of the parenchyma with obscuration of the underlying vessels. The distribution of abnormalities was categorized as focal (when unilobar) or diffuse (when involving more than one lobe), and the findings were stratified by zone (upper, middle, and lower lung).[14] Continuous variables were expressed as mean and standard deviation, whereas categorical variables were expressed as absolute and relative frequencies.

RESULTS

Among the 402 lung transplant recipients evaluated, we identified 20 who were diagnosed with pulmonary tuberculosis. Of those 20 patients, one was excluded due to coinfection with cytomegalovirus. Therefore, the final sample comprised 19 patients (12 males and 7 females), ranging from 11 to 65 years of age (mean, 33 ± 18 years). The underlying diseases that led to transplantation were the following: pulmonary emphysema, in 7 patients (36%); pulmonary fibrosis, in 7 (36%); silicosis, in 3 (15.7%); and pulmonary hypertension, in 2 (10.5%). All of the patients had asthenia and cough. The mean time from lung transplantation to the diagnosis of pulmonary tuberculosis was 3.2 ± 1.7 months.

Table 1 shows the study sample by HRCT pattern, together with the distribution of the findings within the lung. The main HRCT patterns were ground-glass attenuation with consolidation (in 42% of the patients); cavitation and centrilobular nodules with a tree-in-bud pattern (in 31.5%); and mediastinal lymph node enlargement (in 15.7%). The first two are depicted in Figures 1 and 2, respectively. In 66.6% of patients with cavitation and centrilobular nodules with a tree-in-bud pattern, the distribution was within the upper lobes. No pleural effusion was observed. Two patients died. In those two patients, the HRCT findings were ground-glass attenuation with consolidation and miliary nodules, respectively.

DISCUSSION

To our knowledge, this is the first study to describe the HRCT findings of pulmonary tuberculosis exclusively among lung transplant recipients. The presentation of pulmonary tuberculosis was stratified into four patterns: ground-glass attenuation with consolidation; cavitation and centrilobular nodules with a tree-in-bud pattern; mediastinal lymph node enlargement; and miliary nodules. In over 70% of the cases evaluated, we observed cavitation and centrilobular nodules with

Table 1. HRCT pattern and distribution of findings by lung zone.

HRCT pattern	Prevalence*	Lung zone
Ground-glass attenuation with consolidation	8 (42)	Upper lobes (in 50.0%)
Cavitation and centrilobular nodules with a tree-in-bud pattern	6 (31.5)	Upper lobes (in 66.6%)
Mediastinal lymph node enlargement	3 (15.7)	N/A
Miliary nodules	2 (10.5)	Random
All	19 (100)	N/A

*Data are expressed as n (%).

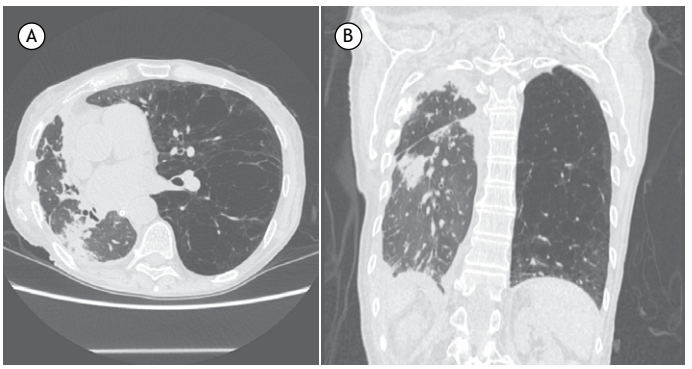

Figure 1. Pulmonary tuberculosis in a 48-year-old man who underwent right lung transplantation. Axial and coronal HRCT scans (A and B, respectively), showing diffuse pleural thickening, peripheral linear opacities, and consolidation in the superior segment of the right lower lobe of the right lung. Note the increased volume of the left lung, due to extensive panacinar emphysema.

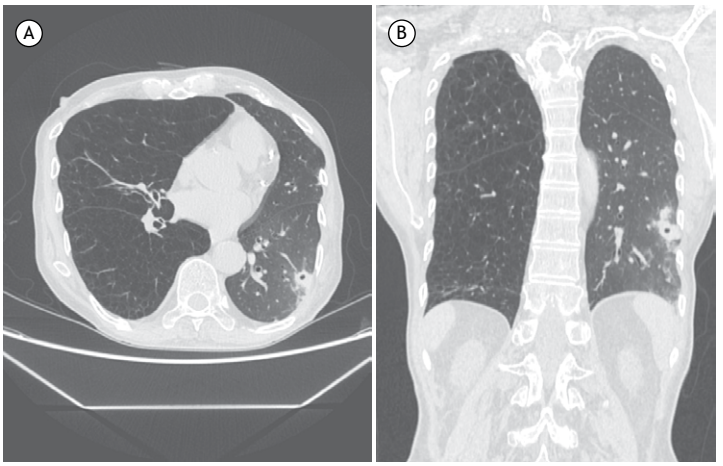

Figure 2. Pulmonary tuberculosis in a 54-year-old man who underwent left lung transplantation. Axial and coronal HRCT scans (A and B, respectively), showing a small, irregular thick-walled cavity in the lateral-basal segment of the left lower lobe and adjacent satellite nodules. Extensive panacinar emphysema can be seen in the right lung.

a tree-in-bud pattern or ground-glass attenuation with consolidation.

Meta-analyses have shown that the average time from solid organ transplantation to tuberculosis infection is 3.5 months, an interval quite similar to that found in our study.[4] All of the patients in our sample were receiving immunosuppression therapy for lung transplantation. The same treatment protocol was followed in every case. The time from lung transplantation to the development of tuberculosis was comparable among the participants, indicating that the sample was fairly homogeneous in terms of the immunosuppressive state of the patients.

None of the patients in our sample showed pleural effusion as a manifestation of pulmonary tuberculosis. In a study that evaluated the radiographic presentations of pulmonary tuberculosis in 226 solid organ transplant recipients, the authors observed pleural effusion in 13%.[4] That discrepancy could be explained by the fact that we evaluated lung transplant recipients exclusively and by local postoperative changes.

In the general population, the most common HRCT patterns of pulmonary tuberculosis are mediastinal lymphadenopathy, cavitation, centrilobular nodules with a tree-in-bud pattern, consolidation, and ground-glass opacities, all of which occur predominantly in the

upper lobes.[16,17] In the present study, we observed the same patterns and also found a predominance of upper lobe findings.

In the general population, the presence of cavities in imaging studies is an important sign of active disease. In a study involving 41 solid organ transplant recipients, Im et al.[18] found that the prevalence of cavities on CT scans was 58%, higher than the 31.5% observed in our study. Those authors showed that, among individuals with active tuberculosis in the general population, the most common CT finding (in 82-100% of cases) was centrilobular nodules with segmental distribution, which represents bronchogenic dissemination of the disease. In our study sample, centrilobular nodules occurred in nearly one third of the patients evaluated, the lower incidence potentially being related to the use of immunosuppression therapy.

In comparison with the HIV-negative population, individuals with AIDS are more likely to demonstrate lymph node involvement and miliary disease.[19] Hilar and mediastinal lymph node enlargement occurs in over 60% of AIDS patients with tuberculosis.[20,21]

In our sample, the miliary nodular pattern was observed in only 2 patients (10.5%), and the mediastinal lymph node enlargement pattern was observed in only 3 (15.7%) These findings suggest that lung transplant recipients with pulmonary tuberculosis present with CT findings that are more similar to those reported for immunocompetent individuals with pulmonary tuberculosis than to those reported for AIDS patients with pulmonary tuberculosis.

One limitation of our study was the small size of the sample. However, this was the largest study to date of pulmonary tuberculosis in lung transplant recipients. In addition, microbiological confirmation was obtained in all of the cases.

In lung transplant recipients with pulmonary tuberculosis, HRCT most often revealed ground-glass attenuation with consolidation or cavitation and centrilobular nodules with a tree-in-bud pattern. The distribution and predominant imaging findings in this patient population are similar to those reported for immunocompetent patients with pulmonary tuberculosis and considerably different from those reported for AIDS patients with pulmonary tuberculosis.

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ORIGINAL ARTICLE

Pneumonia mortality trends in all Brazilian geographical regions between 1996 and 2012

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Study carried out in the Departamento de Saúde Coletiva, Faculdade de Ciências Médicas, Universidade Estadual de Campinas – Unicamp – Campinas (SP) and at the Curso de Medicina, Universidade Federal da Fronteira Sul – UFFS – Chapecó (SC) Brasil.

ABSTRACT

Objective: To analyze the temporal trends in pneumonia mortality rates (standardized by age, using the 2010 population of Brazil as the standard) in all Brazilian geographical regions between 1996 and 2012. **Methods:** This was an ecological time-series study examining secondary data from the Mortality Database maintained by the Information Technology Department of the Brazilian Unified Health Care System. Polynomial and joinpoint regression models, and corresponding 95% CIs, were used for trend analysis. **Results:** The pneumonia mortality rates in the South, Southeast, and Central-West showed a decreasing behavior until 2000, followed by increases, whereas, in the North and Northeast, they showed increasing trends virtually throughout the period studied. There was variation in annual percent change in pneumonia mortality rates in all regions except the North. The Central-West had the greatest decrease in annual percent change between 1996 and 2000, followed by an increase of the same magnitude until 2005. The 80 years and over age group was the one most influencing the trend behavior of pneumonia mortality rates in all regions. **Conclusions:** In general, pneumonia mortality trends reversed, with an important increase occurring in the years after 2000.

Keywords: Pneumonia/mortality; Pneumonia/epidemiology; Time series studies.

INTRODUCTION

Respiratory diseases affect children, adults, and the elderly and are considered important causes of illness and death worldwide. According to data from the World Health Organization, respiratory diseases account for approximately 14% of all deaths globally. Among these, deaths from lower respiratory tract infections range from 31 per 100,000 population in high-income countries to as many as 91 per 100,000 population in those considered low-per-capita-income countries.[1]

In 2012, according to the World Health Statistics, the three leading causes of potential years of life lost worldwide were ischemic heart disease; lower respiratory tract infections, including pneumonia; and stroke.[2]

Chief among lower respiratory tract infections are acute respiratory infections (ARIs), which, although they manifest themselves in benign forms, are more important in some age groups, such as children and the elderly, who are particularly vulnerable to complications of ARIs.[3] Flu epidemics cause excess mortality from pneumonia and from other causes in the elderly.[4,5] Children under 1 year of age are especially predisposed to the development of ARIs because of inherent life cycle characteristics, such as incomplete development of the pulmonary system and a developing immune system, which make them more susceptible to more severe infections; this is especially true among infants under 2 months of age.[6]

ARIs are among the leading causes of childhood mortality. The World Health Organization estimates that, in 2013, approximately 3.257 million children under 5 years of age died from respiratory diseases worldwide, with pneumonia being the leading cause of death in 14.9%.[7]

Community-acquired pneumonia (CAP) has varying risk factors, such as aging, smoking, COPD, heart failure, colonization of the oropharynx, microaspiration/macroaspiration, alcoholism/liver cirrhosis, nutritional deficiency, immunosuppression, and environmental factors.[8]

The magnitude of pneumonia in the population and its social impact are shown by the high mortality and morbidity indicators. In Brazil, according to data recorded by the *Sistema de Informação sobre Mortalidade do Departamento de Tecnologia da Informação do Sistema Único de Saúde* (SIM/DATASUS, Mortality Database maintained by the Information Technology Department of the Brazilian Unified Health Care System), between 1996 and 2012, pneumonia accounted for an approximate median of 37% of all deaths from respiratory diseases. In 1997, the pneumonia mortality rate was 18.8 deaths per 100,000 population, and, in 2013, this rate increased to 34.0 deaths per 100,000 population. Distributionally, 18% of the deaths from pneumonia occurred in children under 5 years of age and 57% occurred in individuals over 60 years of age.[9]

In adolescents, young adults, and adults, pneumonia occurs benignly in most cases and has minor complications compared with those occurring in both age extremities (children and the elderly). However, when individuals in

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those age groups are immunocompromised or have a chronic disease, pneumonia may become more severe and account for high mortality rates.[10] In addition, the impact of pneumonia on population morbidity and mortality varies according to socioeconomic status, among other factors.[11,12] Therefore, although the incidence of respiratory infections may be similar in several regions, mortality from these diseases is particularly important in countries such as Brazil, a country that has continental dimensions and interregional differences marked by social inequalities, especially in access to health care. Acknowledging the importance of the impact that deaths from pneumonia have on potential years of life lost, also in Brazil, the objective of the present study was to analyze the trends in pneumonia mortality in the entire population of all Brazilian geographical regions between 1996 and 2012.

METHODS

This was an ecological time-series study examining secondary data on deaths from pneumonia (codes J12-J18 in the International Classification of Diseases, 10th revision, chapter X: respiratory diseases) that occurred between 1996 and 2012 in all five Brazilian geographical regions. All data were collected from the SIM/DATASUS. Data on the resident population were obtained through the same system, on the basis of estimates provided by the Brazilian Institute of Geography and Statistics, and were stratified by age group and by Brazilian region (North, Northeast, Southeast, South, and Central-West). The response variable was the age-standardized mortality rate (direct method) for each of the five Brazilian regions, using the 2010 population of Brazil as the standard. The calendar years, which were centered on the year 2004 to minimize serial correlation effects, were considered an independent variable.

Mortality trends were analyzed with regression models. For fitting these models, classical assumptions, such as normality, independence, and homoscedasticity of residuals, were checked. First-, second-, and third-degree polynomial models were fitted, and the one judged to be the most appropriate on the basis of its coefficient of determination and/or the one judged to be more parsimonious, with significant coefficients, were selected. These models allow trends to be analyzed globally, identifying the intensity of death occurrence.

In addition, joinpoint regression models were fitted to the natural (neperian) logarithm of the response variable (mortality rates), which allowed us to obtain the annual percent change (APC) and average APC (AAPC) rates and to identify the "inflection" points or change points (points at which the slope of the line changes significantly). This modeling was used to better describe the trends in mortality rates by identifying local changes and time points of significant increase/decrease.

The results for the analyses were obtained using the R software, version 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria); the Statistical Package for the Social Sciences, version 13.0 (SPSS Inc., Chicago, IL, USA); the Joinpoint Regression Program, version 4.1.1.5 (Statistical Methodology and Applications Branch and Data Modeling Branch, Surveillance Research Program, National Cancer Institute, Rockville, MD, USA); and Excel 2013. Joinpoint regression modeling was performed using software provided by the National Cancer Institute. Configurations that satisfied the assumptions of the models were used for all fits.

RESULTS

Of all deaths from respiratory diseases, pneumonia accounted for 38% in 1996, with this rate increasing to 48% in 2012. In the latter year, 58% of all deaths from pneumonia in Brazil occurred in the Southeast (the region with the highest percentage) and 5% occurred in the North (the region with the lowest percentage).

Pneumonia mortality rates (standardized by age) showed a decreasing behavior between 1996 and 2000 (in all regions except the North, in which they showed an increasing behavior in that period), followed by increases, as shown by the trends seen in the various Brazilian regions. The Northeast had the lowest mortality rates. In contrast, the Southeast had the highest mortality rates throughout the period studied (Figure 1 and Table 1).

Polynomial model fit results showed that, in the North, trends were close to linear (Figure 2). This region had the greatest increase in the linear component. The South had the greatest increase in the quadratic component (Table 1).

All regions except the North showed inflection points indicating a shift from decrease to significant increase between 2000 and 2001. The greatest increase in APC in pneumonia mortality rates occurred in the Central-West (APC = 7.7; 95% CI: 3.3-12.4) between 2000 and 2005, but this region was also the one that showed a significant decrease (APC = −7.0; 95% CI: −11.0 to −2.8) between 1996 and 2000. The Northeast had the highest AAPC between 1996 and 2012 (AAPC = 4.3; 95% CI: 3.0-5.7; Table 2 and Figure 3).

DISCUSSION

In the present study, the pneumonia mortality trends for the resident population of all Brazilian geographical regions between 1996 and 2012 were evaluated. The mortality rates showed an increasing trend from 2000 onward, and there were no signs of decrease or stabilization in the years after 2000 in any of the regions. In the North, the rates exhibited a linear behavior, that is, they increased constantly throughout the period. In the other regions, a quadratic behavior better represented the time points of decrease and increase, that is, the rates behaved irregularly over time.

One point that is noteworthy is the existence of demographic and socioeconomic differences among the regions studied, since the North and Northeast still concentrate a less aged population and higher rates

of childhood mortality, even though these regions have succeeded in considerably reducing these rates in recent years, demonstrating repercussions that can arise from each region's age profile itself.[13]

Considering these sociodemographic differences among the different regions, it is important to point out that conditions such as nutritional deficiency, immunosuppression, and environmental factors impact on the occurrence of CAP.[8] The most common types of CAP correspond to infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*,[14] and immunizations by means of the 10-valent pneumococcal vaccine and the pentavalent pneumococcal vaccine are part of the Brazilian National Vaccination Schedule. In addition to these vaccines, there is the 23-valent pneumococcal vaccine, which is offered to at-risk groups among individuals over 2 year of age.

In various countries, vaccination for prevention of infection with *S. pneumoniae* (one of the leading etiologic agents responsible for the pneumonia) in individuals in these at-risk groups has been adopted as a public health measure.[9,15] In Brazil, the 23-valent pneumococcal polysaccharide vaccine is still rarely used in at-risk patients, although it is available in the public health care system and is formally indicated for use in individuals over 60 years of age; inpatients and/or individuals residing in institutions (nursing homes, retirement homes, etc.); patients with chronic cardiovascular, pulmonary, renal, metabolic (such as diabetes mellitus), or liver diseases, or with hemoglobinopathies; and immunocompromised individuals (transplant recipients, patients with neoplasia, and HIV-infected individuals).[9,15] The positive effect of this capsular vaccine against 23 pneumococcal serotypes in reducing the number of hospitalizations for and deaths from pneumonia has been described in several studies.[8,16,17]

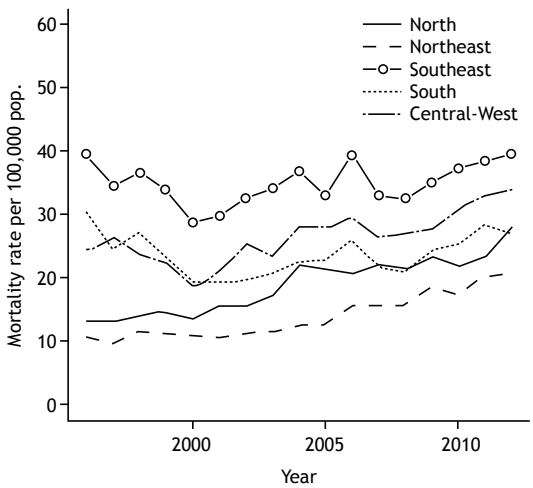

Figure 1. Age-standardized pneumonia mortality rates, by Brazilian geographical region, between 1996 and 2012. pop.: population.

In the present study, the decrease identified between 1996 and 2000, in some regions, is related to the reduction in the mortality rates in all age groups. The resumption of growth after 2000 may have been influenced by the 10- to 49-year age group and, especially, by the over 60-year age group (data not shown).

It is possible that the deaths in children under 5 years of age influenced the decreasing behavior. One study reported, for the same age group, pneumonia mortality rates with a decreasing behavior between 1991 and 2007, with the magnitudes being different in the various Brazilian regions.[18] That same study suggested that the inclusion of vaccination against *H. influenzae* type B and *S. pneumoniae* in the Brazilian National Vaccination Schedule contributed to reducing pneumonia mortality rates.[18] In addition, a study of children under 1 year of age found a 19% reduction in CAP after the implementation of the 10-valent pneumococcal conjugate vaccine in the Brazilian National Vaccination Schedule, which occurred in 2010 via the Brazilian National Immunization Program.[19]

In the present study, we used secondary data from the SIM/DATASUS; the advantages of this include a comprehensive coverage of deaths, the low cost for information collection, and the ease for longitudinal follow-up. The limitations relate to the lack of standardization in data collection, which affects the quality of the recorded data, and to the possibility that the coverage can vary in time and space, as well as to the lack of information that may be important for specific analyses[20] and may be influencing the upward trend behavior of the pneumonia mortality rates.

It should be noted that the main limitation refers to the fact that the analyses did not include correction for ill-defined causes of death. The magnitude of mortality rates is affected by ill-defined causes of death, which introduce a bias in comparisons across areas with different proportions of these causes. The determination and recording of the cause of death or the lack of such a determination and recording (ill-defined causes) during the period studied should be considered because of

Table 1. Polynomial model fit to pneumonia mortality rates (standardized by age) between 1996 and 2012.

Region	B_0	B_1	B_2	R^2	p
North	18.81	0.85	------	0.89	< 0.001
Northeast	12.73	0.67*	0.05*	0.96	< 0.001
Southeast	32.96*	0.18	0.08*	0.39	0.031
South	20.94*	0.05	0.11*	0.60	0.002
Central-West	24.88*	0.63*	0.06*	0.73	< 0.001

B_0: mean annual increase; B_1: increase in the linear component; B_2: increase in the quadratic component; and R^2: coefficient of determination of the model. *Level of significance set at 5%.

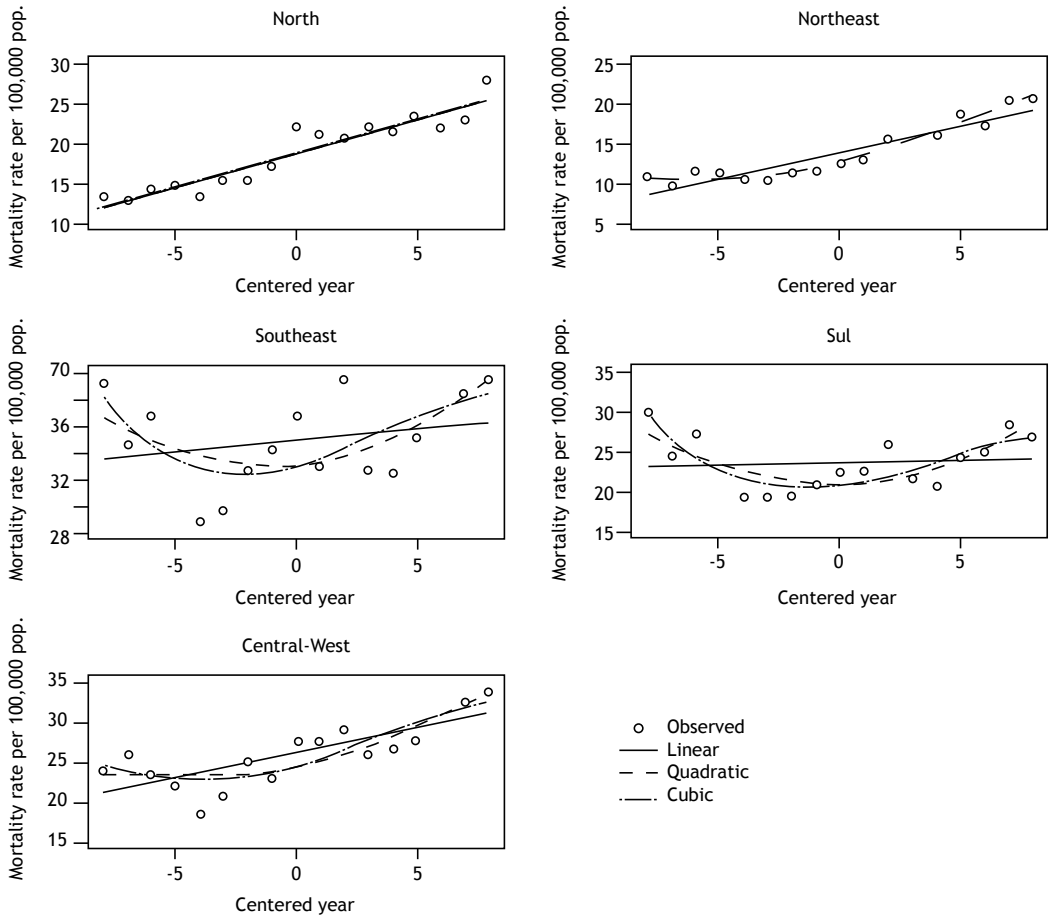

Figure 2. Series of pneumonia mortality rates (standardized by age) and fitted (linear, quadratic, and cubic) polynomial models for each Brazilian geographical region. pop.: population.

regional disparities in this respect. The group of ill-defined causes exhibits a different epidemiological behavior in each region, and data quality and reliability are better in the South, Southeast, and Central-West. [21] In 1996, the proportion of ill-defined causes of death exceeded 30% in the Northeast and was about 25% in the North, whereas, in the other regions, it was approximately 10% (data not shown).

The classification of deaths has improved over time in all regions, especially in the North and Northeast. In 2005, the Brazilian National Ministry of Health started a project to improve mortality data quality, focusing on these two regions.[22] Since 2006, the proportion of ill-defined causes of death in the Northeast has been below 10%, which is similar to that in the Southeast. Currently, in the South and Central-West, the relative importance of ill-defined causes of death is about 5%.[23]

Interventions targeted at improving mortality data reporting and quality in Brazil have been presented as promising alternatives for improving the SIM and increasing the reliability of health information.[22] However, in 2012, the relative importance of ill-defined causes of death in the North exceeded 10%. This may explain the observed differences in rate magnitude and in trend behavior in the period studied. In addition, in the North, the pneumonia mortality trend exhibited a linear behavior and a greater annual increase in the study period, reflecting the changes in the demographic and epidemiological profile of the population that occurred in a polarized way in the country.

In recent years, there have been important decreases in mortality from chronic noncommunicable diseases, especially cardiovascular and respiratory diseases; however, the declines have been smaller for neoplasia and diabetes.[24] In contrast, the present study showed an increase in pneumonia mortality, suggesting a different behavior from that of mortality from other respiratory diseases.

The present study, through the use of secondary data and simple statistical analysis techniques, allowed the identification of pneumonia mortality trends in the different geographical regions of Brazil over a 16-year period, showing that, for all regions, pneumonia mortality increased from 2000 onward, with no signs of decrease or stabilization. Our results provide a framework for planning health promotion interventions, as well as specific protection interventions, especially for the most vulnerable populations, positively

Table 2. Estimates of the annual percent change in pneumonia mortality rates (standardized by age) between 1996 and 2012 (joinpoint regression fit).

Region	Period	APC	95% CI	AAPC	95% CI
North	1996-2012	4.7*	3.8 to 5.6		
Northeast	1996-2001	−0.1	−3.9 to 3.8	4.3*	3.0 to 5.7
	2001-2012	6.5*	5.2 to 7.7		
Southeast	1996-2000	−5.6	−11.7 to 0.9	−0.1	−1.8 to 1.7
	2000-2012	1.9*	0.6 to 3.1		
South	1996-2001	−8.8*	−12.1 to −5.3	−0.1	−4.0 to 3.8
	2001-2005	6.6	−3.0 to 17.0		
	2005-2008	−3.2	−21.7 to 19.8		
	2008-2012	7.2*	2.7 to 11.9		
Central-West	1996-2000	−7.0*	−11.0 to −2.8	1.7	−1.6 to 5.0
	2000-2005	7.7*	3.3 to 12.4		
	2005-2008	−3.1	−19.6 to 16.8		
	2008-2012	7.1*	2.5 to 11.9		

APC: annual percent change; and AAPC: average annual percent change. *Level of significance set at 5%.

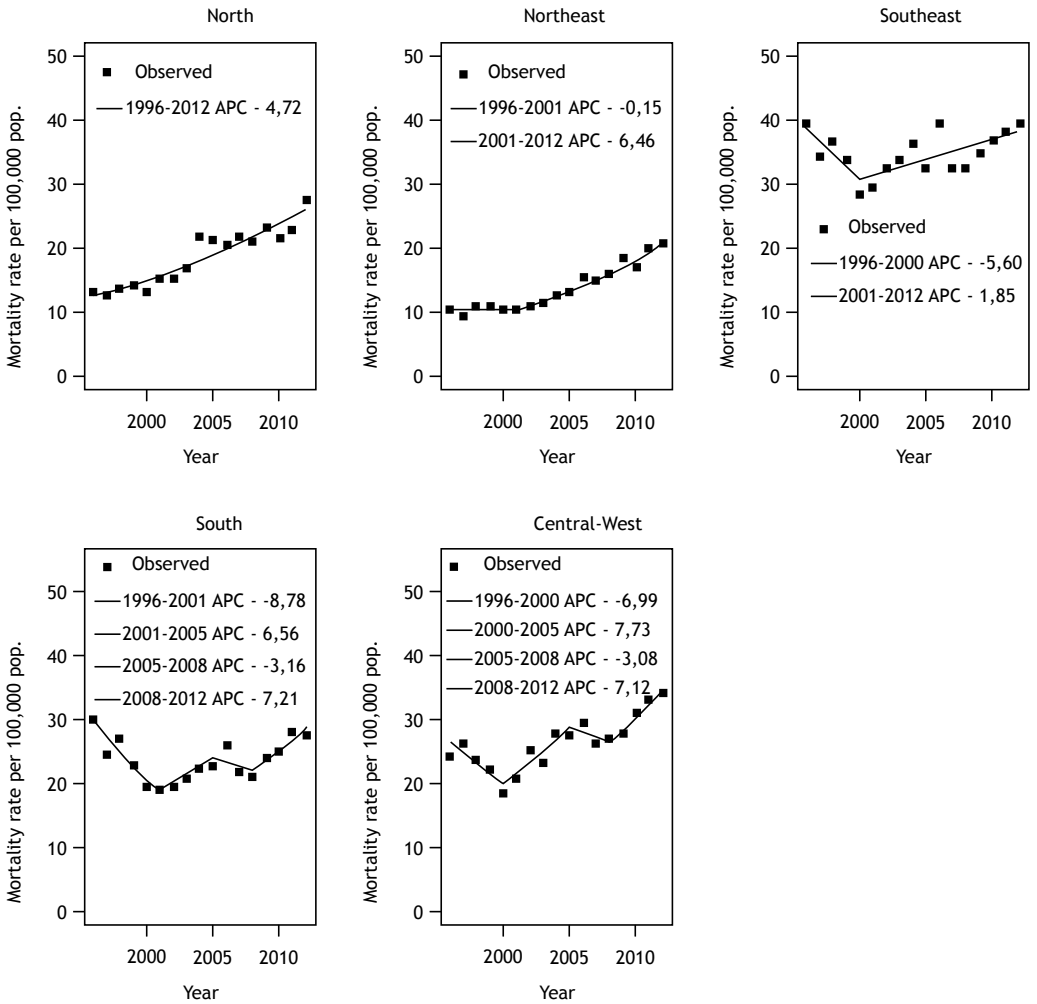

Figure 3. Joinpoint regression by Brazilian geographical region, 1996-2012. pop.: population; and APC: annual percent change.

impacting the reduction in pneumonia mortality. Studies identifying subgroups with low vaccine coverage may contribute to guiding these interventions. Knowledge of pneumonia mortality trends in the different regions of the country can be regarded as a useful strategy for epidemiological surveillance.

Therefore, we emphasize the importance of monitoring pneumonia mortality rates over periods subsequent to that under study here, in order to determine whether prevention interventions, such as vaccination campaigns and improved access to health care, have been effective and have had an influence on the trends in pneumonia mortality rates in all Brazilian geographical regions.

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Can the six-minute walk distance predict the occurrence of acute exacerbations of COPD in patients in Brazil?

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ABSTRACT

Objective: To evaluate whether a six-minute walk distance (6MWD) of < 80% of the predicted value can predict the occurrence of acute exacerbations of COPD in patients in Brazil over a 2-year period. **Methods:** This was a retrospective cross-sectional study involving 50 COPD patients in Brazil. At enrollment, anthropometric data were collected and patients were assessed for pulmonary function (by spirometry) and functional exercise capacity (by the 6MWD). The patients were subsequently divided into two groups: 6MWD ≤ 80% of predicted and 6MWD > 80% of predicted. The occurrence of acute exacerbations of COPD over 2 years was identified by analyzing medical records and contacting patients by telephone. **Results:** In the sample as a whole, there was moderate-to-severe airflow obstruction (mean FEV_1 = 41 ± 12% of predicted) and the mean 6MWD was 469 ± 60 m (86 ± 10% of predicted). Over the 2-year follow-up period, 25 patients (50%) experienced acute exacerbations of COPD. The Kaplan-Meier method showed that the patients in whom the 6MWD was ≤ 80% of predicted were more likely to have exacerbations than were those in whom the 6MWD was > 80% of predicted (p = 0.01), whereas the Cox regression model showed that the former were 2.6 times as likely to have an exacerbation over a 2-year period as were the latter (p = 0.02). **Conclusions:** In Brazil, the 6MWD can predict acute exacerbations of COPD over a 2-year period. The risk of experiencing an acute exacerbation of COPD within 2 years is more than twice as high in patients in whom the 6MWD is ≤ 80% of predicted.

Keywords: Pulmonary disease, chronic obstructive; Risk groups; Exercise.

INTRODUCTION

According to the Global Initiative for Obstructive Lung Disease (GOLD), an exacerbation of COPD is defined as an acute event characterized by worsening from baseline in respiratory symptoms—including increased lung hyperinflation, reduced airflow, dyspnea, and hypoxemia—requiring a change in regular medication.[1] Although exacerbations of COPD are common during the course of the disease, they should be prevented in order to avoid worsening of the pulmonary and systemic involvement characteristic of COPD.

Acute exacerbations of COPD commonly result in reduced lung function,[2] reduced peripheral muscle strength,[3] reduced respiratory muscle strength,[4] reduced physical activity in daily life,[5] reduced exercise capacity,[6] increased mortality,[7] increased health care costs,[8,9] and reduced health-related quality of life.[10] Therefore, it is important to prevent exacerbations of COPD. Predictors of COPD exacerbations include lung function, a history of exacerbations, exercise capacity, and health status,[1,11] all of which can contribute to improving the clinical management of patients with COPD.

Given that the six-minute walk test (6MWT) is simple, is easy to perform, is inexpensive, and has good responsiveness,[12,13] it is widely used in order to assess functional exercise capacity and predict exacerbations of COPD.[14,15] A six-minute walk distance (6MWD) of < 350 m has been employed as a predictor of COPD exacerbation.[14] Given that the 6MWD is longer in individuals in Brazil than in those in other countries,[16] the aforementioned 6MWD might not be applicable to COPD patients in Brazil, a different cut-off point therefore being required.

Although a cut-off point for the 6MWD has yet to be established in Brazil, previous studies have used a cut-off point of 80% of the predicted value.[17,18] A cut-off point expressed as a percentage of the predicted value might be more appropriate for two reasons: 1) it takes into account individual patient characteristics; and 2) it prevents the introduction of an absolute value bias when it is applied to different populations, the 6MWD being longer in Brazil than in other countries.[16]

Individuals in whom the 6MWD is > 80% of predicted are considered to have preserved exercise capacity. To the best of our knowledge, there have been no studies examining the

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6MWD as a predictor of COPD exacerbations in patients in Brazil not participating in a rehabilitation program and not recently hospitalized, currently participating in a rehabilitation program and having recently been hospitalized being factors that influence the prediction of exacerbations. Therefore, the objective of the present study was to evaluate whether the 6MWD can predict acute exacerbations of COPD over a 2-year period in COPD patients in Brazil. Our hypothesis was that the risk of acute exacerbation of COPD over a 2-year period would be higher in patients in whom the 6MWD was ≤ 80% of the predicted value than in those in whom the 6MWD was > 80% of the predicted value.

METHODS

This was a retrospective observational study involving a convenience sample and including data collected in the 2010-2013 period regarding COPD patients who had been invited to participate in a rehabilitation program but for various reasons (including difficulties with transportation and lack of time) underwent the initial evaluation only; that is, they did not undergo physical training. The criteria for inclusion in the present study were as follows: having been diagnosed with COPD in accordance with the GOLD criteria[1]; being clinically stable, i.e., having had no exacerbations in the last 3 months; having no comorbidities that could affect the tests performed; and having participated in no exercise training programs in the year prior to the study. The exclusion criteria were as follows: unavailable medical records; inability to contact patients or close relatives by telephone; and a 6MWD and pulmonary function test results characterizing outliers (i.e., values within ± 2 SDs of the mean).

The present study was conducted in the Respiratory Therapy Research Laboratory of the State University at Londrina and at the Health Sciences Research Center of the University of Northern Paraná, both of which are located in the city of Londrina, Brazil, and was approved by the Human Research Ethics Committee of the State University at Londrina (Protocol no. 123/09). All patients gave written informed consent.

Pulmonary function testing (spirometry)

Spirometry was performed with a Pony® spirometer (Cosmed, Rome, Italy). All tests were performed in accordance with the American Thoracic Society and European Respiratory Society guidelines,[19] and post-bronchodilator values were used. The reference values for the Brazilian population were those established by Pereira et al.[20]

6MWT

The 6MWT was performed in accordance with international guidelines by trained raters.[12] Patients were instructed to walk in a 30-m corridor for 6 min, receiving standard encouragement during the test. Two tests were performed, at least 30 min apart, the longer 6MWD being used for analysis. Blood pressure, HR, and SpO_2, as well as dyspnea and fatigue (as assessed by the modified Borg scale), were assessed before and after each test.

For all analyses, patients were divided into two groups: that of those in whom the 6MWD was > 80% of the distance predicted by applying a formula proposed by Britto et al. (equation 1)[21]; and that of those in whom the 6MWD was ≤ 80% of the predicted distance.[17,18]

Evaluation of exacerbations

The occurrence of exacerbations of COPD within 2 years of the evaluation of exercise capacity by the 6MWT was determined by analyzing medical records and contacting patients by telephone. We investigated the occurrence of acute exacerbations of COPD independently of the number of events occurring during the study period. An exacerbation of COPD was defined as a worsening of respiratory symptoms that is beyond normal day-to-day variations and that requires a change in regular medication, although it does not require hospitalization.[1]

Statistical analysis

All statistical analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). Normality of the data was tested by the Shapiro-Wilk test, and the results were described as means and standard deviations. The two groups of patients were compared by unpaired t-test. The log-rank test and the Kaplan-Meier method were used in order to compare the groups in terms of the occurrence of exacerbations. Cox regression adjusted for confounding variables (gender, body mass index—BMI—and lung function) was used in order to determine whether a 6MWD = 80% of predicted was able to predict exacerbations over a 2-year follow-up period. The level of significance was set at $p < 0.05$.

RESULTS

Our convenience sample consisted of 67 patients. However, 9 were excluded because we were unable to gain access to all relevant information and 8 were excluded because they were considered to be outliers regarding pulmonary function test results, the 6MWD, or a combination of the two. Of the 50 patients who remained in the study (Table 1), 5 died (4 from pneumonia and 1 from acute myocardial infarction) and 25 experienced exacerbations during the 2-year follow-up period. With regard to functional exercise capacity, the mean 6MWD was 469 ± 60 m (86 ± 10% of predicted).

There were no significant differences between the patients in whom the 6MWD was > 80% of predicted (n = 33) and those in whom the 6MWD was ≤ 80% of predicted (n = 17) regarding age, gender, height, weight, BMI, or lung function.

The Kaplan-Meier curves (Figure 1) showed a significant difference ($p = 0.01$) between the two groups of patients regarding the occurrence of

exacerbations, which were more common in those in whom the 6MWD was ≤ 80% of predicted than in those in whom the 6MWD was > 80% of predicted. This difference was more pronounced from the tenth month of follow-up onward.

The Cox regression model showed that, even after adjustment for confounding variables, patients in whom the 6MWD is ≤ 80% of predicted are 2.6 times more likely to experience exacerbations over the course of 2 years than are those in whom the 6MWD is > 80% of predicted (95% CI: 1.1-5.8; p = 0.02).

DISCUSSION

The results of the present study show that, in Brazil, COPD patients in whom the 6MWD is < 80% of the predicted value are more than twice as likely to experience exacerbations within 2 years after the 6MWT as are those whose exercise capacity is preserved.

In addition to normal day-to-day variations in the natural course of the disease, patients with COPD experience exacerbations requiring at least 90 days for a return to baseline health status; in some cases, recovery is incomplete even after 90 days.[22] Given that morbidity and mortality are high in patients with COPD, it is extremely important to prevent and predict acute exacerbations in order to avoid loss of lung function and the high costs of treatment.

Previous studies[14,15] have shown that the 6MWD can predict exacerbations in patients with COPD. Andrianopoulos et al.[15] recommended that a 6MWD of 375 m be used as a cut-off point to predict a higher risk of COPD exacerbation over a 3-year follow-up period. However, that cut-off point might not be appropriate for the Brazilian population, given that the 6MWD is greater in Brazil than in other countries.

In a study conducted in Brazil,[23] multidimensional indices were used in order to predict COPD exacerbations, including the Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity (BODE) index,[24] which is more comprehensive than the 6MWD alone. Given that the BODE index assesses different outcomes (BMI, FEV_1, dyspnea—as assessed by the modified Medical Research Council scale—and the 6MWD), it is more difficult to perform and it takes longer to be calculated, therefore being more difficult to use in clinical practice. The present study showed that, in COPD patients in Brazil, the 6MWD alone can predict acute exacerbations of the disease. Casanova et al.[16] showed that the 6MWD is longer in healthy individuals in Brazil than in those in other countries, whereas Pitta et al.[25] showed that daily physical activity levels are higher in COPD patients in Brazil than in those in Europe. The fact that daily physical activity levels in the Brazilian population correlate, albeit moderately, with functional exercise capacity[26] reinforces the need to adopt specific indices for different populations.

In the present study, the Kaplan-Meier curves showed a significant difference between the patients in whom the 6MWD was > 80% of the predicted value and those in whom the 6MWD was ≤ 80% of the predicted value regarding the exacerbation rate. This finding is consistent with the literature,[15] and this difference apparently becomes more pronounced after the tenth month of follow-up.

To the best of our knowledge, this is the first study to evaluate the role of the 6MWD in predicting exacerbations of COPD in patients in Brazil not participating in a rehabilitation program. Marino et al.[27] demonstrated that the 6MWD and dependent covariates (BMI and lean body mass) are associated with risk of exacerbation; however, the fact that the aforementioned study involved patients in Brazil participating in a physical therapy program constitutes a limitation, given that physical activity prevents exacerbations.[1]

Table 1. General characteristics of the patients.

Characteristic	6MWD ≤ 80% of predicted (n = 17)	6MWD > 80% of predicted (n = 33)	Study sample (n = 50)
Gender (M/F)	10/7	16/17	26/24
Age, years	70 ± 7	66 ± 7	67 ± 7
BMI, kg/m^2	22 ± 5	25 ± 4	24 ± 5
GOLD, I/II/III/IV	0/3/5/9	1/11/16/5	1/14/21/14
FEV_1, % of predicted	37 ± 19	43 ± 13	41 ± 15
FEV_1/FVC, %	52 ± 11	52 ± 9	52 ± 10
6MWD, m	374 ± 73	495 ± 55*	454 ± 84
6MWD, % of predicted[a]	73 ± 13	95 ± 12*	84 ± 15
Pre-6MWT Borg dyspnea	1 ± 1	1 ± 1	1 ± 1
Post-6MWT Borg dyspnea	3 ± 2	3 ± 2	3 ± 2
Pre-6MWT Borg fatigue	1 ± 2	1 ± 1	1 ± 1
Post-6MWT Borg fatigue	3 ± 2	3 ± 2	3 ± 2
Pre-6MWT HR, bpm	85 ± 17	84 ± 17	84 ± 17
Post-6MWT HR, bpm	106 ± 15	115 ± 13	112 ± 14
Pre-6MWT SpO_2, %	92 ± 3	94 ± 2	94 ± 3
Post-6MWT SpO_2, %	92 ± 3	92 ± 3	92 ± 3

6MWT: six-minute walk test; 6MWD: six-minute walk distance; M: male; F: female; BMI: body mass index; GOLD: Global Initiative for Chronic Obstructive Lung Disease; and Borg: modified Borg scale. [a]Value predicted by applying a formula developed by Britto et al.[21] *p < 0.05 vs. 6MWD < 80% of predicted.

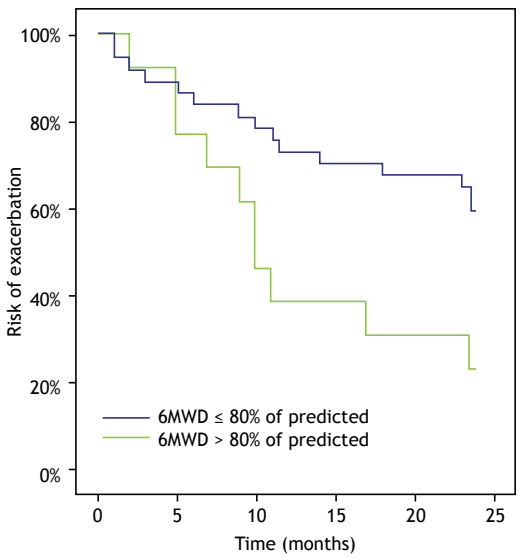

Figure 1. Kaplan-Meier curves for the risk of COPD exacerbation in patients in Brazil in whom the six-minute walk distance (6MWD) was > 80% of the predicted value or ≤ 80% of the predicted value.

Zanoria et al.[14] used a 6MWD of < 350 m as a cut-off point for predicting mortality in patients with COPD.[28] The authors showed that patients in whom the 6MWD was < 350 m were 8.4 times more likely to experience exacerbations of COPD over a 1-year period. The present study proposes a new cut-off point for the 6MWD (i.e., a 6MWD ≤ 80% of the predicted value) as a predictor of exacerbation risk in COPD patients in Brazil.

Potential limitations of the present study include the methodology used in order to collect data on exacerbations of COPD and the power of Cox regression. However, great care was taken in exploring the data in order to ensure the accuracy of the information obtained. Other limitations include the fact that this was a retrospective study involving a convenience sample and the fact that we did not investigate the frequency of exacerbations; we simply determined whether exacerbations of COPD had occurred during the study period. Prospective studies and similar studies involving larger samples might contribute to the established literature and to clinical practice.

In conclusion, the 6MWD can predict COPD exacerbations occurring over a 2-year period in patients in Brazil. The risk of experiencing an exacerbation of COPD within 2 years is more than twice as high in patients in whom the 6MWD is ≤ 80% of predicted.

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Sleep quality in medical students: a comparison across the various phases of the medical course

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ABSTRACT

Objective: To evaluate and compare subjective sleep quality in medical students across the various phases of the medical course. **Methods:** This was a cross-sectional study involving medical undergraduates at one medical school in the city of Botucatu, Brazil. All first- to sixth-year students were invited to complete the Pittsburgh Sleep Quality Index, which has been validated for use in Brazil. Participants were divided into three groups according to the phase of the medical course: group A (first- and second-years); group B (third- and fourth-years); and group C (fifth- and sixth-years). The results obtained for the instrument components were analyzed for the total sample and for the groups. **Results:** Of the 540 students invited to participate, 372 completed the instrument fully. Of those, 147 (39.5%) reported their sleep quality to be either very or fairly bad; 110 (29.5%) reported taking more than 30 min to fall asleep; 253 (68.0%) reported sleeping 6-7 h per night; 327 (87.9%) reported adequate sleep efficiency; 315 (84.6%) reported no sleep disturbances; 32 (8.6%) reported using sleeping medication; and 137 (36.9%) reported difficulty staying awake during the day at least once a week. Group comparison revealed that students in group A had worse subjective sleep quality and greater daytime dysfunction than did those in groups B and C. **Conclusions:** Medical students seem to be more exposed to sleep disturbance than other university students, and first- and second-years are more affected than those in other class years because they have worse subjective sleep quality. Active interventions should be implemented to improve sleep hygiene in medical students.

Keywords: Students, medical; Quality of life; Sleep.

INTRODUCTION

Sleep quality has been studied among university students.[1-4] Such studies have shown impairments in sleep quality, which are even greater when it comes to medical undergraduates,[5] who have a heavy academic schedule and responsibilities in various activities, all of which significantly impact sleep quality.[6-9]

University students experience disturbances in their circadian cycle because of the stress of the academic environment,[1] which is increased by habits such as surfing the Internet, watching television,[2] and using alcohol and tobacco,[3] habits that are common in this population. Improved sleep quality is associated with engaging in sports and extracurricular activities.[8]

Since impairment in sleep quality directly affects academic performance[4] and also emotional aspects,[6] we emphasize the importance of measuring sleep quality in medical students and monitoring it across the various phases of the medical course. To that end, there are instruments for self-assessment of sleep quality in the literature, such as the Pittsburgh Sleep Quality Index (PSQI),[10] which has been validated for use in Brazil[11] and which, because of its high efficacy (high specificity and high sensitivity), is recommended for use in clinical practice and research. The PSQI contains 19 items, which address sleep latency, usual bedtime and wake time, and sleep and nap quality.[10] Therefore, the objective of the present study was to evaluate and compare subjective sleep quality in medical students across the various phases of the medical course, by using the PSQI.

METHODS

This was a cross-sectional study involving medical undergraduates at the Botucatu School of Medicine, located in the city of Botucatu, Brazil. All first- to sixth-year students (N = 540) were invited to participate. Data were collected over two months. The study was approved by the local human research ethics committee (Protocol no. 400/08). All participants gave written informed consent.

All students who completed the PSQI fully within the specified period were included in the study. The students who declined the invitation to participate in the study or who did not complete the entire questionnaire were excluded.

The research instrument selected was the PSQI[11] because this is an analysis instrument that is used

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worldwide and is validated for assessing sleep disturbances, as well as allowing assessment of questions in isolation or the overall result. Its seven components—subjective sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbances; use of sleeping medication; and daytime dysfunction—were analyzed separately. The range of this instrument is from 0 to 21 points, and scores ≥ 5 signify poor sleep quality, indicating possible sleep disturbance. The sum of the seven component scores produces a global score.

Statistical analysis

The data from the completed questionnaires were entered into tables using Microsoft Excel, one of which showing the results for the total sample and the others showing the results for each undergraduate class year. The class years were then grouped according to the traditional phases of the medical course (initial phase, pathophysiology phase, and clinical clerkship phase) and participants were divided into three groups: group A, with first- and second-year students; group B, with third- and fourth-year students; and group C, with fifth- and sixth-year students. The results were described for the total sample and for the groups, and among- and between-group comparisons were conducted.

Analysis was performed using the proportions of different responses as a function of each component. In the inductive analysis, the chi-square test was used for among-group comparisons of the seven components of the PSQI, whereas the Wilcoxon test was used for between-group comparisons of the components and the Student's t-test was used for between-group comparisons of the global score. Values of $p < 0.05$ were considered significant.

RESULTS

Of the total of 540 students who were invited to participate in the study, 372 (68.9%) completed the PSQI, being distributed by class year as follows: 72, first-years; 53, second-years; 86, third-years; 67, fourth-years; 30, fifth-years; and 64, sixth-years. As for gender distribution, there was a larger proportion of females (Table 1).

The results for the seven components of the PSQI were analyzed for the total sample and for the three study groups (Table 2). Of the total sample, 39.5% of the participants classified their sleep quality as either very or fairly bad, and 29.5% reported taking more than 30 min to fall asleep two or more times a week. The average number of hours slept per night ranged from 6 h and 14 min among fifth-years to 6h and 34 min among second-years. Inductive statistical results showed no significant differences among the three groups regarding subjective sleep quality, sleep latency, or sleep duration.

Table 1. Sample distribution by group and gender.

Sample characteristics		Students, n (%)
Group	A	125 (33.6)
	B	153 (41.1)
	C	94 (25.3)
Gender	Male	138 (37.1)
	Female	234 (62.9)

A: first- and second-year students; B: third- and fourth-year students; and C: fifth- and sixth-year students.

A more thorough analysis of subjective sleep quality, by using the classification of this quality as "very good" as a reference, revealed that only students in group A were statistically significantly likely to have "very bad" subjective sleep quality (Figure 1). Habitual sleep efficiency was considered adequate in 87.9% of the total sample, and the frequency of sleep disturbances was considered low in 84.6% of the total sample. In the group analysis, neither component showed significant differences.

Of the total sample, 8.6% of the participants reported using sleeping medication at least once a week, and 87.4% reported having difficulty staying awake during the day at least once a week. In addition, 50.4% reported having trouble engaging in daily activities at least once a week, and 70.6% reported dozing; of the latter, 47.7% did not intend to doze and 44.0% regarded dozing as necessary. In the group analysis, p values = 0.72 were obtained for use of sleeping medication, whereas, for daily dysfunction, group A showed a significant difference ($p = 0.006$; Figure 2).

The mean global PSQI scores for groups A, B, and C were, respectively, 6.62 ± 2.55, 6.20 ± 2.65, and 6.66 ± 2.64, and 12.9% of the total sample had scores < 5 (Table 3). Analysis by undergraduate class year revealed scores < 5 in 5.5% of first-years, 7.6% of second-years, 15.9% of third-years, 10.1% of fourth-years, 10.0% of fifth-years, and 9.4% of sixth-years. Logistic regression, considering results > 5 (1) and ≤ 5 (0) for assessing group influence, revealed no significant intergroup influence ($p = 0.24$).

In addition, the mean scores on the seven components of the PSQI were compared between groups, and no significant differences were found between any of the groups (Table 4).

DISCUSSION

Sleep quality among medical students is a subject that has been studied worldwide because of its repercussions on the academic routine and personal life of this population. Therefore, investigating sleep quality by means of an instrument that has been validated for use in Brazil and allows quantification, such as the PSQI,[11] is extremely important for the monitoring of sleep health in such students, aiding in the planning of interventions aimed at raising awareness of this problem. By this means, we found that aspects of sleep quality were altered in our sample, with 12.9% of the participants having scores < 5, which indicate significant impairment in sleep quality.

Table 2. Results for the Pittsburgh Sleep Quality Index components as a function of the number (considering each of the three study groups) and proportion (considering the total sample) of students who selected each response option.

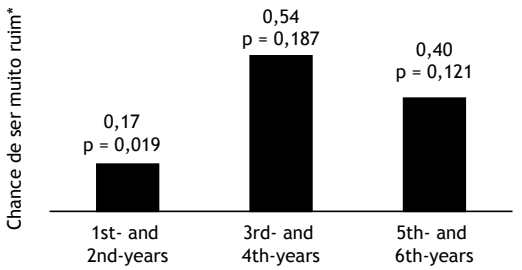
Component	Group A n = 125 (33.6)	Group B n = 153 (41.1)	Group C n = 94 (25.3)	Students, n (%)	p*
Subjective sleep quality					
Very good	10	15	10	35 (9.4)	< 0.0001
Fairly good	65	68	57	190 (51.1)	
Fairly bad	43	67	24	134 (36.0)	
Very bad	7	3	3	13 (3.5)	
Sleep latency					
≤ 15 min	32	52	20	104 (28.0)	0.07
16 to 30 min	63	47	48	158 (42.5)	
31 to 60 min	25	40	11	76 (20.4)	
> 60 min	5	14	15	34 (9.1)	
Sleep duration					
> 7 h	24	17	18	59 (15.9)	0.10
6 to 7 h	78	110	65	253 (68.0)	
5 to 6 h	19	16	10	45 (12.1)	
< 5 h	4	10	1	15 (4.0)	
Habitual sleep efficiency					
> 85	108	132	87	327 (87.9)	0.58
75 to 84	14	19	7	40 (10.8)	
65 to 74	2	2	0	4 (1.1)	
< 65	1	0	0	1 (0.3)	
Sleep disturbances					
0	8	6	4	18 (4.8)	0.29
1 to 9	104	122	71	297 (79.8)	
10 to 18	13	25	19	57 (15.3)	
19 to 27	0	0	0	0 (0)	
Use of sleeping medication					
Not during the past month	115	142	83	340 (91.4)	0.72
Less than once a week	5	7	4	16 (4.3)	
Once or twice a week	2	1	3	6 (1.6)	
Three or more times a week	3	3	4	10 (2.7)	
Daytime dysfunction					
1 to 2	10	34	3	47 (12.6)	< 0.0001
3 to 4	46	55	30	131 (35.2)	
5 to 6	32	53	54	139 (37.4)	
Every day	37	11	7	55 (14.8)	

A: first- and second-year students; B: third- and fourth-year students; and C: fifth- and sixth-year students. *Chi-square test.

Adherence in this study was nearly 70%, which is consistent with literature findings on the rate of return of this type of questionnaire (73.3%).[7] In terms of participation by gender, we found a female predominance in effective participation in the study, which is not true for other studies that used this instrument with medical students, in which there was a predominance of males—73%[8] and 54.7%.[9]

Nearly 40% of the students in our sample classified their sleep quality as either very or fairly bad, a proportion that is lower than that reported in the literature, with findings of poor sleep quality in 61.5%[12] and 61.9%,[7] specifically among medical students. The poor sleep quality observed in group A is consistent with reports from other studies, which also observed these findings in incoming students, emphasizing the correlation between poor sleep quality and first-year undergraduates, in whom poor sleep hygiene habits, such as Internet surfing at night, poor social life, and bad eating habits, are found to be aggravating factors.[13] Poor sleep quality is associated with excessive daytime sleepiness.[7,9] In the present study, daytime dysfunction was reported by 36.9% of the participants, who had difficulty staying awake during the day at least once a week. This is consistent with the literature, although there are variations across studies in the proportion of medical students reporting daytime sleepiness: 31%[7]; 42.1%[12]; and 63%.[6] Therefore, students in group A experienced greater deleterious effects on subjective sleep quality and daytime dysfunction than did those in the other groups, with daytime dysfunction showing a trend toward a significant

difference when comparing groups A and C (p = 0.05). This can be explained by the fact that incoming students go through a transitional period of change from attending preparatory courses for college entrance examinations and/or attending high school to attending an undergraduate course, which is characterized by too many academic activities and irregular daily routines, which vary too much because of the class load, shifts, breaks, and free study periods. It should also be emphasized that attending a medical course requires a high level of dedication and selflessness, signifying harmful lifestyle changes,[14-16] such as sleep deprivation and poor sleep hygiene habits.[16,17] After the second year of the undergraduate course, there may be accommodation and better adaptation to the routine of studies and visits.



*Reference: very good

Figure 1. Inductive statistics for the subjective sleep quality component and corresponding p values. Chi-square test.

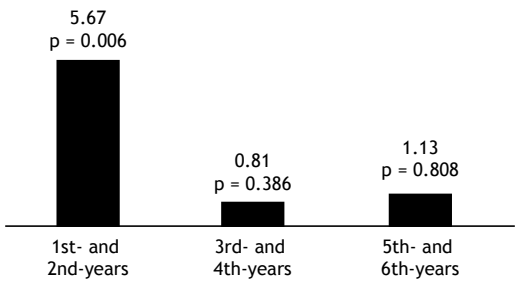


Figure 2. Inductive statistics for the daytime dysfunction component and corresponding p values. Chi-square test.

Table 3. Global Pittsburgh Sleep Quality Index (PSQI) scores as a function of the number of students (total sample).

Global PSQI scores	Students, n (%)	p*
≤ 4	48 (12.9)	
5-8	207 (55.6)	0.27
9-16	117 (31.5)	

*Chi-square test.

The results for the sleep latency component showed that sleep latency was slightly altered in 29.9% of the participants, whereas the results for the sleep duration component revealed that 68.0% of the participants reported sleeping 6-7 h per night, which is similar to the variation from 6 h and 55 min to 7 h and 25 min found in one study[18] and the average of 6.48 h reported by students at the *Universidad Adventista del Plata*,[19] but different from the average of 5.8 h of sleep per night reported by students at the Saudi Medical School.[20]

Frequent use of sleeping medication was identified in 8.6% of the participants in the present study, but this proportion is lower than that found in a study involving medical students in Saudi Arabia, which identified that 17% of those students used drugs for sleep induction; this fact indicates the need for early intervention programs targeting poor lifestyle habits.[21]

Global PSQI scores > 5 were observed in 87.1% of the our total sample, surpassing the literature findings of 59.4%[5] and 20.7%.[22]

When we analyzed mean global PSQI scores, we found results between 6 and 7 in the different groups, values that are lower than those reported in another study (8.1).[23]

In summary, we investigated sleep quality in medical students at one medical school in the city of Botucatu, Brazil, and found impairments in certain PSQI components, which suggests that investigations should continue in different regions of the country and the world, in order to monitor the profile of such students and encourage the translation of findings into health promotion practices. Our results are in agreement with literature findings of a high frequency of altered aspects in sleep quality, a high frequency that is not regarded as a problem or disorder, which may have harmful effects on health.

Since the most substantial results were obtained for the sleep quality and daily dysfunction components, a limitation of the present study was that we did not use other instruments, such as the Epworth Sleepiness Scale, which could provide details on daytime sleep dysfunction. In addition, specific protocols for assessing sleep habits could have been used to better compare student behaviors across the various phases of the medical course, given that students in group A had greater problems regarding subjective sleep quality and daytime dysfunction than did those in groups B and C.

Table 4. Values of p* for between-group comparisons of the seven components and the global score of the Pittsburgh Sleep Quality Index.

Groups	COMPONENTS							Global score
	1st	2nd	3rd	4th	5th	6th	7th	
A vs. B	0.59	0.19	0.70	0.21	0.68	0.78	0.10	0.37
A vs. C	0.40	0.90	0.53	0.65	0.19	0.37	0.05	0.10
B vs. C	0.19	0.26	0.73	0.09	0.37	0.22	0.74	0.37

A: first- and second-year students; B: third- and fourth-year students; and C: fifth- and sixth-year students. *Wilcoxon test for the components and Student's t-test for the global score.

There is a need for health promotion measures, such as proposals of changes in adopted health behaviors specifically related to good sleep hygiene, among the population of higher education students. Such proposals are found in the literature and are targeted at the general population,[24,25] but they are also applicable to and indispensable for populations such as that of the present study.

We therefore conclude that poor subjective sleep quality was high for students in all class years of the undergraduate medical course. The comparison across the various phases of the course showed that first- and second-years (group A) reported worse sleep quality and greater daytime dysfunction than did those in other class years (groups B and C).

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Recommendations for the pharmacological treatment of COPD: questions and answers

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ABSTRACT

The treatment of COPD has become increasingly effective. Measures that range from behavioral changes, reduction in exposure to risk factors, education about the disease and its course, rehabilitation, oxygen therapy, management of comorbidities, and surgical and pharmacological treatments to end-of-life care allow health professionals to provide a personalized and effective therapy. The pharmacological treatment of COPD is one of the cornerstones of COPD management, and there have been many advances in this area in recent years. Given the greater availability of drugs and therapeutic combinations, it has become increasingly challenging to know the indications for, limitations of, and potential risks and benefits of each treatment modality. In order to critically evaluate recent evidence and systematize the major questions regarding the pharmacological treatment of COPD, 24 specialists from all over Brazil gathered to develop the present recommendations. A visual guide was developed for the classification and treatment of COPD, both of which were adapted to fit the situation in Brazil. Ten questions were selected on the basis of their relevance in clinical practice. They address the classification, definitions, treatment, and evidence available for each drug or drug combination. Each question was answered by two specialists, and then the answers were consolidated in two phases: review and consensus by all participants. The questions answered are practical questions and help select from among the many options the best treatment for each patient and his/her peculiarities.

Keywords: Pulmonary disease, chronic obstructive/drug therapy; pulmonary disease, chronic obstructive/prevention & control; pulmonary disease, chronic obstructive/therapy.

INTRODUCTION

The treatment of COPD has become increasingly effective. Measures that range from behavioral changes, reduction in exposure to risk factors, education about the disease and its course, rehabilitation, oxygen therapy, management of comorbidities, and surgical and pharmacological treatments to end-of-life care allow health professionals to provide a personalized and effective therapy. However, having accurate knowledge of the indications for, limitations of, and potential risks and benefits of each treatment modality has become a challenge. This challenge is even more acute when we have to adapt evidence in the literature to fit the peculiarities of our country, given the frequent challenges faced in both public and private clinical practice.

The pharmacological treatment of COPD is one of the cornerstones of COPD management, and there have been many advances in this area in recent years.[1] In 2011, a systematic review of the advances in the pharmacological treatment of COPD was published in the JBP. It is striking the extent to which the knowledge of and the resources available to treat COPD have evolved since then.[2]

The individualization of treatment is essential and should be based on the availability of existing drugs, disease severity, patient preferences, drug interactions, and comorbidities. The goal should always be to meet the disease control objectives effectively. In order to critically evaluate recent evidence and systematize the major

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questions regarding the pharmacological treatment of COPD, specialists from all over Brazil gathered to develop the present recommendations.

It is always important to emphasize that the pharmacological treatment of COPD should be complemented by measures such as smoking cessation, encouragement for physical activity, pulmonary rehabilitation, and vaccination to prevent viral infections and pneumonia, as well as by measures against advanced disease, such as oxygen therapy, surgical treatment, endoscopic treatment, and lung transplantation.[3] These treatment measures should always be considered and, when indicated, should be implemented together with the appropriate drug therapy.[4]

Chart 1 shows the major drugs available for the treatment of COPD, and Chart 2 serves as a guide for the classification and treatment of COPD, both of which were adapted to fit the situation in Brazil. The 10 questions answered in the present recommendations are practical questions and help select from among the many options the best treatment for each COPD patient.

1. HOW SHOULD COPD SEVERITY BE CLASSIFIED?

The first international consensus guidelines on COPD used the degree of FEV_1 impairment for determining disease severity. Current guidelines, however, combine

Chart 1. Main drugs for the treatment of COPD.[a]

Drug	Dose, μg (except where otherwise indicated)	Duration of action, h
Short-acting β_2 agonist		
Fenoterol	**MDI 100 and 200**	4 a 6
Albuterol	**MDI 100, 120, 200**	4 to 6, 12
Long-acting β_2 agonist		
Formoterol	**DPI 12**	12
Salmeterol	**MDI 25 and DPI 50**	12
Indacaterol	**DPI 150 and 300**	24
Olodaterol	**SMI 2.5**	24
Short-acting anticholinergic		
Ipratropium (bromide)	**MDI 20 e 40**	6 to 8
Long-acting anticholinergic		
Glycopyrronium (bromide)	**DPI 50**	12 to 24
Tiotropium	**SMI 2.5**	24
Umeclidinium (bromide)	DPI 62.5	24
β_2 agonist plus short-acting anticholinergic		
Fenoterol/ipratropium	**MDI 50/20**	6 to 8
Albuterol/ipratropium	**MDI 120/20**	6 to 8
β_2 agonist plus long-acting anticholinergic		
Formoterol/aclidinium	DPI 12/400	12
Formoterol/glycopyrronium	MDI 9.6/14.4	12
Indacaterol/glycopyrronium	**DPI 110/50**	12 to 24
Vilanterol/umeclidinium	**DPI 25/62.5**	24
Olodaterol/tiotropium	SMI 2.5/2.5	24
Long-acting β_2 agonist plus inhaled corticosteroid		
Formoterol/beclomethasone	**MDI and DPI 6/100**	12
Formoterol/budesonide	**DPI 6/200, 12/400, and 12/200** **MDI 6/200**	12
Formoterol/mometasone	MDI 5/50, 5/100, and 5/200	12
Salmeterol/fluticasone	**DPI 5/100, 50/250, and 50/500** **MDI 25/50, 25/125, and 25/250**	12
Vilanterol/fluticasone	**DPI 25/100**	24
Phosphodiesterase-4 inhibitor		
Roflumilast	**Tablet, 500 mg**	24
Macrolide		
Azithromycin	**Tablet or capsule, 250 and 500 mg**	24
Mucolytic		
N-acetylcysteine	**Powder, 200 and 600 mg; syrup, 30 mg/mL; and tablet, 600 mg**	8 to 12

MDI: metered dose inhaler; DPI: dry powder inhaler; and SMI: soft mist inhaler. [a]In bold, formulations currently available in Brazil. The others are, at the time of this publication, in the process of approval by the Brazilian National Health Oversight Agency or in the process of being released by the pharmaceutical industry.

assessment of symptoms and exacerbations of COPD (ECOPD) with spirometry results to classify disease severity, acknowledging that spirometric measurements alone are insufficient. In fact, dyspnea intensity and impaired health status correlate poorly with FEV_1.[5]

The classification of COPD severity is aimed at determining the degree of airflow obstruction, determining symptom intensity (specifically the degree of dyspnea), and evaluating the risk of ECOPD.

Dyspnea

Dyspnea is the major factor responsible for the development of disability in COPD. Patients who have the same degree of airflow obstruction can exhibit different degrees of dyspnea.[6] The modified Medical Research Council (mMRC) dyspnea scale is easy to administer, expresses the intensity of the impact of the symptom, and predicts 5-year survival.[7] Chart 3 shows an adapted version of the mMRC dyspnea scale for use in Brazil. It is important to question patients with COPD about the time of day they most often experience dyspnea so that it is possible to adapt their daily lives to their degree of dyspnea. A shorter-acting drug may eventually provide more benefits for patients who most often experience dyspnea in the morning.[8]

Questionnaire on health status in COPD

Dyspnea is not the only symptom of COPD. COPD impacts health status for several reasons that are not quantified in assessment of dyspnea in isolation. Quality of life questionnaires are quite important for evaluating the efficacy of treatments but are impractical for use in routine practice.

To fill the need for an easy-to-administer instrument that assessed health status multidimensionally and had an impact on the evaluation and follow-up of COPD, several questionnaires have been developed, the most widely used of which is the COPD Assessment Test (CAT). Chart 4 shows the Portuguese-language version of the CAT, with its questions and scoring system.[9] The CAT correlates well with quality of life questionnaires, FEV_1, and dyspnea as measured by the mMRC dyspnea scale. In addition, the CAT provides complementary information on issues such as cough, expectoration, sleep, and vitality, among others that are not addressed in traditional assessments.[10-12]

For the proposed classification (Chart 2), a CAT score ≥ 10 (Chart 4) distinguishes patients with COPD who are highly asymptomatic from those who are mildly asymptomatic and should be used, together with mMRC dyspnea scale scores (Chart 3) and pulmonary function results, to determine disease severity.

FEV_1

FEV_1 is the simplest measure of the degree of airway obstruction in COPD. A reduced FEV_1 is associated with increased mortality in COPD, in addition to its role in identifying the disease and classifying disease severity. FEV_1 is also associated with quality of life in patients with COPD.[13-15] Although FEV_1 does not reflect all domains of the disease, its use, in combination with assessment of dyspnea intensity with the mMRC dyspnea scale, is simple and applicable to the care provided by general practitioners and specialists.[16-19]

The classification of COPD severity proposed by the Brazilian Thoracic Association uses post-bronchodilator FEV_1 values (expressed as percent of predicted value) and mMRC dyspnea scale scores (Chart 3) or CAT scores (Chart 4). The worst-result criterion should be used. COPD should be classified as mild, moderate, severe, or very severe, and treatment should be recommended for each severity class (Chart 2).

Chart 2. Classification and pharmacological treatment of COPD.

	Non-exacerbator		Dual bronchodilator therapy (LABA + LAMA)	
	Bronchodilator monotherapy (LABA or LAMA)			
Severity	Mild	Moderate	Severe	Very severe
Dyspnea (mMRC scale)	0- 1	2	3	4
Symptoms (CAT)	<10	≥10		
Obstruction (Post-BD %FEV_1)	≥ 80	< 80 ≥ 50	< 50 ≥ 30	< 30
Frequent exacerbations (previous year) ≥ 2 exacerbations or ≥ 1 hospitalization	Dual therapy (LABA + LAMA)# Combination therapy (LABA + ICS) Monotherapy (LAMA)		Triple therapy* Add Roflumilast¶* Consider macrolíde* or NAC*	

First-line treatment
* If exacerbations persist despite first-line treatment
¶ Indicated in patients with COPD and chronic bronchitis

LABA: long-acting β_2 agonist; LAMA: long-acting anticholinergic; mMRC: modified Medical Research Council dyspnea scale; CAT: COPD Assessment test; %FEV_1: percent predicted FEV_1; BD: bronchodilator; ICS: inhaled corticosteroid; and NAC: N-acetylcysteine.

Chart 3. Adapted version of the Modified Medical Research Council dyspnea scale for use in Brazil.

Pontuação (*Score*)	Sintomas (*Symptoms*)
0	Tenho falta de ar ao realizar exercício intenso.
1	Tenho falta de ar quando apresso o meu passo, ou subo escadas ou ladeira.
2	Preciso parar algumas vezes quando ando no meu passo, ou ando mais devagar que outras pessoas de minha idade.
3	Preciso parar muitas vezes devido à falta de ar quando ando perto de 100 metros, ou poucos minutos de caminhada no plano.
4	Sinto tanta falta de ar que não saio de casa, ou preciso de ajuda para me vestir ou tomar banho.

2. WHAT IS A COPD EXACERBATOR? ARE THERE DIFFERENCES IN PROGNOSIS AND TREATMENT?

Several definitions exist for ECOPD in the literature. About 30 years ago, Anthonisen et al.[20] defined ECOPD as the presence of at least two of the following changes: increased dyspnea; increased expectoration; and increased sputum purulence. These criteria are still used. ECOPD are events in the natural course of the disease characterized by a sustained worsening of the patient's usual respiratory symptoms that is beyond normal day-to-day variations and warrants a change in regular medication.[21]

Although ECOPD can be caused by several factors, most are associated with viral or bacterial infections. More than 40% of ECOPD are related to respiratory viruses, but non-infectious agents that irritate the airways, such as air pollution, can also be triggering factors.[22]

ECOPD increase the inflammatory process, accelerate disease progression, worsen quality of life, and increase the risk of recurrent ECOPD and hospitalizations that may lead to the death of patients. ECOPD are also associated with an increased risk of cardiovascular events, especially acute myocardial infarction.[22,23]

In-hospital mortality during ECOPD ranges from 3.6% to 11%; the risk of hospitalization can increase by 23% to 43% during the year following hospitalization; among ICU patients, in-hospital mortality is 24% and can be as high as 42% after 1 year; and the calculated fatality rate (excess mortality compared with stable COPD) is 15.6%, which underscores the importance of measures to prevent and treat ECOPD.[17,24]

Risk factors for frequent ECOPD include advanced age, very compromised pulmonary function, cough with expectoration, comorbidities, gastroesophageal reflux disease, and, in particular, a history of ECOPD.[25]

A study[26] that followed 2,138 treated patients with COPD over 3 years found that the major predictor of ECOPD was a history of ECOPD in the preceding year (OR = 4.30; 95% CI: 3.58-5.17) and that the exacerbator phenotype was generally maintained in the following years of follow-up. Exacerbators are a distinct group of patients, and being an exacerbator is unrelated to disease severity. In that same study, among patients with moderate COPD as defined by spirometry (FEV_1 between 50% and 80%), there were 22% of exacerbators.[26]

Based on morbidity and prognosis studies, frequent exacerbators were defined as patients with COPD who experience two or more ECOPD over a 1-year period, each at least 4 weeks apart after the end of the treatment of a previous ECOPD or 6 weeks apart, beginning at the event onset, in untreated cases.[4] Patients who experienced an ECOPD requiring hospitalization in the preceding 12 months should also be treated as exacerbators.

The relationship observed between ECOPD and worsened prognosis in several studies warrants that special attention that exacerbators should be given with regard to the maintenance pharmacological treatment of COPD.[24,27-30] One of the goals of the present recommendations was to separate the pharmacological treatment of exacerbators from that of non-exacerbators. Both treatments depend on pulmonary function results for definition of the most appropriate drugs (Chart 2).

3. WHAT ARE THE GOALS OF THE PHARMACOLOGICAL TREATMENT OF COPD?

The goals of the pharmacological treatment of COPD are to reduce symptoms, which includes relieving dyspnea and cough; to improve health status and exercise tolerance; to reduce risk, which includes mitigating disease progression; to prevent and treat ECOPD; and to reduce mortality.

The choice of the most appropriate treatment should take into account symptom intensity, ECOPD, adverse effects, comorbidities, cognitive changes, adaptation to the device, and drug availability and costs. Therefore, pharmacological treatment should be individualized, there being drug options suited to each patient's profile. However, some general considerations should be made to avoid inappropriate or excessive drug use.[4]

In patients who are at low risk of ECOPD and are mildly asymptomatic, the first consideration to be made is whether maintenance treatment is required. The evidence regarding this specific profile will be discussed later. If the decision is for symptomatic treatment, patients can be started on an inhaled long-acting bronchodilator alone, no class being preferred in the choice. Long-acting β_2 agonists (LABAs) and long-acting antimuscarinic agents (LAMAs) are options. Long-acting bronchodilators are more effective than short-acting bronchodilators and should be prioritized in the treatment of patients with persistent symptoms.

Chart 4. Portuguese-language version of the COPD Assessment Test.

O seu nome:

Data de hoje:

CAT™
COPD Assessment Test

Como está a sua DPOC (Doença Pulmonar Obstrutiva Crônica)? Faça o Teste de Avaliação da DPOC (COPD Assessment Test™–CAT)

Esse questionário irá ajudá-o e ao seu profissional da saúde a medir o impacto que a DPOC (Doença Pulmonar Obstrutiva Crônica) causa no seu bem estar e o no seu dia a dia.As suas respostas e a pontuação do teste podem ser utilizadas por você e pelo seu profissional da saúde para ajudar a melhorar o controle da sua DPOC e a obter o máximo benefício do tratamento.

Para cada um dos itens a seguir, assinale com um (X) o quadrado que melhor o descrever presentemente. Certifique-se de selecionar apenas uma resposta para cada pergunta.

Por exemplo: Estou muito feliz ☐ ☒ ☐ ☐ ☐ ☐ **Estou muito triste**

								PONTUAÇÃO
Nunca tenho tosse	0	1	2	3	4	5	Tenho tosse o tempo todo	
Não tenho nenhum catarro (secreção) no peito	0	1	2	3	4	5	O meu peito está cheio de catarro (secreção)	
Não sinto nenhuma pressão no peito	0	1	2	3	4	5	Sinto uma grande pressão no peito	
Não sinto falta de ar quando subo uma ladeira ou um andar de escada	0	1	2	3	4	5	Sinto bastante falta de ar quando subo uma ladeira ou um andar de escada	
Não sinto nenhuma limitação nas minhas atividades em casa	0	1	2	3	4	5	Sinto-me muito limitado nas minhas atividades em casa	
Sinto-me confiante para sair de casa, apesar da minha doença pulmonar	0	1	2	3	4	5	Não me sinto nada confiante para sair de casa, por causa da minha doença pulmonar	
Durmo profundamente	0	1	2	3	4	5	Não durmo profundamente devido à minha doença pulmonar	
Tenho muita energia (disposição)	0	1	2	3	4	5	Não tenho nenhuma energia (disposição)	
								PONTUAÇÃO TOTAL

If symptoms remain despite initial treatment, a LABA/LAMA combination should be prescribed.[31,32]

In patients with more severe dyspnea but at low risk of ECOPD, dual LABA/LAMA bronchodilation therapy is indicated, always taking into account availability, side effects, and individual response. Inhaled corticosteroids (ICSs) are rarely indicated for patients at low risk of ECOPD; ICSs should be added to the treatment when both COPD and asthma are present.[33]

Exacerbators who are mildly asymptomatic and have no severe functional limitation (FEV_1 > 50%) can be initially treated with a long-acting bronchodilator alone. In such cases, LAMAs are superior to LABAs in preventing ECOPD.[34]

For exacerbators who are more symptomatic or have more severe functional limitation, treatment can be initiated with a LABA/LAMA combination or, if the patient is already using such a combination, an ICS can be added, constituting triple therapy.

An ICS, always in combination with a LABA, is indicated in selected patients. LABA/ICS combinations are indicated in patients with specific phenotypes, such as those with asthma and COPD or with blood or sputum eosinophilia. The indications for LABA/ICS combination therapy will be discussed later.

There are as yet no studies to determine whether triple therapy is superior to LABA/LAMA combination therapy in preventing ECOPD. As previously mentioned,

patients with asthma and COPD should always be treated with ICSs, irrespective of the number of ECOPD.[33] For patients who continue to have ECOPD despite triple therapy, there are second- and third-line options for preventing ECOPD that will be discussed later.

4. WHAT SHOULD BE THE PHARMACOLOGICAL TREATMENT FOR MILD COPD (FEV_1 > 80% OF PREDICTED AND MMRC SCALE SCORES ≤ 1)?

Patients with mild COPD have structural changes in the airways and lung parenchyma, as well as several physiological changes. However, there is no evidence of clinical importance of these changes in asymptomatic patients. In one study,[35] in which 519 individuals with an FEV_1/FVC ratio < 0.70 and an FEV_1 > 80% of predicted were followed, 56.8% of those patients had no respiratory symptoms. Multivariate adjusted analysis showed that there were no differences between asymptomatic patients and the reference group (asymptomatic patients with normal pulmonary function test results) regarding health care utilization or quality of life.[35] The presence of symptoms was one of the best predictors of health care utilization in those with mild obstruction.[35-38] In that group, 3 years of treatment with budesonide did not affect the rate of decline in FEV_1 or respiratory symptoms, including ECOPD.[35-38]

It has been demonstrated that dynamic hyperinflation occurs even in patients with mild-to-moderate disease. Treatment with tiotropium improved dynamic hyperinflation in patients with moderate disease but not in those with mild disease. It was also demonstrated that 6 weeks of treatment with tiotropium modestly improved inspiratory capacity in those patients but had no effect on exercise tolerance.[39] In another study, there was improvement in airflow limitation.[40]

The Global Initiative for Chronic Obstructive Lung Disease recommends the use of a short- or long-acting bronchodilator to relieve dyspnea,[4] which does not apply to patients with mild COPD and an mMRC score ≤ 1 (Chart 3).[9] There is no evidence of benefit of pharmacotherapy for other outcomes.[5,10] In summary, although pharmacological therapy has effects on some physiological changes, to date, there have been no studies on which to base a recommendation for the use of this form of therapy in asymptomatic patients with mild COPD. If the symptoms are considered relevant, short- or long-acting bronchodilators can be used depending on patient preference and can be continued depending on symptom improvement. As symptoms become more prominent and frequent or ECOPD occur, the option should be for a long-acting bronchodilator.[4]

5. DOES A LABA/LAMA COMBINATION PROVIDE GREATER BENEFITS THAN LABA OR LAMA MONOTHERAPY IN PATIENTS WITH COPD?

Bronchodilators are the cornerstone of COPD treatment. The addition of a second long-acting bronchodilator as a different mechanism of action increases the benefits for various outcomes, especially dyspnea and the frequency and severity of ECOPD. LABA/LAMA combinations are indicated in symptomatic patients with moderate-to-very-severe COPD and in exacerbators.[4]

A study conducted in Brazil and involving patients who remained symptomatic despite treatment with salmeterol showed that the addition of tiotropium was able to improve pulmonary function, decrease dyspnea during physical activity, and improve performance in activities of daily living within 2 weeks.[41]

Exacerbations

Only one study has been aimed primarily at evaluating the effect of a LABA/LAMA combination vs. monotherapy on ECOPD, and it demonstrated that indacaterol/glycopyrronium decreased the annual rate of moderate or severe ECOPD and the rate of all ECOPD, including mild ones, and increased morning pre-dose FEV_1 relative to glycopyrronium alone.[42]

Comparisons of umeclidinium/vilanterol for 24 weeks vs. umeclidinium, vilanterol, or tiotropium alone found no differences in the time to first ECOPD. Those studies, however, were not designed to assess ECOPD as a primary outcome.[43,44] Likewise, comparisons of aclidinium/formoterol vs. either monotherapy in 24-week studies, which were also not designed to assess ECOPD, showed no significant differences in the rate of ECOPD.[45,46]

Tiotropium/odolaterol is still being studied regarding the frequency of ECOPD. In a recent study, tiotropium/odolaterol was superior to either monotherapy in improving FEV_1, dyspnea, hyperinflation, and rescue medication use. The improvement, although statistically significant, was below the minimal clinically important difference (MCID).[47]

Dyspnea

Dyspnea is the most common complaint of patients with COPD. The most common assessment tool is the Transition Dyspnea Index (TDI), which considers an MCID of 1 point. Most studies assess dyspnea as a secondary outcome. A 6-week study assessed dyspnea as a primary outcome, comparing glycopyrronium/indacaterol vs. placebo or tiotropium alone.[48] A 26-week study, in which dyspnea was a secondary outcome, showed significant improvement in dyspnea with glycopyrronium/indacaterol vs. tiotropium but not with glycopyrronium/indacaterol vs. either monotherapy.[49] Umeclidinium/vilanterol, in a 24-week study in which the degree of dyspnea was a secondary outcome, was shown to be more likely to achieve a decrease in dyspnea, as measured by the TDI, when compared with vilanterol alone but not when compared with umeclidinium alone.[43] In two randomized, parallel studies involving a total of more than 3,000 patients, a higher proportion of patients reached the MCID of the TDI with aclidinium/formoterol than with either monotherapy.[45]

Data from a meta-analysis of the efficacy and safety of LABA/LAMA combinations vs. LABAs or LAMAs alone in the treatment of patients with moderate-to-severe COPD, using data from 23 randomized clinical trials of at least 12 weeks' duration, showed that patients on LABA/LAMA achieved better TDI scores than did those on monotherapy and that LABA/LAMA combinations were more effective in reducing the number of (moderate-to-severe) ECOPD when compared with LABAs but not when compared with LAMAs.[50] The evidence indicates that, in terms of efficacy, LABA/LAMA combinations provide more benefits than do LABA and LAMA monotherapies in patients with moderate-to-very-severe COPD who remain symptomatic, because of the improvement in TDI scores. The effect of LABA/LAMA combinations in preventing ECOPD appears to be greater than that of LABAs alone, but it has not yet been conclusively demonstrated to be greater than that of LAMAs alone.

6. WHICH PATIENTS WITH COPD BENEFIT MOST FROM LABA/ICS COMBINATIONS?

ICSs modify gene transcription in the cell nucleus, increasing the production of anti-inflammatory proteins and the amount of β_2 receptors on the cell surface, which explains the synergistic action of ICSs when combined with LABAs. In contrast, corticosteroid resistance and poor corticosteroid response have been reported in patients with COPD.[51]

ICSs can cause several side effects: candidiasis; dysphonia; superficial hematomas secondary to minor trauma; osteopenia; cataracts; glaucoma; diabetes mellitus; adrenal suppression; mycobacterial infections (including tuberculosis); and pneumonia. Pneumonia has been the subject of several publications and is associated with long-term use of ICSs, high doses, and more potent corticosteroids, as well as with smokers, previous episodes of ECOPD or pneumonia, age > 55 years, body mass index < 25 kg/m^2, and severe airway obstruction.[52]

The use of ICSs in combination with LABAs has been mentioned as a therapeutic option aimed at reducing the number of ECOPD and improving quality of life and pulmonary function. Meta-analyses have confirmed that LABA/ICS combinations, as compared with LABAs or ICSs alone, are superior in terms of improvement in pulmonary function, although one may question the mean difference not reaching the current MCID for these outcomes. In terms of improvement in quality of life, LABA/ICS combinations appear to be superior to either monotherapy in patients with COPD and an FEV_1 < 50% of predicted.[53]

Blood eosinophil levels may be a predictor of ICS response in individuals with COPD. One study showed that patients with COPD and pretreatment blood eosinophil levels ≥ 2% had a greater reduction in the frequency of ECOPD with LABA/ICS combination therapy than did those with pretreatment blood eosinophil levels < 2%.[54] LABA/ICS combination therapy is also indicated when both COPD and asthma are present.[55]

Patients on LABA/ICS should be carefully evaluated if ICS discontinuation is planned. The ICS can be discontinued in all non-exacerbators who were started on it although there was no indication for it. ICS discontinuation is possibly associated with an increase in the rate of ECOPD per year, worsening of symptoms, and worsening of pulmonary function. This effect is more pronounced in patients with peripheral eosinophilia.[56-58]

Although COPD is an inflammatory disease, the accumulation of evidence regarding the side effects of ICSs and the uncertainties about the action of ICSs in patients with COPD result in the LABA/ICS option being indicated to treat patients with COPD and asthma, patients who have ECOPD and have had an unsatisfactory response to LABA/LAMA, and those with the COPD exacerbator phenotype and peripheral eosinophilia. Eosinophil cut-off values indicating benefit of ICS therapy remain controversial and require confirmation in future studies.

7. IN WHICH CLINICAL CONDITION SHOULD A LAMA BE ADDED TO LABA/ICS COMBINATION THERAPY (TRIPLE THERAPY)?

The addition of a LAMA to LABA/ICS combination therapy for the treatment of obstructive diseases is called triple therapy. Treating COPD systematically requires individualized clinical judgment in searching for appropriate treatment options. Although LABA/ICS/LAMA triple therapy is routinely used in clinical practice, there are important issues regarding this treatment modality that need to be clarified.

Studies involving patients with severe or very severe COPD who had more than one ECOPD per year have reported a reduction in the number of hospitalizations and ECOPD with LABA/ICS/LAMA triple therapy. Triple therapy produced improvement in symptoms, pulmonary function, and quality of life scores when compared with LABA/ICS combination therapy and with LAMA monotherapy.[6,59-63] A systematic review comparing triple therapy vs. LABA/ICS combination therapy or tiotropium alone reported improvement in pulmonary function and health-related quality of life for the group treated with triple therapy. However, no differences were observed in the number of ECOPD or in the occurrence of pneumonia, dyspnea, or severe adverse events. The safety profile of triple therapy was similar to that of other treatment options available.[64,65] Observational studies have demonstrated that a prescribing preference for triple therapy exists in several regions of the world, despite the lack of clear criteria for its use, as recommended in guidelines.[66]

The heterogeneity of COPD allows the identification of subgroups of patients with distinct clinical features for whom triple therapy can be indicated. On the basis of the above data, we recommend that LABA/

ICS/LAMA triple therapy be used in patients with COPD who remain symptomatic despite LABA/LAMA combination therapy, in those who have ECOPD (2 or more per year) despite maximal bronchodilator therapy with LABA/LAMA, and in patients with COPD and asthma who remain symptomatic despite LABA/ICS combination therapy.[67]

Post hoc analyses from clinical trials suggest that increased serum eosinophil levels can be a biomarker for future risk of ECOPD in exacerbators, as well as predicting the benefits of ICS therapy in preventing ECOPD.[54,58,68,69] The finding of an eosinophil count greater than 300 cells/μL in patients with moderate-to-severe COPD, with a history of ECOPD, and receiving LABA/LAMA can aid in making a decision to initiate triple therapy.[54,70] However, future prospective clinical trials are needed to validate the use of eosinophil counts and to determine a cut-off point for them so that they can be useful in daily practice.[71,72]

8. WHAT IS THE INDICATION FOR ADDING ROFLUMILAST TO PREVENT ECOPD?

Roflumilast is a selective phosphodiesterase-4 (PDE4) inhibitor and acts by blocking this enzyme activity, increasing intracellular levels of cAMP, which results in reduction of cellular inflammatory activity. PDE4 receptors are also expressed in the airway smooth muscle cells; however, this direct bronchodilator effect is modest.[73,74]

Roflumilast is indicated for the treatment of patients with severe or very severe COPD (FEV_1 < 50% of predicted) who continue to have ECOPD, cough, and phlegm despite maximal inhaled therapy. The recommended dose is 500 μg/day orally, and the long half-life of the terminal N-oxide metabolite of roflumilast allows the drug to be administered in a single daily dose.[75]

A post hoc evaluation of the initial studies of roflumilast involving a total of 2,686 patients showed a significant reduction of 14.3% in ECOPD in patients with COPD receiving the recommended dose of 500 μg/day vs. placebo over 52 weeks of evaluation. The factors associated with this reduction were presence of chronic bronchitis (reduction of 26.2%); cough (reduction of 20.9%); expectoration (reduction of 17.8%); and concomitant ICS use (reduction of 18.8%).[76]

A recent study conducted in 380 centers in 17 countries and involving 2,354 randomized patients (1,178 receiving roflumilast and 1,176 receiving placebo) showed that the rate of moderate or severe ECOPD was reduced with roflumilast vs. placebo (28.5%), but this difference did not reach significance. The proportion of patients who did not have severe ECOPD over the 52 weeks of treatment was greater in the roflumilast group than in the placebo group (54.2% vs. 48.5%). The time to the onset of severe ECOPD was 319 and 286 days, respectively, in the roflumilast and placebo groups, with the difference not being significant.[77]

A meta-analysis of 14 studies involving 12,654 patients with severe or very severe COPD associated with chronic bronchitis showed that roflumilast in combination with an ICS, a LABA, and a LAMA significantly improves FEV_1 (mean, 45.60 mL) and reduces the frequency of moderate and severe ECOPD compared with placebo (OR = 0.77).[78] In a post hoc analysis of the same study, in patients with more than three ECOPD per year, the rate of moderate or severe ECOPD decreased by 39% in the group receiving roflumilast compared with the group receiving placebo, with the difference being significant.[79]

Roflumilast is generally well tolerated with adverse events consistent with those expected for PDE4 inhibitors. However, it has more adverse effects than do the inhaled drugs used in the treatment of COPD. The most common adverse effects, reported in combined data from clinical trials involving 8,630 patients, are gastrointestinal disorders (diarrhea and nausea), decreased appetite, insomnia, depression, headache, and weight loss. These adverse effects are stronger at the beginning of treatment, are reversible, and improve over time (generally within 4 weeks).[79] In another combined safety analysis, which included data from 14 clinical trials of roflumilast in 12,054 patients, the rates of adverse events in the roflumilast and placebo groups were, respectively, 67.2% and 62.8%, whereas the rates of severe adverse events were 13.5% vs. 14.2%.[77]

The evidence from those studies provides additional information on the patient subgroup that is likely to benefit from the addition of roflumilast to the treatment regimen. Roflumilast is indicated for patients with severe or very severe COPD (FEV_1 < 50% of predicted), chronic bronchitis (cough and expectoration), and frequent ECOPD despite appropriate inhaled therapy.

9. DOES THE PROPHYLACTIC USE OF ANTIBIOTICS IN PATIENTS WITH STABLE COPD PREVENT ECOPD?

ECOPD are triggered by viral infections or by acquisition of a new bacterial strain in the lower airways. Studies suggest that the presence of bacteria in the lower airways contributes to chronic inflammation, resulting in disease progression. Therefore, it is possible that, in chronically infected patients, the bacterial load reduction caused by long-term use of antibiotics reduces the frequency and severity of ECOPD. Macrolides have been indicated because of their anti-inflammatory and immunomodulatory effects. In addition, macrolides alter biofilm production and improve phagocytosis and bacterial clearance by alveolar macrophages.[80-82]

A study on the use of erythromycin for 12 months found that such use led to a reduction in ECOPD and in the risk of hospitalization.[83] In a subsequent study, it was demonstrated that the duration of ECOPD was shorter with continued use of erythromycin.[84] In 2011, a study evaluating 1,142 patients on long-term home oxygen therapy or with a history of ECOPD

found that, when added to the usual treatment, daily azithromycin for 1 year reduced the frequency of ECOPD and improved quality of life.[85]

A meta-analysis of six studies reported a 37% reduction in the risk of ECOPD with antibiotic therapy compared with placebo.[86] .A systematic review of seven studies involving more than 3,000 patients identified a significant effect of continued antibiotic therapy on the reduction in the number of ECOPD.[87]

The use of intermittent courses of oral fluoroquinolone therapy reduced the likelihood of ECOPD by approximately 25%, as demonstrated in a study evaluating treatment with daily moxifloxacin for 5 days every 8 weeks for a total of 6 courses.[88] Patients with mucopurulent sputum before treatment experienced a reduction of up to 45% in ECOPD. However, the lack of studies, the risk of inducing bacterial resistance, and the side effects of chronic antibiotic use limit the routine use of this strategy.[88]

The use of inhaled antibiotic therapy in patients with COPD cannot be recommended yet because of the lack of randomized clinical trials in which the efficacy of such use has been proven. Despite the reduction in bronchial inflammation in patients chronically colonized with *Pseudomonas aeruginosa* after 2 weeks of treatment with inhaled tobramycin, the few existing studies have been unable to demonstrate clinical benefits of inhaled antibiotic therapy in preventing ECOPD.[89,90]

The indication for prophylactic antibiotics in COPD should be determined on a case-by-case basis. Prophylactic antibiotics are a third-line therapy for the treatment of exacerbators. The available evidence lends support to the use of azithromycin 250 mg daily or azithromycin 500 mg three times a week or the use of erythromycin 500 mg twice daily for 1 year in patients with severe or very severe COPD and in exacerbators despite usual pharmacological treatment. Long-term use is associated with an increased risk of adverse events and development of bacterial resistance. Special care should be taken in patients with concomitant heart disease, tachycardia at rest, or a history of arrhythmias. Ototoxicity and gastrointestinal side effects should also be monitored. It is recommended that, before initiation of such therapy, sputum samples be collected for bacterial and mycobacterial culture, given that continued use of a macrolide can make it difficult to diagnose chronic lung infections with low-virulence microorganisms.[91,92]

10. CAN N-ACETYLCYSTEINE (NAC) BE USED FOR PREVENTING ECOPD?

There are consistent data in the literature showing that airway oxidative stress in patients with COPD plays an important role in the development of the disease and is associated with future risk of ECOPD and with a greater influx of inflammatory cells and inflammatory cytokines. The use of antioxidant and anti-inflammatory agents in COPD has been studied for the control of ECOPD. In this context, the efficacy and safely of NAC in COPD are being investigated regarding prevention of ECOPD.[93]

NAC has direct action, because of the presence of the free sulfhydryl group, which serves as a ready source of redox equivalents, and indirect action, because of the intracellular replacement of glutathione antioxidant levels. However, there is still much discussion regarding the efficacy of NAC in controlling ECOPD events and regarding the optimal dose for controlling such events.[94]

In a randomized clinical trial conducted in the United States,[95] 51 patients with COPD due to tobacco exposure and with symptoms of chronic bronchitis (cough and secretion) were allocated to receive NAC, 1,800 mg twice daily, or placebo for 8 weeks. However, the sample size did not reach the goal of 130 patients, which may have influenced the results showing no change in quality of life, in pulmonary function, or in markers of systemic inflammation and oxidative stress. The most common adverse events were mild nausea and diarrhea.[95] In contrast, a randomized study conducted in China, comparing NAC, 600 mg twice daily, vs. placebo in 1,006 patients with COPD and at least two ECOPD in the preceding 2 years, showed that NAC treatment was more effective in patients with moderate COPD than in those with severe COPD, with a significant reduction in the rate of ECOPD after 1 year. The time to first ECOPD was not different between the groups. Ten percent of the patients in the NAC group and 9% of those in the placebo group had serious adverse events, most of which were due to hospitalization for ECOPD.[96] Another randomized study conducted in China, comparing NAC, 600 mg twice daily, for 1 year vs. placebo in 120 patients, demonstrated a significant reduction in the rate of ECOPD in the NAC group compared with the control group (0.96 vs. 1.71 ECOPD/patient/year).[97] In 2005, a study comparing NAC, 600 mg once daily, for 3 years vs. placebo in 523 patients showed that there was no difference between the NAC and the control groups. However, in the subgroup of patients who were not receiving ICSs (155 patients), there was a 26% reduction in the risk of ECOPD.[98]

Two meta-analyses showed that NAC treatment reduced the rate of ECOPD (risk ratio = 0.85; 95% CI: 0.76-0.96). The findings were consistent regarding the reduction in the number of exacerbations with treatment with high doses (1,200 mg) of NAC in patients with COPD and with treatment with low doses (600 mg) of NAC in patients with chronic bronchitis who did not have COPD, but NAC had no effect on pulmonary function. Therefore, the recent studies show that NAC can be safely used for the prevention of ECOPD when used for more than 6 months and at daily doses greater than 1,200 mg.[99,100]

Given the safety profile of NAC and the evidence of its efficacy, its use as a third-line drug in the prevention of ECOPD is recommended; the profile of patients who obtain greater benefits from NAC treatment appears to be that of patients with chronic bronchitis, but this is still controversial.

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Long-acting muscarinic antagonists vs. long-acting β_2 agonists in COPD exacerbations: a systematic review and meta-analysis

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Study carried out at the Universidade Federal de Santa Catarina, Florianópolis (SC), at the Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP), and at Hospital Alemão Oswaldo Cruz, São Paulo (SP) Brasil.

ABSTRACT

Objective: To determine whether long-acting muscarinic antagonists (LAMAs) provide superior therapeutic effects over long-acting β_2 agonists (LABAs) for preventing COPD exacerbations. **Methods:** This was a systematic review and meta-analysis of randomized clinical trials involving patients with stable, moderate to severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease criteria, treated with a LAMA (i.e., tiotropium bromide, aclidinium, or glycopyrronium), followed for at least 12 weeks and compared with controls using a LABA in isolation or in combination with a corticosteroid. **Results:** A total of 2,622 studies were analyzed for possible inclusion on the basis of their title and abstract; 9 studies (17,120 participants) were included in the analysis. In comparison with LABAs, LAMAs led to a greater decrease in the exacerbation rate ratio (relative risk [RR] = 0.88; 95% CI: 0.84-0.93]; a lower proportion of patients who experienced at least one exacerbation (RR = 0.90; 95% CI: 0.87-0.94; $p < 0.00001$); a lower risk of exacerbation-related hospitalizations (RR = 0.78; 95% CI: 0.69-0.87; $p < 0.0001$); and a lower number of serious adverse events (RR = 0.81; 95% CI: 0.67-0.96; $p = 0.0002$). The overall quality of evidence was moderate for all outcomes. **Conclusions:** The major findings of this systematic review and meta-analysis were that LAMAs significantly reduced the exacerbation rate (exacerbation episodes/year), as well as the number of exacerbation episodes, of hospitalizations, and of serious adverse events.

Keywords: Pulmonary disease, chronic obstructive; Muscarinic antagonists; Adrenergic beta-agonists; Bronchodilator agents; Aerosol/therapeutic use; Disease management.

INTRODUCTION

COPD is a common preventable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response to noxious particles or gases.[1] According to the World Health Organization, COPD is the fourth leading cause of death worldwide,[2] and its burden is projected to increase in the coming decades due to the aging of the population worldwide and the continuous exposure to risk factors.[3] COPD is the fifth leading cause of hospitalization.[4] Most information comes from high-income countries, but it is known that almost 90% of COPD deaths occur in low- and middle-income countries.[2] In Latin America, the prevalence of COPD in 2005 was the highest among those over 60 years of age, ranging from 7.8% in Mexico City to 19.7% in Montevideo, Uruguay.[5] In Brazil, the prevalence rate of COPD was 15.6% in 2010,[5] with 33,000 deaths per year.[6]

The clinical presentation of COPD is progressive loss of lung function, worsening of quality of life, and increasing severity of the symptoms. In addition to chronic impairment, this disease can progress with periods of acute decline by exacerbations, defined as acute events characterized by the worsening of the respiratory symptoms of the patient beyond normal day-to-day variations, which leads to a change in medication.[7] COPD exacerbations are major contributors to deterioration of lung function, worsening of quality of life, increases in health care costs, need for hospitalization, and risk of death.[7,8] Therefore, decreasing the exacerbation rate is an important therapeutic goal for COPD patients. Therapy with a long-acting muscarinic antagonist (LAMA) or a long-acting β_2 agonist (LABA) is recommended as the first-line maintenance therapy for patients with moderate to very severe COPD.[1] These medications were primarily introduced to provide symptomatic control. On the basis of their efficacy in recent clinical trials against placebo, they are now recommended for preventing exacerbations in patients with moderate to severe COPD.[9-11] Current treatment guidelines,[1] however, do not specify whether a LAMA or a LABA should be the preferred agent.

In a meta-analysis performed by Chong et al. in 2012,[12] a LAMA (tiotropium) reduced the number of patients experiencing one or more exacerbations when compared with the use of various LABA formulations. Since that review, new formulations of LAMAs and LABAs have been introduced,[13-15] and larger trials comparing LAMAs with LABAs have been recently published.[16,17]

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Furthermore, the lack of summary statistics in order to measure the ratio of exacerbations per year and the need for updating the quality of evidence justify the interest in and the relevance of the present review, whose objective was to determine whether LAMAs are superior to LABAs in preventing COPD exacerbations.

METHODS

This review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA)[18] guidelines and was registered with the International Prospective Register of Systematic Reviews (PROSPERO; Protocol no. CRD42015024682). The construction of the population, intervention, control, and outcome in the present study were, respectively, COPD patients, LAMAs, LABAs, and COPD exacerbations. No research ethics committee approval was needed for the present systematic review.

The study inclusion criteria were as follows: randomized clinical trials (RCTs) involving patients with stable, moderate to severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease criteria,[1] treated with a LAMA (i.e., tiotropium bromide, aclidinium bromide, or glycopyrronium), who were followed for at least 12 weeks and compared with controls using a LABA in isolation (i.e., salmeterol, formoterol, or vilanterol) or as fixed-dose combinations of LABAs and inhaled corticosteroids (i.e., formoterol/budesonide, formoterol/mometasone, or salmeterol/fluticasone). No language or timeframe restrictions were included. The study exclusion criteria were observational studies, studies with no information regarding the severity of COPD, and studies performed with generic drugs. The literature search strategy included the terms "COPD", "LAMA", "LABA", and the derivative terms shown in Appendix 1 (all of the appendices in the present study are available online at http://jornaldepneumologia.com.br/detalhe_anexo.asp?id=54).

We used the following databases in order to retrieve the RCTs: PubMed; EMBASE; Cochrane Library; LILACS; Cumulative Index of Nursing and Allied Health Literature; Web Of Science; Scopus; Grey Literature Report; and the Brazilian *Fundação de Apoio ao Desenvolvimento do Ensino, Ciência e Tecnologia/Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* Thesis Bank. In addition, we searched proceedings of conferences and workshops (abstracts). Authors of unpublished abstracts were contacted. We also consulted the online ClinicalTrials.gov registry and results database. The searches were performed between April and May of 2015.

Data collection and analysis

Study selection

After the preliminary search results were obtained, we eliminated duplicate citations and the remaining citations were screened in two steps. In the first step, the title and the abstract of each article were examined, and citations not meeting the inclusion criteria were discarded. In the second step, we obtained full-text copies of the remaining citations. Two of the authors independently assessed all of the studies retrieved during the search and listed all eligible RCTs. Differences and uncertainties regarding the inclusion list were resolved by discussion to reach a consensus. A third reviewer was consulted when a consensus was not achieved.

Data extraction and management

Two reviewers extracted the data independently. A third reviewer helped in cases of disagreement. Data extraction included the name of the first author; year of publication; study design; number of participants; mean age and gender of the participants in each group; diagnostic criteria; drug and dosage for each study group; and outcome measures. The primary outcome measures were COPD exacerbation rate in each group, exacerbation rate ratio, and proportions of patients who experienced at least one exacerbation during the study period. The secondary outcome measures included the number of hospitalizations due to COPD exacerbations, mortality, and the number of serious adverse events.

Assessment of risk of bias

We assessed the risk of bias of the included studies using the Cochrane Risk of Bias Tool.[19]

Data synthesis

In the binomial data analysis, an event was considered present if a patient had at least one exacerbation during the course of the RCT. Summary data were reported as relative risk (RR) and 95% CI. Wherever the rate ratio was reported, log transformation was performed before the rate ratios were analyzed and combined across studies using the generic inverse variance method. An approximate standard error of the log rate ratio was calculated in accordance with the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0.[19] The number needed to treat (NNT) to prevent one event was calculated using the risk difference between groups. The data were analyzed with the Review Manager software, version 5.3 (RevMan 5; Cochrane Collaboration, Oxford, UK). Trials were pooled using a fixed effects model to ensure that larger trials would have adequate weight in the overall treatment effect.

Assessment of heterogeneity

For pooled effects, we tested heterogeneity using the *I2* statistics.[19] Values of 25%, 50%, and 75%, respectively, are representative of low, moderate, and high heterogeneity.

Subgroup analysis and heterogeneity investigation

We evaluated the studies by stratifying them into studies including only patients with frequent exacerbations and studies in which the presence of

frequent exacerbations was not an inclusion criterion. We also evaluated low vs. high risk of bias using the Cochrane Risk of Bias Tool.[19]

Sensitivity analysis

The sensitivity analysis was performed with RCTs in which the comparator group included a combination of inhaled corticosteroids and LABA, those including ultra-long-acting drugs, and those with a follow-up time of 48 weeks or less.

Quality of evidence

The quality of the evidence was measured for the primary outcomes using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[20]

RESULTS

Search results

A total of 2,622 studies were analyzed by title and abstract for possible inclusion, leading to the exclusion of 2,609 studies. Thus, 13 RCTs met the inclusion criteria and were selected for the full-text phase. Four of these studies[21-24] were excluded, 9 studies remaining for the final quantitative analysis[16,17,25-31] (Figure 1). A total of 17,120 participants were included, and the main characteristics of this population are described in Table 1. Table 2 shows the types of analyses, specified treatment groups, and follow-up times. Three studies[16,17,30] included only patients with frequent exacerbations, defined as a documented history of at least one exacerbation leading to treatment with systemic glucocorticosteroids or antibiotics, or hospitalizations within the previous year.[17] All studies excluded patients with asthma, other related previous medical conditions, and COPD exacerbations within the past 4 weeks. Four studies[25,27,28,30] had both symptom-based and event-based definitions of COPD exacerbation.[32] Three studies[17,26,29] applied only a symptom-based definition, and the remaining 2 applied only an event-based definition.[16,31] Age (range: 61.8-65.0 years), proportion of male patients (range: 65-84%), and mean baseline FEV_1 in percentage of the predicted value (range: 37.7-54.5%) were comparable across the studies. Two studies[27,28] were open label for the LAMA treatment arm, which compromises blinding in this group.

Interventions

All studies compared LAMAs directly with a LABA formulation. Tiotropium HandiHaler® (18 µg; Boehringer Ingelheim, Ingelheim, Germany) was used as LAMA in all but one study,[31] which used aclidinium HandiHaler® (400 µg; Boehringer Ingelheim). As for LABAs, salmeterol (50 µg) and formoterol (12 µg), both delivered by metered dose or dry power inhalers, were used in 6 studies,[16,25-27,30,31] and an ultra-long indacaterol (150 µg) formulation was used in 3 studies.[17,28,29] A combined LABA/inhaled corticosteroid formulation was used in 1 study[16] (salmeterol, 50 µg + fluticasone propionate, 500 µg) delivered by Diskus/Accuhaler® (GlaxoSmithKline, Bretford, UK).

Risk of bias in the included studies

The methodological quality of the included studies was assessed by the Cochrane Risk of Bias Tool,[19] as shown in Figure 2. To investigate publication bias, a contour-enhanced funnel plot (Appendix 2) and analyses using Harbord's and Peter's tests were carried out.

Effect of the interventions

Primary outcomes

- Exacerbation rate ratio

The exacerbation rates with the use of LAMAs were lower than those with the use of a LABA alone (RR = 0.88; 95% CI: 0.84-0.93), as estimated by the fixed effects model. The number of randomized participants was 14,488 from 6 RCTs. Heterogeneity among the studies was low ($I2$ = 48%; Figure 3). A random effects model was applied and revealed no change in heterogeneity and negligible change in the treatment effect.

A subgroup analysis based on the history of frequent exacerbations and follow-up time of at least 48 weeks was performed, showing no change in the treatment effect (RR = 0.86; 95% CI: 0.81-0.91; Figure 3). However, heterogeneity was high ($I2$ = 74%) due to the study using an inhaled corticosteroid.[16] Those studies that included patients with or without frequent exacerbations had a similar RR (0.86) and a larger and nonsignificant 95% CI (0.73-1.02), as estimated by the fixed effects model (Figure 3). Subgroup analysis of the studies stratified by low and high risk of bias showed a smaller treatment effect in the group with a high risk of bias (Figure 3).

- Number of participants who experienced at least one exacerbation

Patients treated with LAMAs had a lower risk of exacerbation than those treated with LABAs (RR = 0.90; 95% CI: 0.87-0.94; p < 0.00001), as estimated by the fixed effects model, with no evidence of heterogeneity (I^2 = 0%; Figure 4). The subgroup analysis based on a history of frequent exacerbations is shown in Figure 4. In the subgroup of patients without frequent exacerbations (RR = 0.92; 95% CI: 0.81-1.04; p = 0.19),[25-29,31] the exacerbation rate was not significantly different between LAMAs and LABAs. In the subgroup analysis of those studies that included patients with frequent exacerbations,[16,17,30] the exacerbation rate was significantly different among the groups favoring LAMAs (RR = 0.90; 95% CI: 0.86-0.94; p < 0.00001). The overall NNT with LAMAs to prevent one exacerbation was 29, and this number was reduced to 24 when only patients with frequent exacerbations were considered.

Secondary outcomes

- Hospitalizations

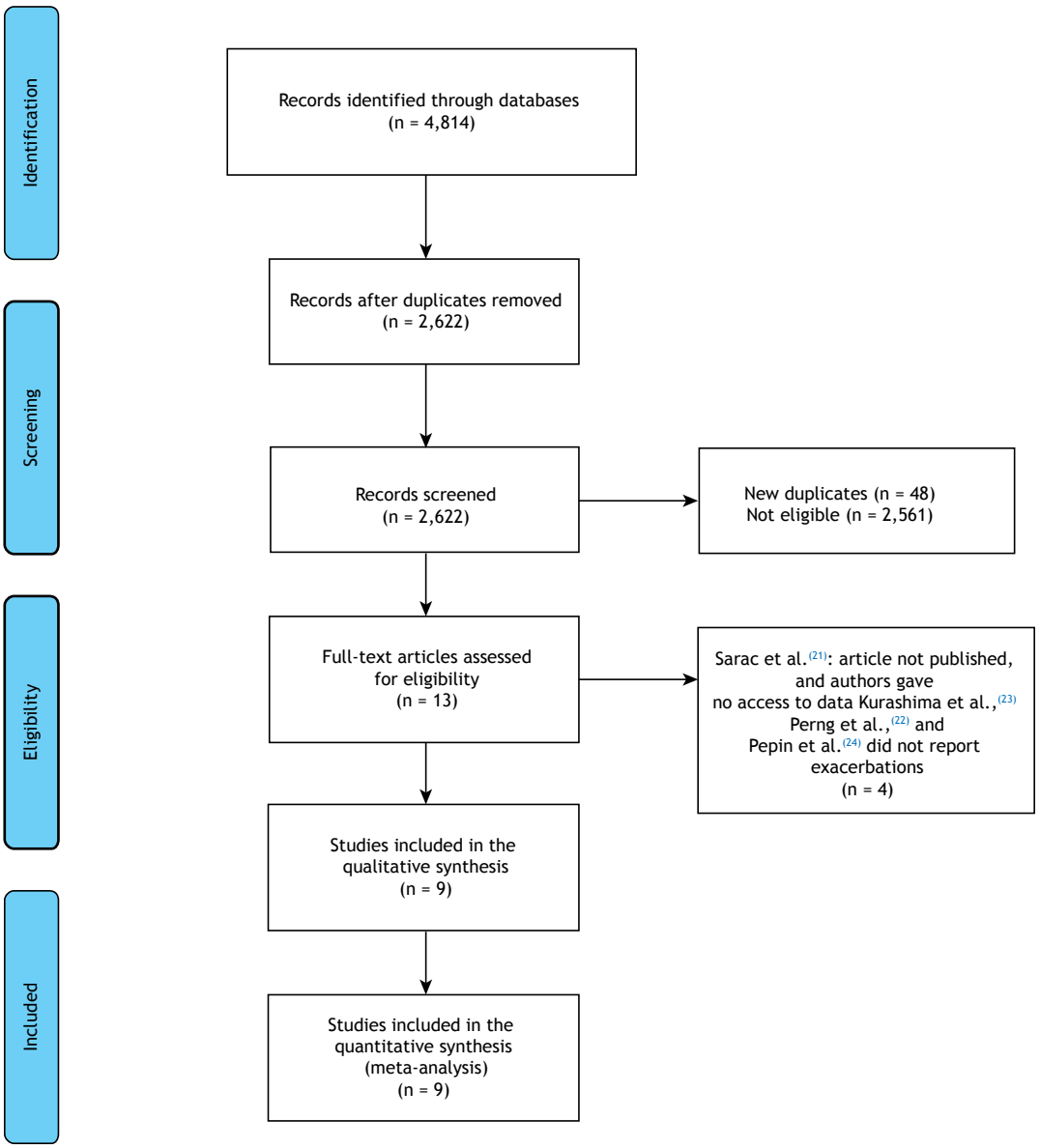

Figure 1. Flow chart of the article selection process in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[18]

Six studies,[16,17,26,27,30,31] involving 13,899 participants reported the number of patients who had had at least one hospitalization related to a COPD exacerbation. The patients treated with LAMAs had a lower risk of hospitalization when compared with those treated with LABA (RR = 0.78; 95% CI: 0.69-0.87; p < 0.0001; Figure 5). The *I2* statistic showed low heterogeneity (42%), which was completely explained when we considered only those studies that included patients with frequent exacerbations.[16,17,30]

- Mortality

Eight studies, involving 16,746 participants reported the number of deaths in each group.[16,17,25,26,28-31] None of the events were reportedly related to the medications under investigation. The number of deaths did not differ significantly between the treatment groups (RR = 1.00; 95% CI: 0.79-1.27; Figure 5).

- Serious adverse events

Five trials involving 13,738 participants reported serious adverse effects.[16,17,28,30,31] The risk of severe adverse effects was significantly lower in the patients using LAMAs than in those using LABAs (RR = 0.91, 95% CI: 0.84-0.97; p = 0.0007; Figure 5). The major reported severe adverse effects were respiratory complications, such as COPD worsening and pneumonia, and cardiac disorders.

- Publication bias

Analyses using Harbord's and Peter's tests (p = 0.4716 and p = 0.2585, respectively) and a contour-enhanced

Table 1. Characteristics of the selected studies.[a]

First author	Year	Male, %		Age, years		Smoking history, years		COPD duration, years		FEV_1%		FEV_1/FVC%	
		LAMA	LABA	LAMA	LABA	LAMA	LABA	LAMA	LABA	LAMA	LABA	LAMA	LABA
Brusasco et al.[25]	2003	77.4	75.0	63.8 (8.0)	64.1 (8.5)	44.1 (22.9)	44.8 (24.1)	9.0 (7.3)	9.9 (8.0)	39.2 (11.6)	37.7 (11.7)	43.7 (9.7)	42.3 (9.5)
Briggs et al.[26]	2005	65	68	64.2 (8.6)	64.6 (7.8)	55.6 (29.6)	56.1 (27.9)	9.4 (6.5)	9.4 (6.8)	37.7 (11.9)	37.7 (12.2)	43.7 (10.0)	43 (9.7)
Buhl et al.[29]	2011	67	70	63.4 (8.3)	63.6 (8.6)	41.8 (19.8)	43.2 (20.9)	7.0 (6.0)	7.0 (6.3)	54.3 (12.8)	54.6 (12.8)	51.2 (9.4)	51.0 (9.4)
Decramer et al.[17]	2013	76	78	64	64	43.2 (23.9)	42.8 (23.8)	6.6 (5.4)	7.0 (5.7)	40.7 (6.1)	40.2 (6.0)	46.5 (9.8)	46.0 (9.7)
Donohue et al.[28]	2002	74	75	64.5 (7.9)	64.6 (8.1)	47 (25)	48 (26)	9.2 (7.8)	10.4 (8.2)	ND	ND	43.6 (9.8)	42.0 (9.5)
Vogelmeier et al.[27]	2008	79.2	75.7	63.4 (9.5)	61.8 (8.8)	38.6 (19.3)	35.4 (18.0)	6.9 (6.3)	7.0 (6.0)	51.6 (11.2)	51.6 (10.6)	54.4 (9.6)	54.6 (10.2)
Vogelmeier et al.[30]	2013	74.4	74.9	62.9 (9.0)	62.8 (9.0)	38.8 (20.0)	37.8 (19.2)	8.0 (6.7)	7.9 (6.5)	49.2 (13.3)	49.4 (13.1)	52.5 (10.8)	52.4 (11.2)
Singh et al.[31]	2014	66.5	66.4	63.1 (8.2)	63.4 (7.8)	NI	NI	NI	NI	53.6 (13.0)	54.5 (13.2)	NI	NI
Wedzicha et al.[16]	2008	84	81	65	64	39.5	41.3	ND	ND	39.4	39.1	ND	ND

LAMA: long-acting muscarinic antagonist; LABA: long-acting β_2 agonist; ND: not done; and NI: not informed. [a]Values expressed as mean (SD), except where otherwise indicated.

Table 2. Study interventions.

First author	Year	Participants, n		Type of analysis	Intervention	Control	Follow-up time, weeks
		LAMA	LABA		LAMA	LABA	
Brusasco et al.[25]	2003	402	405	ITT	Tiotropium, 18 µg	Salmeterol, 50 µg	24
Briggs et al.[26]	2005	308	300	ITT	Tiotropium, 18 µg	Salmeterol, 50 µg	12
Buhl et al.[29]	2011	799	794	ITT	Tiotropium, 18 µg	Indacaterol, 150 µg	12
Decramer et al.[17]	2013	1,689	1,693	Per protocol	Tiotropium, 18 µg	Indacaterol, 150 µg	52
Donohue et al.[28]	2010	415	416	ITT	Tiotropium, 18 µg	Indacaterol, 150 µg	26
Vogelmeier et al.[27]	2014	385	384	ITT	Aclidinium, 400 µg	Formoterol, 12 µg	24
Vogelmeier et al.[30]	2008	221	210	ITT	Tiotropium, 18 µg	Formoterol, 12 µg	24
Singh et al.[31]	2013	3,707	3,669	ITT	Tiotropium, 18 µg	Salmeterol, 50 µg	52
Wedzicha et al.[16]	2008	665	658	ITT	Tiotropium, 18 µg	Salmeterol, 50 µg + fluticasone propionate, 500 µg	104

LAMA: long-acting muscarinic antagonist; LABA: long-acting β_2 agonist; and ITT: intention to treat

funnel plot (Appendix 2) provided no evidence of publication bias.

- GRADE

The evaluation using GRADE included three outcomes: exacerbation rate, number of people experiencing one or more exacerbations, and number/duration of hospitalizations. The overall quality of evidence was moderate for all outcomes (Appendix 3).

DISCUSSION

The present systematic review and meta-analysis revealed a 12% reduction in the exacerbation rate in patients on LAMA treatment when compared with those on LABA treatment, as well as a 10% reduction in the number of patients that experienced at least one exacerbation episode during the follow-up period. Treatment with LAMAs significantly reduced the number of hospitalizations due to COPD exacerbations (resulting in a decrease of 22% in RR), as well as resulting in a significant decrease (9%) in the RR of severe adverse effects. However, LAMA treatment did not significantly alter mortality.

The results of the present meta-analysis relied on head-to-head RCTs. Although a previous review evaluated these two treatments for COPD,[12] it neither reported on exacerbation rates nor on publication bias, and the treatment effect in a subgroup of patients with frequent exacerbations was not considered. The studies included in the present review had a large number of events, a large sample size, a low risk of bias, and low heterogeneity, leading to high consistency and precision of our findings.

Exacerbations and hospitalizations are important outcomes[20] that are critical for decision-making. The evidence summarized in the present review indicates that LAMA therapy provides significant advantages

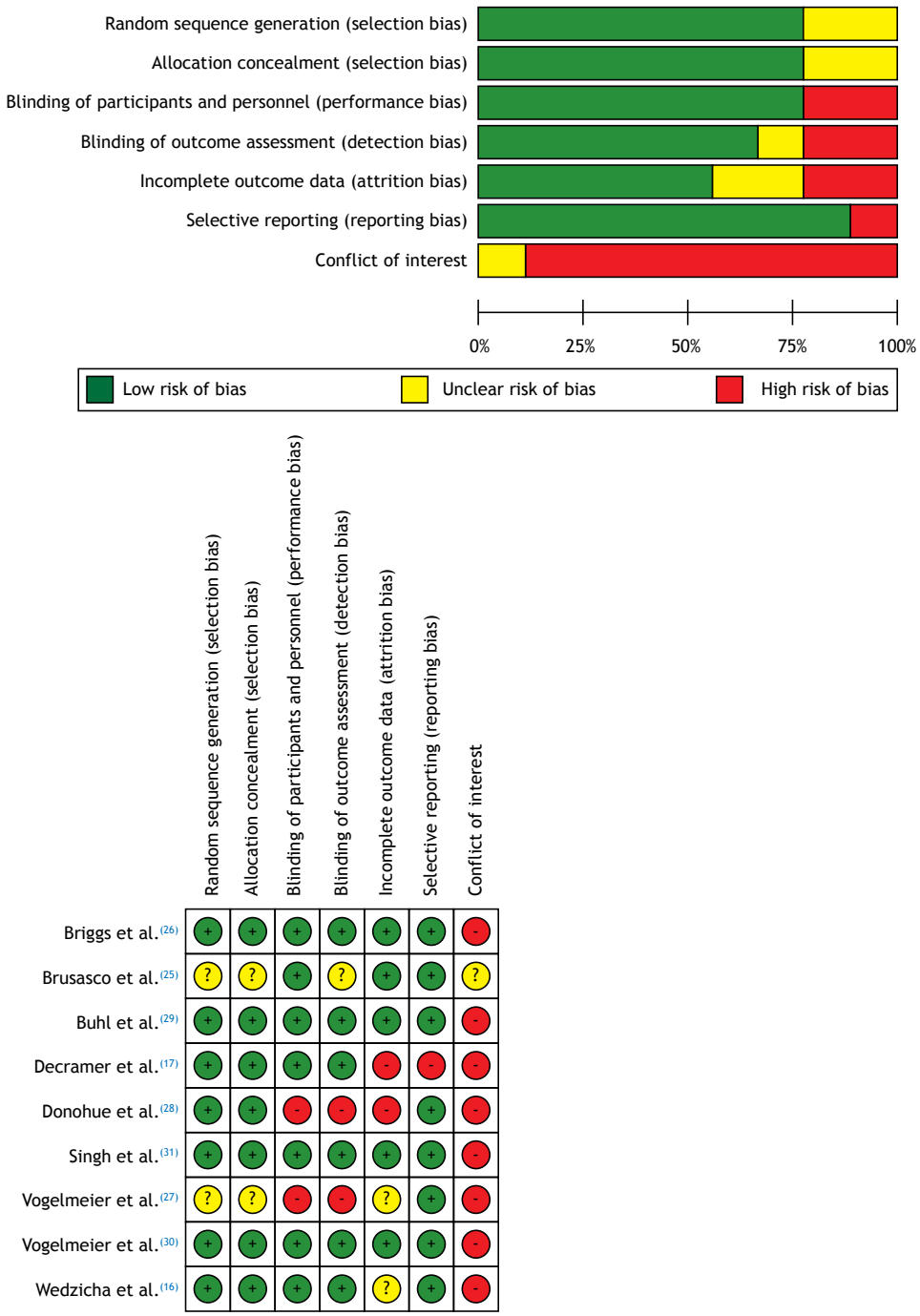

Figure 2. Risk of biases in the included studies.

when compared with LABA therapy; however, the size of the effect is likely to be a source of ongoing debate. The minimal clinically important difference for the exacerbation rate is suggested to be 22%,[33] but the lack of a uniform definition of exacerbation, the lack of severity grading, and the underreporting of exacerbations make it difficult to establish a valid minimal clinically important difference.[34]

Due to seasonal variation, evaluating the frequency of exacerbations requires follow-up periods of at least 1 year.[35] In the long term, patients with previous frequent exacerbations have a high probability of suffering from frequent exacerbations in the future.[36,37] The present review included studies involving patients with a low probability of exacerbations and follow-up times shorter than 1 year. Therefore, this can explain

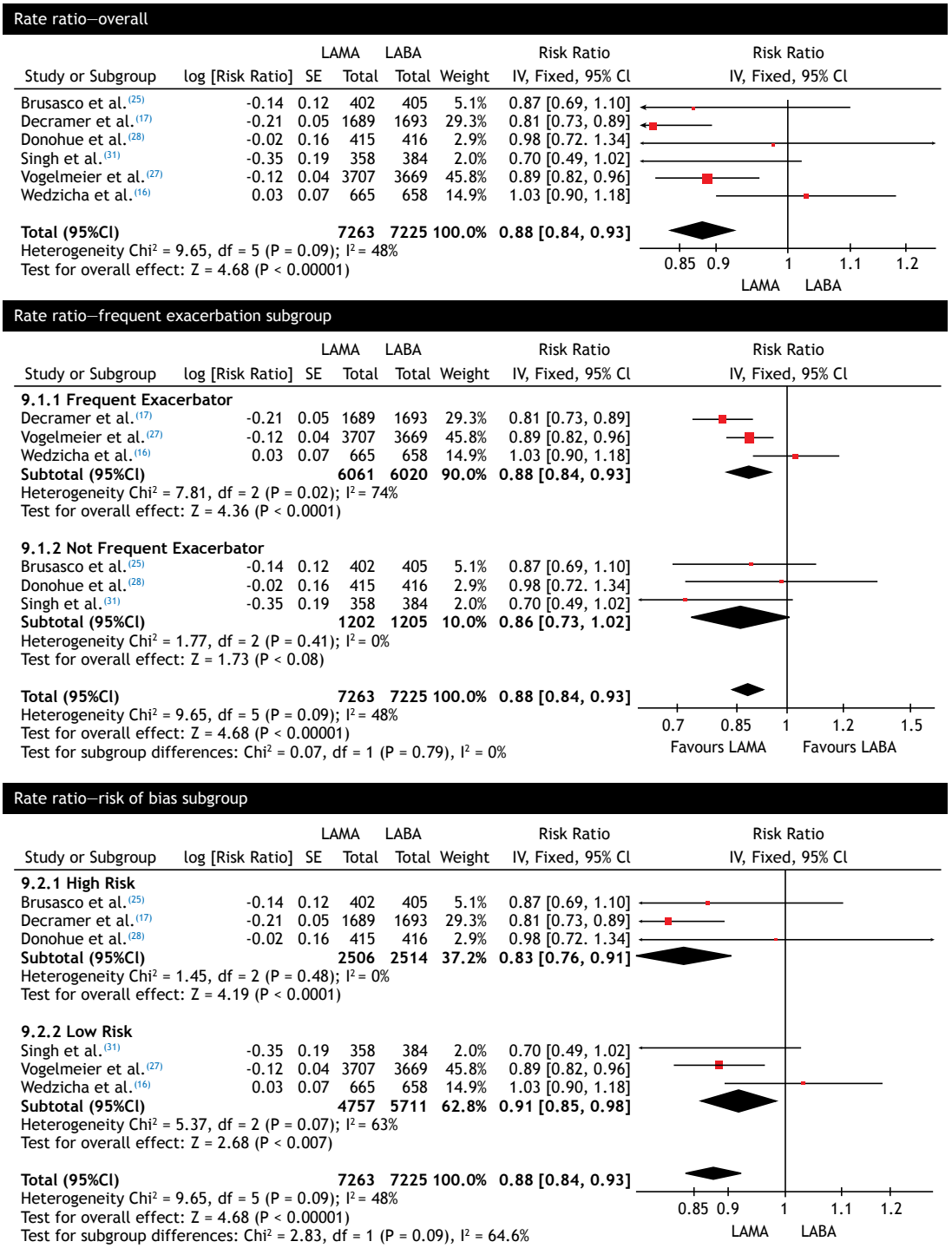

Figure 3. Rate ratio—overall and subgroups.

why the estimated treatment effect was not significant in the subgroup analysis of studies that included COPD patients with infrequent exacerbations.

Inhaled corticosteroids alone or in combination with LABAs reduce airway inflammation (detected by endobronchial biopsy),[38,39] leading to a reduction in the risk of exacerbations.[40] One of the studies included in the analysis compared a LAMA with a LABA in combination with an inhaled corticosteroid.[16] The inclusion of that study in the data synthesis compromised the results of the rate ratio of exacerbations regarding heterogeneity. However, the compromise in the overall effect after excluding that study was small, with a reduction of 0.2 in the rate ratio and of 0.1 in the number of exacerbations, which made the authors decide to keep the study in the analysis.

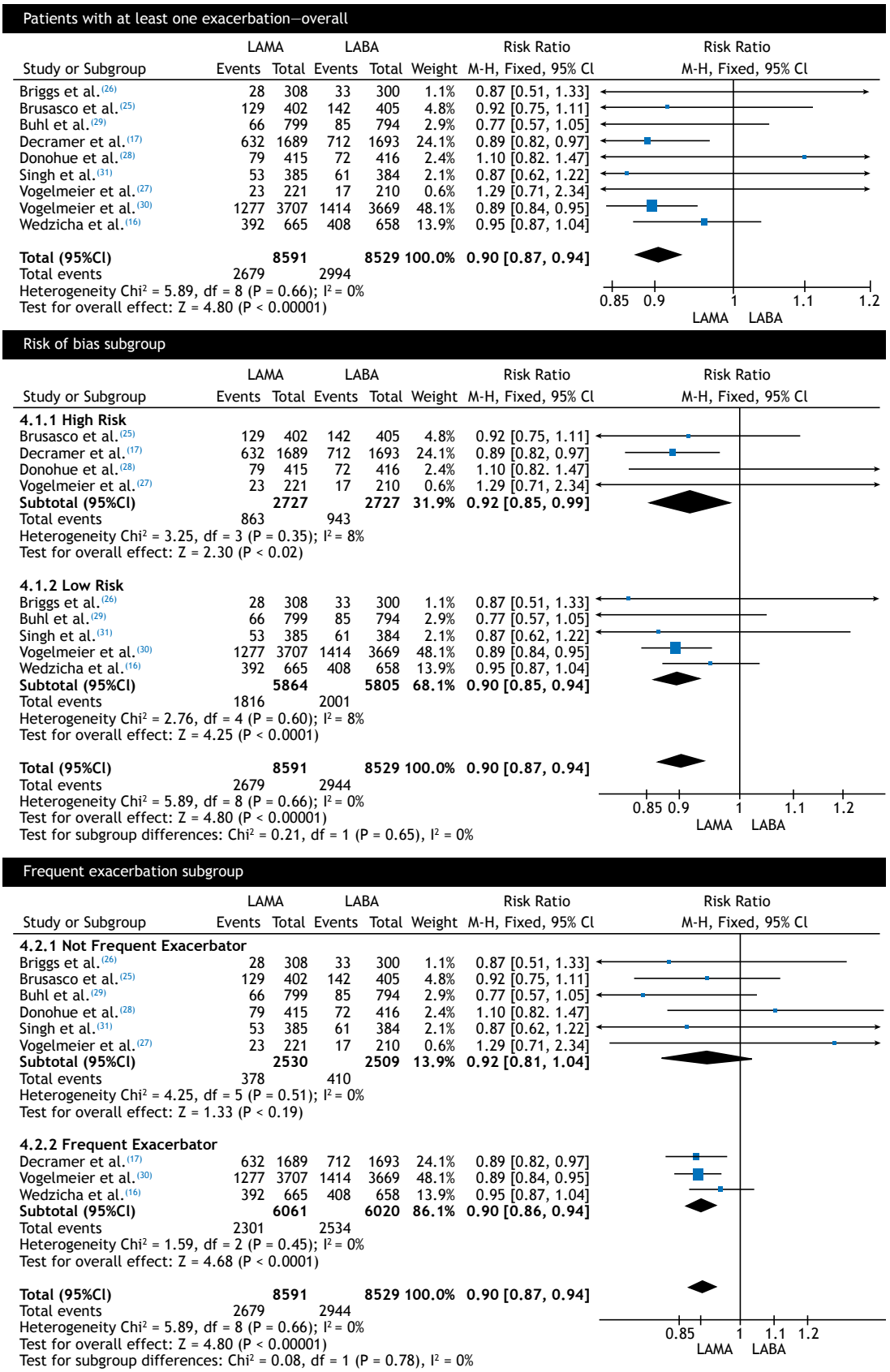

Figure 4. Proportion of patients with at least one exacerbation and subgroups.

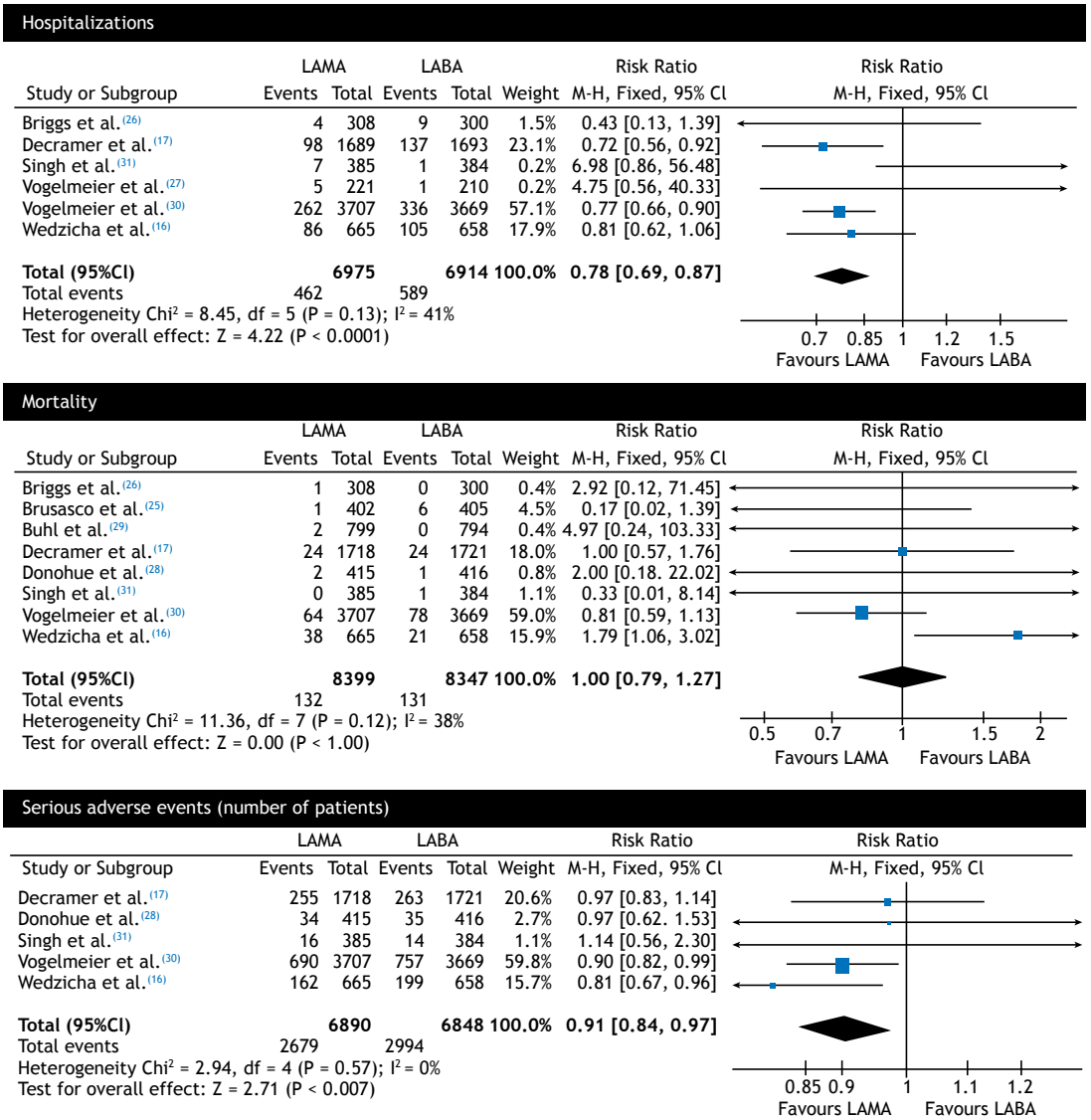

Figure 5. Secondary outcomes.

The definitions of exacerbation and exacerbation severity need to be standardized. There is a symptom-based definition that uses a complex of worsening respiratory symptoms to define exacerbation, and there is an event-based definition that requires a therapeutic intervention or a change in health care utilization.[32] The latter approach has more objective and more easily measured parameters, but it can lead to underreporting of mild exacerbation episodes,[34,41,42] which can be a source of bias, since not all of the studies included symptom diaries to report exacerbations. Blinded adjudication of exacerbation events by an adjudication committee can help classify COPD exacerbations.[43] The RCTs included here did not employ blinded adjudication, making the information reliant on individual investigators, which can be uncertain.

Exacerbation rates can be influenced by a small minority of patients who experience multiple exacerbation events. The summary statistic is the rate ratio. The best statistical approach for evaluating this ratio is a weighted approach that adjusts the ratio for asymmetry in the follow-up time, producing an unbiased estimate.[44] The authors of the studies covered by the present review used a weighted statistical approach of the exacerbation rates,[16,17,28,30] which increases the reliability of this finding.

The evaluation of outcomes in the GRADE system included exacerbation rate (moderate quality), number of people experiencing one or more exacerbations (moderate quality), and hospitalizations (moderate quality). We did not further downgrade the risk of bias, because most of the RCTs were at a low risk for that (as assessed by to the Cochrane Risk of Bias Tool), although there was some confusion in some small RCTs regarding randomization, allocation concealment, and attrition bias.

The findings of the present review are in agreement with those of a previous review[12] reporting that

LAMAs reduced the number of patients experiencing an exacerbation with a similar estimated effect. However, the exacerbation rate was not reported, whereas the present review demonstrated that the LAMA treatment reduced the exacerbation rate. Heterogeneity was found within this outcome, but it could be explained.

Considering that COPD is a chronic and prevalent disease,[5,6] decisions about which medication should be recommended must take into consideration the relatively large NNT to prevent one exacerbation. Furthermore, studies focusing on cost effectiveness are needed to guide the decision-making process in public health care systems.

The major findings of this systematic review and meta-analysis were that LAMAs, when compared with LABAs, significantly reduced the number of COPD patients experiencing exacerbation episodes, as well as the number of exacerbations per year, of exacerbation-related hospitalizations, and of severe adverse effects.

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Chest CT findings in patients with dysphagia and aspiration: a systematic review

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ABSTRACT

The objective of this systematic review was to characterize chest CT findings in patients with dysphagia and pulmonary aspiration, identifying the characteristics and the methods used. The studies were selected from among those indexed in the Brazilian Virtual Library of Health, LILACS, *Indice Bibliográfico Español de Ciencias de la Salud*, Medline, Cochrane Library, SciELO, and PubMed databases. The search was carried out between June and July of 2016. Five articles were included and reviewed, all of them carried out in the last five years, published in English, and coming from different countries. The sample size in the selected studies ranged from 43 to 56 patients, with a predominance of adult and elderly subjects. The tomographic findings in patients with dysphagia-related aspiration were varied, including bronchiectasis, bronchial wall thickening, pulmonary nodules, consolidations, pleural effusion, ground-glass attenuation, atelectasis, septal thickening, fibrosis, and air trapping. Evidence suggests that chest CT findings in patients with aspiration are diverse. In this review, it was not possible to establish a consensus that could characterize a pattern of pulmonary aspiration in patients with dysphagia, further studies of the topic being needed.

Keywords: Respiratory aspiration; Tomography, X-ray computed; Lung.

INTRODUCTION

The epidemiology of aspiration syndromes is not well described in the literature because of the lack of specificity and sensitivity markers; however, the literature indicates that 5-15% of the cases of community-acquires pneumonia are due to aspiration.[1] Lung injury caused by aspiration of saliva or food particles can often result from dysphagia.[2,3] Dysphagia can be of neurogenic, mechanical, or psychogenic origin and manifests itself through a series of signs and symptoms, such as cough, choking, and pharyngeal globus, being a major risk factor for malnutrition, dehydration, and aspiration pneumonia.[4-6]

Evaluation of dysphagia involves clinical evaluation and speech pathology assessment, as well as ancillary tests, such as videofluoroscopic swallowing study (VFSS) and fiberoptic endoscopic evaluation of swallowing (FEES), which serve to aid in the diagnosis of swallowing disorders, such as aspiration.[7-9] In contrast, chest CT is used to evaluate pulmonary lesions, being of great importance in the diagnosis of aspiration disorders, since pulmonary symptoms can be the first manifestation of aspiration.[10]

Imaging findings of aspiration are numerous and usually nonspecific, pulmonary infection being the most serious complication of aspiration.[10,11] Therefore, knowledge about the different types of pulmonary aspiration is important for drawing correlations between the clinical information and the main CT findings, including diffuse aspiration bronchiolitis, aspiration pneumonitis, aspiration pneumonia, foreign body aspiration, and exogenous lipoid pneumonia.[11] By specifically detailing the imaging findings of aspiration pneumonia, segmental or lobar airspace consolidation can be observed, which may or may not be associated with pleural effusion.[11]

Knowledge about the CT findings of aspiration is essential for establishing the diagnosis of aspiration disorders and for attempting to prevent lung injury. Here, we aimed to perform a systematic literature review of chest CT findings that characterize pulmonary aspiration in patients with dysphagia, identifying the characteristics and the methods used.

METHODS

Research strategies

This systematic review followed the recommendations of the latest version of the Cochrane Handbook for Systematic Reviews of Interventions,[12] which involve formulating the research question, finding and selecting scientific articles, and critically assessing the selected articles. The research question used was: "What chest CT image findings are diagnostic markers of aspiration in patients with dysphagia?" The review was developed by three researchers, two of whom searched for articles independently and blindly and one of whom was assigned as a reviewer, being consulted in cases of uncertainty so as to establish agreement. All of the researchers involved—two speech-language pathologists and one

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radiologist who works in thoracic radiology—have over 10years of clinical and practical experience in the study area. Studies were selected by using the following search terms: "*pneumonia aspirativa*" and "aspiration pneumonia"; "*aspiração*" and "aspiration"; "*pulmonar*" and "pulmonary"; and "*tomografia computadorizada*" and "computed tomography". These search terms were obtained from DeCS and MeSH and were used to search the Brazilian Virtual Library of Health, LILACS, *Indice Bibliográfico Español de Ciencias de la Salud*, Medline, Cochrane Library, SciELO, and PubMed online databases. The search was carried out between June and July of 2016, on the basis of the intersection of the chosen search terms.

Selection criterion

Studies in humans, written in English, Portuguese, or Spanish, regardless of the publication year, and whose title, abstract, or body of text contained any of the search terms chosen for this review were selected. Studies mentioning aspiration of food particles into the upper digestive tract and chest CT were included. Repeated studies were excluded, as were studies whose abstracts or full texts were not found in the databases consulted, review articles, dissertations, theses, case studies, and studies in which the underlying disease was tuberculosis. No search filters were applied. The article selection process is described as a flowchart in Figure 1, as recommended in the PRISMA statement.[13]

Data analysis

After the abstracts of the studies found were selected, the full texts of the articles were retrieved. After full text reading, the following data were extracted: names of the authors; year of publication; country where the study was conducted; study design; study subjects; sample size; diagnostic tests used; underlying disease; and chest CT findings, which were defined in accordance with the glossary of terms for thoracic imaging from the Fleischner Society.[14]

RESULTS

Five articles were selected for inclusion in the present systematic review, all of them carried out in the last 5 years, published in English, and coming from different countries (Italy, USA, Japan, China, and Brazil; Table 1). Sample sizes in the studies ranged from 43 to 56 patients, the predominant population being adults (19-59 years) and elderly subjects (≥ 60 years).

Most of the studies evaluated in this review had a retrospective, cross-sectional design.[15-18] The sample characteristics varied. The patients studied had laryngeal cancer,[15] acute pneumonia associated with dysphagia,[16] or chronic aspiration,[17,18] and a study of healthy subjects assessed the presence or absence of aspiration.[19] The diagnostic tests used in the studies were VFSS,[15,16,18] FEES,[15,19] bronchoscopy,[17] HRCT,[15] and conventional CT.[16-19]

The CT findings in patients with dysphagia-related aspiration were varied, including emphysema,[15] bronchiectasis,[15,16,19] bronchial wall thickening,[15,16,18,19] nodules,[15,16,18] tree-in-bud pattern,[15,19] consolidation,[15-18] pleural effusion,[15-17] ground-glass attenuation,[15,16,18] septal thickening,[15,16] cavitary lesions,[15] lymph nodes,[15] atelectasis,[16-18] bronchiolectasis,[18,19] fibrosis,[19] and air trapping.[18,19] One of the studies demonstrated a higher frequency of findings in the right lung,[17] and two found changes that were more prevalent in lower lung zones.[16,18] In the study by Simonelli et al.,[15] it was not possible to describe the proportion of findings, because they

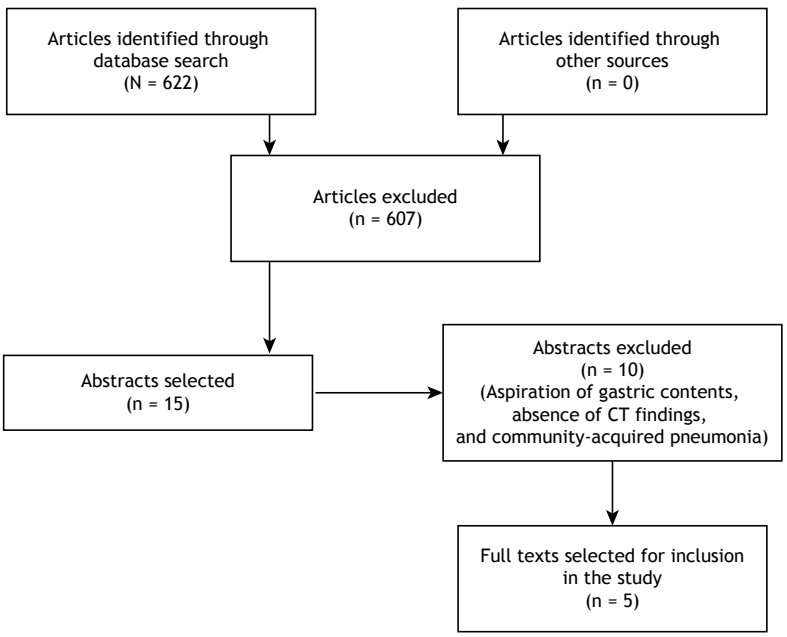

Figure 1. Article selection flowchart of the present systematic review.

Table 1. Characteristics of the selected articles.

Study	Year	Country	Population	Study design	Sample size and characteristics	Diagnostic tests used	Chest CT findings
Simonelli et al.[15]	2010	Italy	A/G	RS	45 patients after partial laryngectomy (mean age = 67 years; 92.2% men) and 45 controls (patients with COPD and normal swallowing)	FEES, VFSS, and HRCT	Emphysema; bronchiectasis; bronchial wall thickening; pulmonary nodules or cysts; tree-in-bud pattern; consolidation; pleural effusion; septal thickening; cavitary lesions; and lymph nodes
Komiya et al.[16]	2013	Japan	G	RS	53 patients admitted to the hospital with pneumonia and dysphagia (mean age = 84 years; 66% of men)	VFSS and conventional CT	Centrilobular nodules (74%); ground-glass attenuation (74%); peribronchovascular thickening (42%); airspace consolidation (34%); atelectasis (17%); septal thickening (13%); pleural effusion (13%); and traction bronchiectasis (2%)
Lin et al.[17]	2014	China	A/G	RS	43 patients with aspiration (G = 17; A = 26; mean age = 56 years; 70% of men)	Bronchoscopy and conventional CT	[a]Consolidation (93%/92%); atelectasis (14%/23%); high-density airway lesion (29%/4%); pleural effusion (0%/8%); foreign body — food particles — (21%/35%): left lung (35%/31%) and right lung (65%/69%)
Butler et al.[19]	2014	USA	G	PS	50 healthy patients divided into 2 groups: aspirators (n = 25; mean age = 77 years; 15 women) and non-aspirators (n = 25; mean age = 76 years; 16 men)	FEES and conventional CT	[b]Bronchiectasis (2%/8%); bronchiolectasis (10%/6%); bronchial wall thickening (22%/12%); parenchymal band (8%/4%); fibrosis (16%/16%); air trapping (20%/26%); intraluminal airway debris (6%/8%); and tree-in-bud pattern (6%/4%) p > 0.05 for all
Scheeren et al.[18]	2016	Brazil	A/G	RS	56 patients divided into 2 groups: non-aspirators and aspirators (n = 28 in each group; mean age = 65 years; 29 men)	VFSS and conventional CT	[b]Bronchial wall thickening (54%/53%)*; bronchiolectasis (15%/0%)**; centrilobular nodules (16%/4%)**; ground-glass attenuation (4%/0%)**; atelectasis (18%/2%)**; consolidation (6%/0%)**; and air trapping (54%/53%)* *p = 0.208; **p < 0.001

A: adult; G: geriatric: RS: retrospective study; FEES: fiberoptic endoscopic evaluation of swallowing; VFSS: videofluoroscopic swallowing study; and PS: prospective study. [a]G patients/A patients. [b]Aspirators/non-aspirators.

were reported by degree of aspiration. It is of note that, in two studies, aspirators and non-aspirators were compared.[18,19]

DISCUSSION

The selection, reading, and analysis of articles revealed that there have been few studies attempting to define a pattern of chest CT findings related to dysphagia-related pulmonary aspiration. The five articles selected in the present review were published in the last 5 years, which may explain the recent concern over early identification of patients with dysphagia who aspirate and over strategies that may intervene in the etiology. One study found a significant correlation between the degree of dysphagia and the relative risk of pneumonia, demonstrating that patients with tracheal aspiration are ten times more likely to develop pneumonia than individuals with normal swallowing.[20]

The most serious complication associated with aspiration in patients with dysphagia is pulmonary infection.[10] Studies indicate aspiration pneumonia as a cause of community-acquired pneumonia.[21,22] It is important to note that, in addition to the respiratory

complication, the swallowing disorder is a risk factor for malnutrition and functional decline.[23] Aspiration pneumonia is the leading cause of death in patients with dysphagia, a condition that affects 300,000-600,000 people per year in the USA.[1]

Simonelli et al.[15] addressed the relationship between dysphagia and aspiration in laryngectomized patients, compared with a control group of patients with COPD, and found no significant differences in radiological findings between the groups. It is currently known that patients with COPD have dysphagia symptoms related to airway protection because of changes in the breathing pattern and in the coordination of swallowing and breathing, leading to a greater likelihood of developing pneumonia.[24] It should be noted here that, of the 116 patients selected for the study,[15] only 45 had aspiration by VFSS and then underwent chest CT scans to assess the radiological manifestations of aspiration. In the two groups, the findings with the highest incidence rates were bronchial wall thickness, bronchiectasis, nodules, emphysema, consolidation, and septal thickening, with rates varying according to the degree of aspiration in the study group.

In the study by Komiya et al.,[16] the pulmonary CT findings were described in patients with an acute condition, that is, presenting with pneumonia at hospital admission, and dysphagia was confirmed by VFSS. The most frequent chest CT findings were airspace consolidation, ground-glass attenuation, centrilobular nodules, and peribronchovascular thickening. Pulmonary opacities predominated in lower or diffuse areas of the lung and were distributed posteriorly. The authors did not enroll a control group (without dysphagia/aspiration). In the study,[16] there was a predominance of elderly patients (geriatric population), among whom the risk of aspiration of oropharyngeal secretions and food particles is increased.[25] There is evidence in the literature that the frequency of dysphagia is higher in the elderly, and aspiration is an important etiologic factor leading to pneumonia in this population.[26]

One of the studies analyzed in the present review did not use ancillary tests to assess swallowing or detect dysphagia; the presence of acute aspiration of large food particles was identified solely by bronchoscopy.[17] The most prevalent chest CT findings in the study were consolidation, atelectasis, and high-density airway lesion, predominantly in the right lung and lower lobe.[17]

In the study by Butler et al.[19] aspiration status was prospectively evaluated by administering liquid boluses, and other bolus consistencies were not used, which could result in an increased number of pulmonary imaging findings. In addition, the authors did not use VFSS, which is considered the gold standard for detecting aspiration, choosing to use FEES. FEES is an exam that is performed with a nasal endoscope and allows direct observation and evaluation of laryngopharyngeal structures, as well as of swallowing; however, aspiration can only be observed after the swallow, through visualization of the presence of dyed food particles in the trachea.[27] The authors did not find significant differences in the radiological pattern between the case and control groups, the findings being bronchiectasis, bronchiolectasis, bronchial wall thickening, air trapping, and fibrosis.[19]

The most recent study addressing pulmonary findings in patients with chronic aspiration[18] included patients with and without aspiration diagnosed by VFSS who underwent chest CT. A comparison of the two groups revealed that the patients with aspiration had a higher frequency of changes such as atelectasis, centrilobular nodules, bronchiolectasis, consolidation, and ground-glass attenuation. Bronchial wall thickening and air trapping were the most prevalent findings in both groups; however, no significant differences were demonstrated. In addition, the authors reported that the findings were more prevalently distributed in lower lung zones. Figures 2 and 3 exemplify some of the CT findings described.

One of the limitations of the present systematic review was the lack of articles published on the subject,

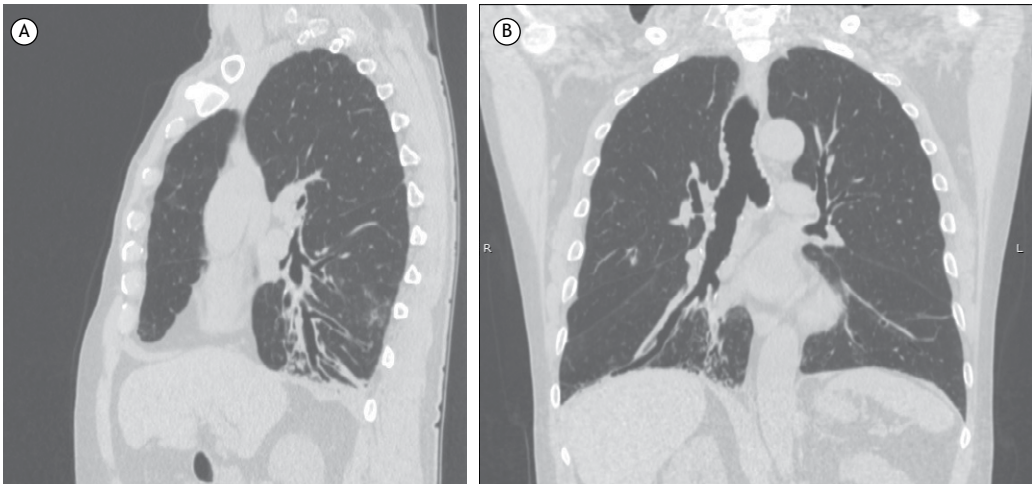

Figure 2. In A, sagittal chest CT scan demonstrating bronchiolectasis, atelectasis, and areas of ground-glass opacity in the lower lobes. In B, coronal chest CT scan demonstrating better visualization of bronchiolectasis in the right lower lobe.

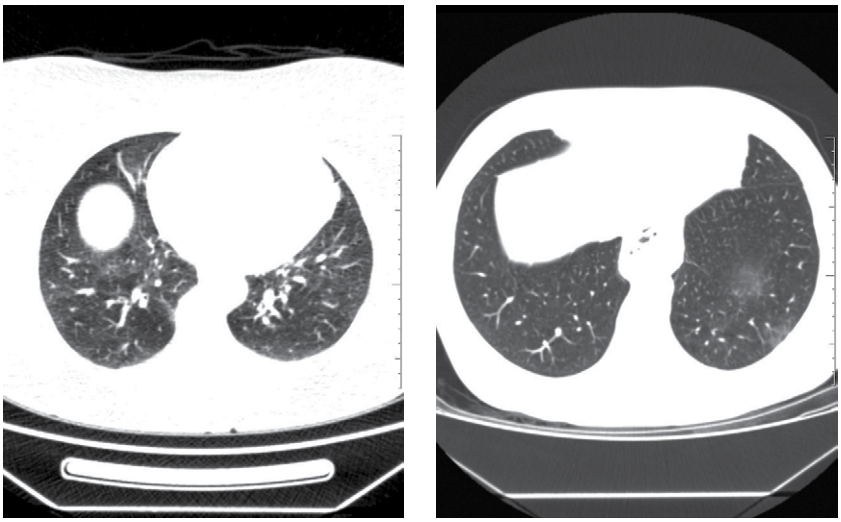

Figure 3. Axial chest CT scans showing areas of ground-glass attenuation in the left lower lobe.

as well as the varied sample characteristics. In this review, it was not possible to establish a consensus that could characterize a pattern of pulmonary aspiration in patients with dysphagia, and further studies on the subject are needed. Evidence suggests that chest CT findings in patients with aspiration are diverse; however, the articles mentioning the location of pulmonary findings detected that the findings were more prevalently distributed in the right lung and in lower lung zones.

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Multislice CT in the diagnosis of bronchopleural fistula

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

A 55-year-old man underwent right upper lobe resection after sustaining a chest injury in an automobile accident. An air leak persisted for 5 days after the surgery. On the fifteenth postoperative day, the patient was referred to our emergency ward due to respiratory difficulty. Examination confirmed that he was experiencing mild respiratory difficulty; RR was 25 breaths/min and HR was 98 bpm. Examination of the respiratory system revealed subcutaneous emphysema and the absence of pulmonary sounds in the right hemithorax. A chest X-ray showed right hydropneumothorax. A multislice CT scan confirmed this finding, and multiplanar reconstruction demonstrated the presence of a bronchopleural fistula in the anterior segment of the right lower lobe (Figure 1). Video-assisted thoracoscopic surgery and antibiotics were used in order to manage this lesion.

The persistence of bronchopleural fistulae has been documented to lead to significant morbidity and mortality.[1-3] Prolonged air leakage from these lesions is frequently observed,[1-3] and several procedures have been proposed for the treatment of this complication. Recent innovations include the use of endobronchial valves. Multislice CT may be an important tool for the precise identification of the bronchi responsible for air leakage in cases of bronchopleural fistulae.

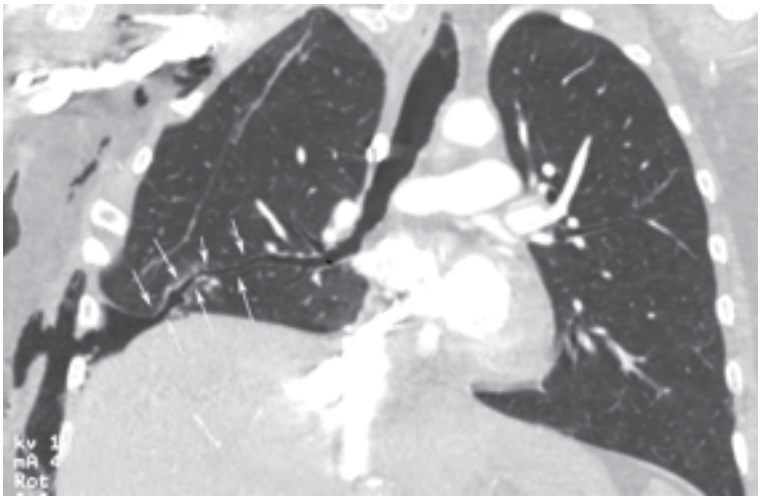

Figure 1. Curved coronal CT reconstruction showing a bronchopleural fistula in the anterior segment of the right lower lobe.

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CASE REPORT

Pulmonary foreign body granulomatosis in a chronic user of powder cocaine

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Study carried out at the Houston Methodist Lung Center, Houston (TX) USA.

ABSTRACT

We describe the case of a 33-year-old man, a chronic user of powder cocaine, who presented with dyspnea, fever, night sweats, and significant weight loss. Chest HRCT revealed centrilobular nodules, giving an initial impression of miliary tuberculosis. Therefore, he was started on an empirical, four-drug antituberculosis treatment regimen. Four weeks later, despite the tuberculosis treatment, he continued to have the same symptoms. We then performed transbronchial lung biopsy. Histopathological analysis of the biopsy sample revealed birefringent foreign body granuloma. A corroborative history of cocaine snorting, the presence of centrilobular nodules, and the foreign body-related histopathological findings led to a diagnosis of pulmonary foreign body granulomatosis. This report underscores the fact that pulmonary foreign body granulomatosis should be included in the differential diagnosis of clinical profiles resembling tuberculosis.

Keywords: Lung; Granuloma, foreign-body; Cocaine-related disorders.

INTRODUCTION

Physicians frequently encounter cocaine abuse in clinical practice. It is the leading cause of illicit drug-related deaths worldwide.[1] Cocaine is abused by multiple methods, the snorting of powder cocaine being the most common. Pulmonary complications, such as alveolitis, barotrauma, talcosis, organizing pneumonia, bullous emphysema, and pulmonary fibrosis, are frequently reported as a result of crack cocaine smoking or intravenous cocaine use.[2] However, there has been only one report to date of pulmonary foreign body granulomatosis (PFBG) secondary to cocaine snorting.[3]

CASE REPORT

A 33-year-old Hispanic male of average build was admitted to our facility, complaining of dyspnea, fever, night sweats, and rapid weight loss (18 kg over a four-month period). A pertinent positive finding on the initial history taking was his having traveled to a country where tuberculosis is endemic. Physical examination revealed no acute distress and no stigmata of intravenous drug abuse. He was febrile (≤ 38.5°C), with a blood pressure of 124/72 mmHg, a heart rate of 76 bpm, a respiratory rate of 18 breaths/min, and a constant SpO_2 at rest of 98%. The initial total leukocyte count was 8,200 cells/μL, with a predominant neutrophilic reaction. Blood culture was negative for aerobic and anaerobic microorganisms. Urine toxicology and HIV tests were negative. Chest X-ray and HRCT showed micronodules (1-3 mm in size) bilaterally in centrilobular distribution (Figure 1). An IFN-γ assay and sputum smear microscopy for acid-fast bacilli were carried out in order to rule out mycobacterial infection. Although the results were negative for tuberculosis, the high clinical suspicion of the disease prompted empirical initiation of the four-drug antituberculous therapy. Four weeks later, the patient returned to the emergency room with worsening of the shortness of breath. A repeat HRCT revealed similar centrilobular nodules with no radiological improvement (Figure 2). At that time, bronchoscopy with transbronchial lung biopsy was performed for further evaluation of the pulmonary micronodules. Examination of the BAL fluid, with Ziehl-Neelsen staining, revealed no acid-fast bacilli. Histopathological analysis of the transbronchial lung biopsy specimen showed multiple granulomas with birefringent material in the center (Figure 3), confirming the diagnosis of PFBG. The patient strongly denied intravenous drug use. Unfortunately, he experienced a progressive course with a further decline in his lung function. After progressive fibrosis over the following one-year period, the patient died of chronic respiratory failure.

DISCUSSION

The lungs are frequently affected by cocaine abuse, regardless of the delivery method. Clinical presentation and radiological findings are varied and highly nonspecific.[4] PFBG is a rare condition, and its true incidence is unknown. It is commonly encountered secondary to intravenous injection of pulverized pharmaceutical tablets containing insoluble binders, such as talc, cellulose, starch, and other street adulterants. The tiny particles lodge in the vascular bed and interstitium to cause granulomatous reactions and fibrosis.[5] Prior to this report, there had been only one reported case of PFBG in a user of powder cocaine (intranasal route), which was determined to be caused by cellulose filler.[3] Radiologically, PFBG can present as small diffuse centrilobular nodules, conglomerated masses, diffuse ground-glass opacities, and lower-lobe

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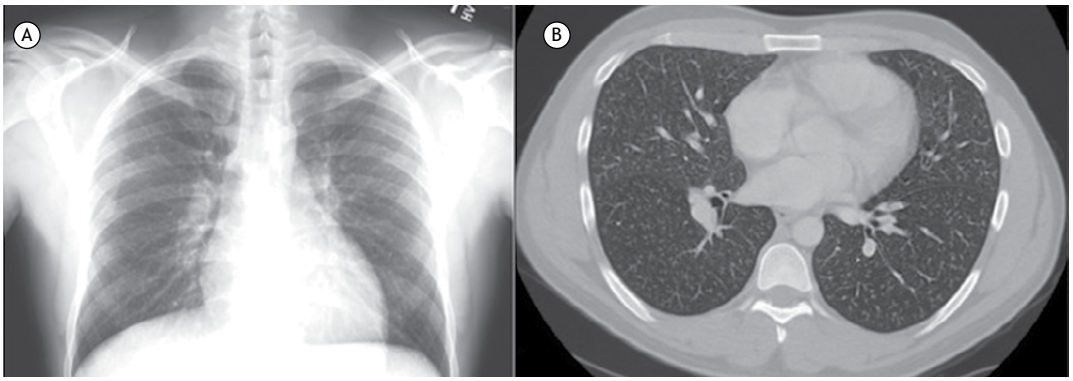

Figure 1. In A, a chest X-ray showing micronodular shadows. In B, a CT scan of the chest, showing centrilobular nodules in both lung fields.

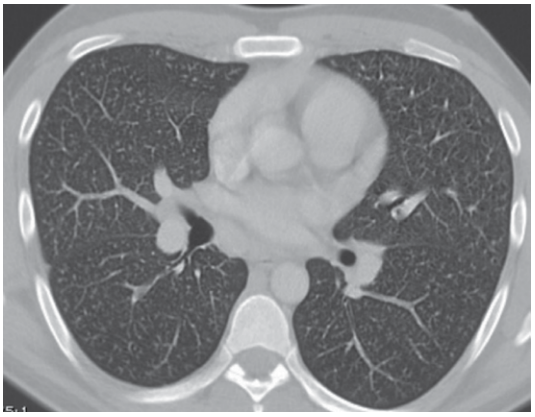

Figure 2. A CT scan of the chest showing the persistence of centrilobular nodules in bilateral lung fields after four weeks of treatment with antituberculosis drugs.

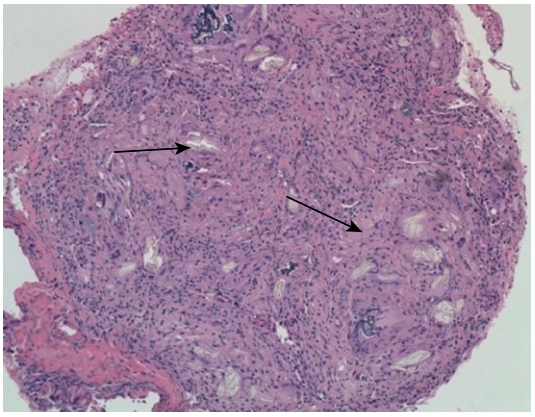

Figure 3. Photomicrograph of the transbronchial biopsy specimen (lung tissue) showing birefringent foreign body material (left arrow), together with granuloma formation (right arrow) around the foreign body material (H&E; magnification, ×40).

panlobular emphysema.[6] Because our patient was inhaling cocaine, the appearance of centrilobular nodules on chest CT was consistent with small airway disease, as opposed to miliary tuberculosis, which usually presents as random nodules. It is prudent to consider rare granulomatous conditions such as PFBG in patients with a history of intravenous or inhaled drug abuse. The course of PFBG can be subacute (with fever, weight loss, or hemoptysis) or chronic (with dyspnea and a progressive decline in lung function).[7] Late complications include pulmonary hypertension, *cor pulmonale*, panlobular emphysema, and, rarely, respiratory failure requiring lung transplantation.[8,9] There is no specific treatment for PFBG. A few patients have experienced stabilization of symptoms after cessation of drug use and resolution of acute symptoms with corticosteroid use.[10] Avoidance of exposure continues to be the cornerstone of management.

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The reversed halo sign: also think about chronic eosinophilic pneumonia

Gaetano Rea[1], Giorgia Dalpiaz[2], Alessandro Vatrella[3], Stefania Damiani[4], Edson Marchiori[5,6]

TO THE EDITOR:

The reversed halo sign (RHS) is a focal rounded or lobulated area of central ground-glass opacity surrounded by a more or less complete ring of consolidated lung tissue.[1] Although the RHS was initially described in patients with cryptogenic organizing pneumonia, various authors have demonstrated its presence in a wide spectrum of diseases (e.g., tuberculosis, invasive pulmonary aspergillosis, noninvasive fungal infections, *Pneumocystis jirovecii* pneumonia, pulmonary infarction, nonspecific interstitial pneumonia, granulomatosis with polyangiitis, sarcoidosis, lipoid pneumonia, lung adenocarcinoma, metastatic lung disease, and lymphomatoid granulomatosis); therefore, the RHS cannot be considered to be specific for cryptogenic organizing pneumonia.[2-4]

A 28-year-old nonsmoking male undergraduate with a history of allergic asthma—which had been diagnosed on the basis of clinical findings and pulmonary function test results—had been hospitalized 6 months prior because of an acute episode of cough and fever. Chest X-rays showed bilateral infiltrates in the upper and middle lung fields, and a diagnosis of bilateral pneumonia was made. The patient was treated with ceftriaxone and macrolides for 15 days. Laboratory tests revealed high eosinophil levels (13.5%) and ESR (42 mm/h), as well as normal serum IgE levels (53 IU/mL). Autoantibody testing and fecal parasitology were negative. Because of persistent dry cough and asthma, chest HRCT scans were taken 6 months later, revealing patchy bilateral areas of lobulated ground-glass opacity surrounded by crescent-shaped consolidation in the upper lobes and in the apical segment of the right lower lobe (i.e., the RHS; Figures 1A and 1B). On the basis of patient clinical history, blood eosinophilia, and HRCT findings, a presumptive diagnosis of chronic eosinophilic pneumonia (CEP) was made. A fiberoptic bronchoscopy was performed in order to confirm the diagnosis. Analysis of BAL fluid revealed a marked increase in eosinophils (25%), with mixed granulocytic/lymphocytic alveolitis (neutrophils, 10%; lymphocytes, 21%) and a normal CD4/CD8 ratio. The patient was started on corticosteroid therapy (oral

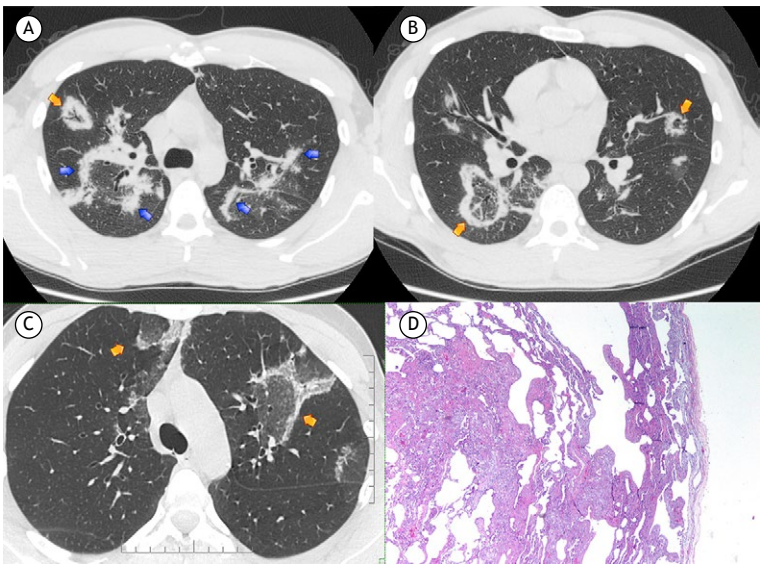

Figure 1. In A (case 1), axial HRCT scan of the chest at the level of the upper lobes showing the reversed halo sign (RHS) in the anterior segment of the right upper lobe (orange arrow), as well as bilateral peripheral and peribronchovascular consolidative opacities (band-like elements; blue arrows). In B (case 1), axial HRCT scan of the chest at the level of the lower lobes showing a well-defined lobulated RHS in the apical segment of the right lower lobe and a small RHS in the posterior segment of the left upper lobe (orange arrows). In C (case 2), axial HRCT scan of the chest at the level of the upper lobes showing the RHS in the anterior segment of the left upper lobe (orange arrow) and a slightly incomplete sign in the anterior segment of the right upper lobe (orange arrow). In D (case 2), note subpleural and septal fibrosis.

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prednisolone at a dose of 12.5 mg/day) after review of the clinical and radiological data. At this writing, he was symptom free, nearly complete resolution of pulmonary infiltrates having been reached. In a second case, a 33-year-old nonsmoking female office worker with a clinical history of surgery for an ovarian cystadenoma was hospitalized because of persistent headache, fever (38.5°C), and dry cough. A chest X-ray showed bilateral pulmonary infiltrates. The patient reported that the symptoms had started after her return from a two-week holiday in Morocco. Laboratory tests showed high eosinophil levels (32.6%), mild anemia (hemoglobin, 9.7 g/dL), and increased ESR (41 mm/h). The patient therefore underwent HRCT, which showed the RHS in the anterior segment of the left upper lobe (Figure 1C) and peripheral RHSs in both lower lobes, with thick, consolidative band-like opacities in the subpleural region on the right. Autoantibody testing, HIV testing, antineutrophil cytoplasmic antibody testing, Mantoux tuberculin skin testing, and microbiological testing were negative. All pulmonary function test results were within normal limits. A fiberoptic bronchoscopy was performed, and the results were negative. An open lung biopsy was performed to assist with diagnosis, showing septal inflammation, septal fibrosis, irregularly distributed lesions, peripheral fibrosis, and eosinophils (Figure 1D). The aforementioned pathological findings were suggestive of advanced healing of CEP. An HRCT scan taken 3 month later showed that the patient had made an almost complete recovery.

Although an uneven distribution of consolidative changes predominantly in the upper lobe has been reported in most cases of CEP, the RHS has only recently been reported in a case of CEP.[5] Given that the RHS is a nonspecific HRCT finding, patient clinical history, laboratory findings, and ancillary radiological findings should also be taken into account in order to narrow the differential diagnosis. In addition, it is useful to determine patient immune status when investigating the RHS, given that delayed diagnosis and treatment can increase mortality. Given that the RHS is a CT finding that is present in multiple diseases, a pathological specimen is needed in order to make an accurate diagnosis (as in our second case); it is equally true, however, that careful clinical and radiological evaluation through a multidisciplinary approach can be diagnostic in the presence of the RHS, without the need for biopsy.

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Pneumothorax: between the beach and the stratosphere

Eduardo Kaiser Ururahy Nunes Fonseca[1], Adham do Amaral e Castro[1], Yoshino Tamaki Sameshima[1]

TO THE EDITOR:

Thoracic ultrasound (US) is an excellent diagnostic tool that is capable of characterizing a broad spectrum of diseases, presenting therapeutic and prognostic applicabilities, even regarding intraoperative approaches.[1-3] Great advances have been made in imaging acquisition and processing, as well as in US equipment portability.[1] The US method is dynamic and highly available; ionizing radiation is absent, and it dispenses with patient transport or with the mobilization of an entire multidisciplinary team.[1,4]

Thoracic US is preferably performed by combining high-frequency linear transducers and low-frequency convex transducers (3-5 MHz) with the patient in the supine position for scanning the intercostal spaces; for the evaluation of dorsal areas, patients can be mobilized in bed.[1] In the context of trauma or unstable patients, US is an auxiliary tool in the diagnosis of pneumothorax and hemothorax.[2]

The US echo signal of the normal pleura is a hyperechoic line that slides in synchrony with breathing. From it, artifact lines can be visualized; we cite, as examples, A-lines, which are equidistant, horizontal, and parallel to the echo signal of the pleura, representing reverberation artifacts; and B-lines, which are vertical, perpendicular to the echo signal of the pleura, with the appearance of a comet tail (representing the interlobular septa), which move along with the pleural line.[1]

In the context of pneumothorax, we can mention some classical criteria for its diagnosis[1]: no visualization of the pulmonary movement with breathing, since air fills the pleural space and prevents the visualization of the movement of the pleural line; the lack of visualization of B-lines, since they emerge from the pleural line, admitting then that their presence discards the diagnosis of pneumothorax; the presence of the so-called "lung point", which represents the visualization of the aerated lung expanding at the site of pneumothorax.[1,2,5] In US M-mode, the area at the site of the pneumothorax demonstrates multiple horizontal bands of hyperechoic artifacts caused by the absence of lung movement. This appearance mimics a bar code (bar code sign) or even the stratospheric layer of Earth's atmosphere (stratosphere sign). In the normal lung, the M-mode study shows a

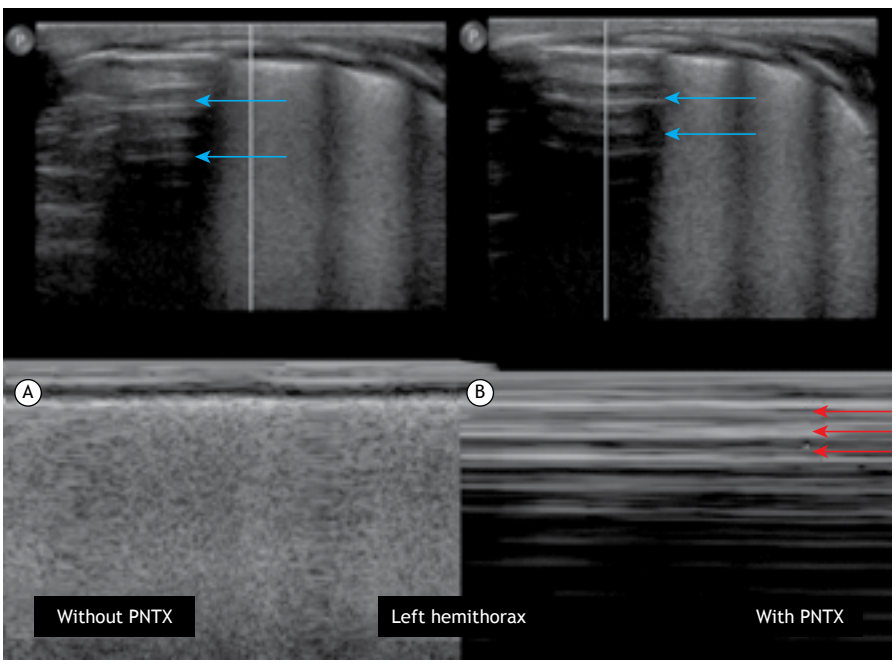

Figure 1. Pneumothorax (PNTX) in the left hemithorax: loss of normal pattern in B-mode. Note the absence of B-lines and the prominence of A-lines (blue arrows). During the examination, normal sliding between the lung pleura was no longer characterized. In M-mode, a stratosphere sign (B) is revealed, with multiple parallel lines equidistant to the echo signal of the pleura (red arrows) due to the absence of movement between the pleural surfaces due to gas interposition in the pleural space (PNTX). In M-mode, we found a pebble beach sign when examining the region of the hemithorax where there was no PNTX (A).

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movement pattern with an image similar to a beach landscape (pebble beach sign).[2]

Another classic and well-known indication of thoracic US is in the evaluation of pleural effusion, allowing the detection of contents that are not totally anechoic and which may denote a bloody or purulent component within the effusion. More than this, thoracic US has been already incorporated into the routine of thoracic drainage, avoiding various accidents that used to be inherent to that procedure.

To give an example, we report the case of a 31-week male infant (weight, 1,695 g) who presented with worsening of his respiratory condition and was submitted to US. On examination, pneumothorax was identified due to the loss of regular sliding lung signs, prominent A-lines, and absence of B-lines. In M-mode, the stratosphere sign was observed, with parallel and equidistant lines to the pleura (Figure 1). The lung point was also evidenced, representing the transition point between the region with and without pneumothorax, a finding considered to be 100% specific.[1,2] After the US diagnosis, water-seal drainage of the chest was carried out with good response.

Other uses of the thoracic US include pneumonia monitoring in order to evaluate the prognosis, risk of necrosis, and length hospital stay; fluid resuscitation protocols by means of the measurement of the dynamic variations of the vena cava diameter, especially in ICU patients; and initial evaluation of patients with respiratory distress, their evolution, and as a guidance to noninvasive alveolar recruitment maneuvers without using ionizing radiation.[3,4] Thoracic US is also a well-established method in the fluid administration limited by lung sonography (FALLS) protocol and in the bedside lung ultrasound in emergency (BLUE) protocol,[3,5] in which US is the central method and the definitive discriminator among the various types of shock. Besides pulmonary evaluation, thoracic US can also be used in the evaluation of the entire thoracic framework, showing excellent accuracy in identifying possible rib fractures, and as a tool for a brief overall assessment of the heart.

It is always important to highlight the fact that US offers a differential that few other imaging methods present: it is innocuous and dynamic; it can be done at bedside; and it avoids patient transport and its inherent risks. Most importantly, however, is the fact that there is no ionizing radiation, which allows it to be used as a control method with very few restrictions.

In summary, thoracic US is very advantageous and shows high accuracy in diagnosing pneumothorax; therefore, its use should be stimulated.

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Publication: J Bras Pneumol. 2017;43(1):4-4.

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