ISSN 1806-3713

JBP
Jornal Brasileiro de Pneumologia
PUBLICAÇÃO OFICIAL DA SOCIEDADE BRASILEIRA DE PNEUMOLOGIA E TISIOLOGIA

Volume 46, Number 3
May | June
2020

Volume 46, Number 3 May | June 2020

HIGHLIGHT

Severe asthma: characterization of a sample in Brazil

Reference values for spirometry in Brazilian children

Palliative care in pulmonary medicine

omnaris®
ciclesonida

O único CTN* hipotônico.[1-5]

Alívio rápido e sustentado.[1-5]

1 hora
de início de ação[2]

1 dia inteiro
de controle de sintomas[3,4]

1 ano
de alívio sustentado[5]

Indicado para crianças acima de 6 anos e adultos

Recomenda-se duas doses (jatos) em cada narina uma vez ao dia[6]

Referências: *Corticosteroide tópico nasal - 1. Meltzer EO. Ann Allergy Asthma Immunol 2007; 98: 12-21. - 2. Patel P et al. ENT J. 2008; 87: 340-353. - 3. Meltzer EO et al. Ann Allergy Asthma Immunol 2007; 98: 175-181. - 4. Ratner PH et al. J Allergy Clin Immunol 2006; 118: 1142-1148. - 5. Chervinsky P et al. Ann Allergy Asthma Immunol 2007; 99: 69-76. - 6. Bula do Produto Omnaris, Data de acesso das informações: 2019.

OMNARIS® (ciclesonida) 1.1618.0265 INDICAÇÕES: Omnaris® é indicado para o tratamento de sintomas de rinite alérgica intermitente ou persistente, incluindo congestão nasal, coriza, prurido e espirros. CONTRAINDICAÇÕES: Omnaris® é contraindicado em pacientes com hipersensibilidade a qualquer dos seus componentes. Omnaris® não deve ser usado no caso de haver uma infecção nasal não-tratada. ADVERTÊNCIAS E PRECAUÇÕES: Raramente podem ocorrer reações imediatas de hipersensibilidade ou dermatite de contato após a administração de corticosteroides intranasais. Os pacientes com reação de hipersensibilidade conhecida a outros preparados de corticosteroides devem tomar cuidado quando usarem spray nasal de ciclesonida, pois pode ocorrer reação cruzada com outros corticosteroides. Pacientes em tratamento com medicamentos supressores do sistema imune são mais suscetíveis a infecções do que os indivíduos sadios. Varicela e sarampo, por exemplo, podem ter um curso mais grave ou até mesmo fatal em crianças ou adultos usuários de corticosteroides. Em crianças ou adultos que não tenham tido estas doenças ou não tenham sido adequadamente imunizadas, deve-se tomar cuidado particular para evitar sua exposição. Em caso de exposição a varicela ou a sarampo, o paciente deve procurar orientação médica adequada para tratamento profilático. Os corticosteroides intranasais devem ser administrados com cuidado principalmente a pacientes com infecções por tuberculose ativa ou inativa do trato respiratório, com infecções fúngicas ou bacterianas, locais ou sistêmicas, com infecções virais ou parasitárias sistêmicas ou com *Herpes simplex* ocular devido ao potencial de piora dessas infecções. Efeitos nasais locais: Ocorreram casos raros de perfuração do septo nasal em pacientes que administraram ciclesonida pela via intranasal. Por causa do efeito inibitório dos corticosteroides sobre a cicatrização de ferimentos, pacientes que tenham tido recentes úlceras no septo nasal ou sofrido cirurgia nasal ou trauma nasal não devem usar um corticosteroide nasal até que tenha ocorrido a cicatrização. Em estudos clínicos com Omnaris®, foi raro o desenvolvimento de infecções localizadas por *Candida albicans* no nariz e na faringe. Quando tal infecção surge, ela pode exigir tratamento com terapia local apropriada e descontinuação de Omnaris®. Portanto, pacientes em tratamento com Omnaris® por vários meses ou por um período mais longo devem ser examinados periodicamente quanto à evidência de infecção por *Candida* ou outros sinais de efeitos adversos sobre a mucosa nasal. Efeitos sistêmicos: Doses de Omnaris® maiores que as recomendadas devem ser evitadas. Quando usados em doses excessivas, efeitos corticoides sistêmicos podem ocorrer, como hipercorticismo e supressão adrenal, retardo de crescimento em crianças e adolescentes, diminuição na densidade mineral dos ossos, catarata e glaucoma. Se tais alterações ocorrerem, a dose de Omnaris® deve ser descontinuada devagar, consistente com os procedimentos aceitos para a descontinuação de terapia corticoide oral. Gravidez e lactação: A experiência com corticosteroides orais desde a sua introdução demonstra que, pelo fato de haver um aumento natural na produção de corticosteroides durante a gestação, a maioria das mulheres precisará de uma dose exógena de corticosteroide menor. Muitas nem precisarão de tratamento com corticosteroides durante a gestação. Categoria C de Risco na Gravidez – não existem estudos clínicos bem controlados em gestantes. Tal como acontece com outros corticosteroides, a ciclesonida deve ser administrada durante a gravidez somente se o benefício potencial para a mãe justificar o risco potencial para a mãe, o feto ou o bebê. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista. Não se sabe se a ciclesonida é excretada no leite humano. Entretanto, outros corticosteroides são excretados no leite humano. Deve-se tomar cuidado se Omnaris® for administrado a lactantes. Omnaris® só deve ser administrado quando o benefício para a mãe que estiver amamentando for considerado maior que o risco potencial para a mãe e/ou criança. Efeitos não-teratogênicos: Pode ocorrer hipoadrenalismo em bebês nascidos de mães que tenham recebido corticosteroides durante a gestação. Pacientes pediátricos: Estudos clínicos controlados demonstraram que os corticosteroides intranasais podem causar redução na velocidade de crescimento de pacientes pediátricos. Os potenciais efeitos sobre o crescimento do tratamento prolongado devem ser ponderados com os benefícios clínicos obtidos e a disponibilidade de tratamentos seguros e efetivos alternativos aos corticosteroides. Pacientes idosos: Os estudos clínicos de Omnaris® não incluíram um número suficiente de indivíduos com 65 anos de idade ou mais para determinar se eles respondem de maneira diferente dos indivíduos mais jovens. Em geral, a seleção da dose para um paciente idoso deve ser cuidadosa, normalmente começando na extremidade inferior da faixa de dosagem, considerando a maior frequência de diminuição da função hepática, renal ou cardíaca e de doenças concomitantes ou aplicação de outras terapias. INTERAÇÕES MEDICAMENTOSAS: Em um estudo de interação medicamentosa, a coadministração de ciclesonida inalada por via oral e de cetoconazol oral, um potente inibidor do citocromo P450 3A4, aumentou a exposição (AUC) da des-ciclesonida em aproximadamente 3,6 vezes no equilíbrio dinâmico (*steady state*), enquanto os níveis de ciclesonida permaneceram inalterados. Portanto, cetoconazol deve ser administrado com cuidado com ciclesonida intranasal. Não se verificaram interações de Omnaris® com a alimentação. POSOLOGIA: Para crianças acima de seis anos de idade e adultos recomendam-se duas doses (jatos) em cada narina uma vez ao dia (50 mcg por jato; total 200 mcg por dia). Não se devem aplicar mais de duas doses (jatos) em cada narina diariamente. Omnaris® deve ser administrado exclusivamente pela via intranasal. A dose máxima diária recomendada é de 200 mcg por dia. A duração do tratamento dependerá da resposta ao uso da medicação e deve ser estabelecida pelo médico. REAÇÕES ADVERSAS: As reações adversas mais comuns que podem ocorrer durante o uso prolongado de Omnaris® são dor de cabeça, sangramento no nariz e infecções das vias aéreas superiores. Reações comuns (> 1/100 e < 1/10): Respiratórias – sangramento do nariz (8,4%), irritação da mucosa do nariz (4,3%); Sistema nervoso – dor de cabeça (1,6%). Reações incomuns (> 1/1.000 e < 1/100): Gastrintestinais – boca seca (0,2%), dispepsia (0,2%); Infecções – candidíase (0,2%), rinite (0,2%); Respiratórias – ressecamento nasal (0,4%), dor na garganta (0,4%), secreção nasal (0,3%,), irritação na garganta (0,2%); Outras – transtorno do paladar (0,2%), aumento do número de leucócitos (0,3%). Reações com frequência não conhecida (frequência não pode ser estimada a partir dos dados disponíveis): Perfuração do septo nasal. VENDA SOB PRESCRIÇÃO MÉDICA.

Contraindicações: Omnaris® é contraindicado em pacientes com hipersensibilidade a qualquer dos seus componentes. Omnaris® não deve ser usado no caso de haver uma infecção nasal não-tratada. **Interações medicamentosas:** Em um estudo de interação medicamentosa, a coadministração de ciclesonida inalada por via oral e de cetoconazol oral, um potente inibidor do citocromo P450 3A4, aumentou a exposição (AUC) da des-ciclesonida em aproximadamente 3,6 vezes no equilíbrio dinâmico (steady state), enquanto os níveis de ciclesonida permaneceram inalterados. Portanto, cetoconazol deve ser administrado com cuidado com ciclesonida intranasal.

COVIS PHARMA

Material exclusivo de uso do representante comercial
para promoção junto a profissionais de saúde habilitados
a prescrever e/ou dispensar medicamentos.
MP 05.2020 - Junho 2020.

moksha8

ISSN 1806-3713

Continuous and Bimonthly Publication, J Bras Pneumol. v. 46, n. 3, May/June 2020

ISSN 1806-3713

JBP
Jornal Brasileiro de Pneumologia

Expediente

BRAZILIAN THORACIC SOCIETY

Office: SCS Quadra 01, Bloco K, Asa Sul, salas 203/204. Edifício Denasa, CEP 70398-900, Brasília, DF, Brazil. Tel. +55 61 3245-1030/+55 0800 616218. Website: www.sbpt.org.br.
E-mail: sbpt@sbpt.org.br

The Brazilian Journal of Pulmonology (ISSN 1806-3713) is published once every two months by the Brazilian Thoracic Society (BTS). The statements and opinions contained in the editorials and articles in this Journal are solely those of the authors thereof and not of the Journal's Editor-in-Chief, peer reviewers, the BTS, its officers, regents, members, or employees. Permission is granted to reproduce any figure, table, or other material published in the Journal provided that the source for any of these is credited.

ADMINISTRATIVE SECRETARIAT OF THE BRAZILIAN JOURNAL OF PULMONOLOGY
Address: SCS Quadra 01, Bloco K, Asa Sul, salas 203/204. Edifício Denasa, CEP 70398-900, Brasília, DF, Brazil. Tel. +55 61 3245-1030/+55 0800 616218.
Assistant Managing Editor: Luana Maria Bernardes Campos.
E-mail: jbp@jbp.org.br | jbp@sbpt.org.br
Circulation: 4.000 copies
Distribution: Free to members of the BTS and libraries
Printed on acid-free paper

SUPPORT:
CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico
CAPES
Ministério da Educação
Ministério da Ciência, Tecnologia e Inovação
GOVERNO FEDERAL BRASIL PAÍS RICO É PAÍS SEM POBREZA

ISSN 1806-3713

Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 46, n. 3, May/June 2020

Contents

ISSN 1806-3713

Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 46, n. 3, May/June 2020

Contents

J Bras Pneumol. 2020;46(3):e20200216
https://dx.doi.org/10.36416/1806-3756/e20200216

EDITORIAL

COVID-19: what have we learned?

Yeh-Li Ho[1], Anna Miethke-Morais[2]

In December of 2019, a number of cases of pneumonia of unknown etiology were reported in China, in the city of Wuhan (Hubei province). On January 7, 2020, confirmation was provided that the cases had been caused by a new coronavirus, which was later named SARS-CoV-2, and the disease was designated coronavirus disease 2019 (COVID-19).[1] Four months later, the disease had been detected in more than 185 countries, affecting almost three million people and accounting for more than 200,000 lives lost.[2]

The exponential escalation in the number of cases led governments around the world to adopt policies to restrict social movement with the aim of reducing the rate of transmission, expressed as the basic reproduction number (R_0), of COVID-19, that is, the number of secondary cases resulting from an infected individual. The R_0 value of an infectious agent is dependent on the characteristics of the disease—time from transmission to the onset of symptoms, duration of transmissibility, and forms of transmission—and, in respiratory infections, on population density and cultural behavior. Studies using mathematical models found that there was a reduction in the R_0 after the city of Wuhan was quarantined and social movement was restricted.[3]

It is of note that social distancing aims to reduce human-to-human transmission, consequently flattening the curve of cases; however, as long as the virus is circulating in the community, social distancing alone does not prevent disease transmission. Nevertheless, social distancing is important because it gives health care systems time to prepare to provide sufficient, appropriate care for patients. Mathematical models developed for the metropolitan area of São Paulo, Brazil, using a mean R_0 value and the proportion of ICU patients then available in the literature, estimated that, within the first 30 days after confirmation of the first case, there would be a demand for approximately 5,300 ICU beds; that is, a demand 130 percent above the actual capacity of the area (study submitted for publication). Similar data were reported for other countries, underscoring the importance of social distancing in reducing the lethality of COVID-19.[4,5]

To increase the capacity of the public health care system to care for patients with COVID-19, officials at various levels of government have implemented measures such as opening field hospitals, increasing the number of ICU beds, and partnering with private hospitals. In the city of São Paulo, for instance, the University of São Paulo School of Medicine *Hospital das Clínicas*—which is the largest public hospital in Latin America and receives highly complex cases—became one of the referral hospitals for the care of critically ill patients with COVID-19, its largest division, the Central Institute, which has 900 beds, being devoted exclusively to the care of such patients. The number of ICU beds has been doubled, to 200.

The high demand for hospital beds results from the difference between COVID-19 and other acute viral respiratory diseases. In patients infected with influenza A(H1N1)pdm09 virus, the course of the infection is short, some patients requiring hospitalization in the first days of illness and most hospital stays being relatively short.[6,7] In patients infected with the SARS-CoV-2 virus, the infection leads to delayed clinical deterioration and most hospital stays are prolonged.[8,9] These characteristics result in the need for longer outpatient monitoring—especially among patients in high-risk groups—and in slower turnover of hospital beds. These factors can contribute to increasing lethality because of the lack of hospital support. There are also certain clinical aspects of COVID-19 that differ from those of other viral respiratory diseases. Worthy of note are the low frequency of upper respiratory symptoms, together with the persistent fever and myalgia, as well as the high frequency of anosmia, with or without ageusia.[10,11]

Despite the clinical differences between COVID-19 and other viral respiratory diseases, confirmation of SARS-CoV-2 as the etiologic agent is dependent on molecular biology techniques, the sensitivity of which varies according to the timing of sample collection and the biological material analyzed.[12] Wang et al.[13] reported that nasopharyngeal swab sampling, the method most widely employed to confirm the diagnosis, has a sensitivity of 63%, compared with only 31% for oropharyngeal swab sampling. In addition, the performance of serological tests varies according to the severity of disease and the timing of sample collection, which limits their utility at the time of hospital admission.[14] In view of this scenario and the risk of exposure for health care workers, various recommendations rapidly emerged in the literature regarding diagnostic aids, supportive therapies (especially in the context of intensive care), and specific antiviral therapies.

Among the auxiliary diagnostic tools, chest CT detection of lung abnormalities, with findings of diffuse ground-glass infiltrates, was the first strategy adopted. However, it is important to bear in mind that various other conditions can lead to this radiological finding, including other viral pulmonary infections, such as influenza.[15] Another recommendation from various medical societies is that support strategies for acute respiratory failure should

1. Divisão de Moléstias Infecciosas e Parasitárias, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Gestão Assistencial Corporativa, Diretoria Clínica, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

be used. The recommendation for early orotracheal intubation to reduce the risk of exposure for health care workers was widely disseminated. However, it should be borne in mind that this measure may lead to the unnecessary intubation of patients with etiologic diagnoses other than SARS-CoV-2. In addition, patients are exposed to the risks and complications of long-term sedation and mechanical ventilation. Recent studies have shown that the use of strategies such as high-flow nasal cannula oxygen therapy and noninvasive ventilation results in shorter viral particle dispersion distances in comparison with the use of conventional nasal cannula oxygen therapy.[16,17]

Therapeutic and antiviral strategies, especially the use of convalescent plasma collected from patients who have recovered from COVID-19, prophylactic or therapeutic anticoagulant therapy, and the use of antiviral drugs, also emerged rapidly in the literature. However, at this writing, no strategy is supported by sufficient scientific evidence to justify its inclusion in routine daily practice. It is in this regard that we, physicians, need to be careful in our decisions, always bearing in mind that we may put our patients at risk of complications. The off-label use of a therapeutic strategy is reserved for life-threatening situations. Patients and their families need to be aware if there is a lack of evidence of efficacy of such strategies. It is up to researchers to maintain high standards of scientific rigor when designing and conducting research on COVID-19, as well as when disseminating the results of studies related to COVID-19, thereby preventing errors of interpretation by the medical community and the lay public.[18,19]

REFERENCES

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern [published correction appears in Lancet. 2020 Jan 29]. Lancet. 2020;395(10223):470-473. https://doi.org/10.1016/S0140-6736(20)30185-9
2. Johns Hopkins University. Center for Systems Science and Engineering (CSSE) [homepage on the Internet]. Baltimore MD: CSSE; c2020 [cited 2020 Apr 26]. COVID-19 Dashboard. Available from: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html/bda7594740fd40299423467b48e9ecf6
3. Zhu Y, Chen YQ. On a Statistical Transmission Model in Analysis of the Early Phase of COVID-19 Outbreak [published online ahead of print, 2020 Apr 2]. Stat Biosci. 2020;1-17. https://doi.org/10.1007/s12561-020-09277-0
4. Demographic science aids in understanding the spread and fatality rates of COVID-19 [published online ahead of print, 2020 Apr 16]. Proc Natl Acad Sci U S A. 2020;202004911. https://doi.org/10.1073/pnas.2004911117
5. Tuite AR, Fisman DN, Greer AL. Mathematical modelling of COVID-19 transmission and mitigation strategies in the population of Ontario, Canada [published online ahead of print, 2020 Apr 8]. CMAJ. 2020;cmaj.200476. https://doi.org/10.1503/cmaj.200476
6. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. N Engl J Med. 2009;361(20):1935-1944. https://doi.org/10.1056/NEJMoa0906695
7. Bassetti M, Parisini A, Calzi A, Bobbio Pallavicini FM, Cassola G, Artioli S, et al. Risk factors for severe complications of the novel influenza A (H1N1): analysis of patients hospitalized in Italy. Clin Microbiol Infect. 2011;17(2):247-250. https://doi.org/10.1111/j.1469-0691.2010.03275.x
8. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-1720. https://doi.org/10.1056/NEJMoa2002032
9. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy [published online ahead of print, 2020 Apr 6]. JAMA. 2020;323(16):1574-1581. https://doi.org/10.1001/jama.2020.5394
10. Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis [published online ahead of print, 2020 Apr 10]. J Infect. 2020;S0163-4453(20)30170-5. https://doi.org/10.1016/j.jinf.2020.03.041
11. Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms [published online ahead of print, 2020 Apr 12]. Int Forum Allergy Rhinol. 2020;10.1002/alr.22579. https://doi.org/10.1002/alr.22579
12. Tahamtan A, Ardebili A. Real-time RT-PCR in COVID-19 detection: issues affecting the results. Expert Rev Mol Diagn. 2020;20(5):453-454. https://doi.org/10.1080/14737159.2020.1757437
13. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens [published online ahead of print, 2020 Mar 11]. JAMA. 2020;e203786. https://doi.org/10.1001/jama.2020.3786
14. Xiang F, Wang X, He X, Peng Z, Yang B, Zhang J, et al. Detection and Dynamic Characteristics in Patients with COVID-19 [published online ahead of print, 2020 Apr 19]. Clin Infect Dis. 2020;ciaa461.
15. Coppola M, Porto A, De Santo D, De Fronzo S, Grassi R, Rotondo A. Influenza A virus: radiological and clinical findings of patients hospitalised for pandemic H1N1 influenza. Radiol Med. 2011;116(5):706-719. https://doi.org/10.1007/s11547-011-0622-0
16. Li J, Fink JB, Ehrmann S. High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion [published online ahead of print, 2020 Apr 16]. Eur Respir J. 2020;2000892. https://doi.org/10.1183/13993003.00892-2020
17. Ferioli M, Cisternino C, Leo V, Pisani L, Palange P, Nava S. Protecting healthcare workers from SARS-CoV-2 infection: practical indications. Eur Respir Rev. 2020;29(155):200068. https://doi.org/10.1183/16000617.0068-2020
18. Kalil AC. Treating COVID-19-Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics [published online ahead of print, 2020 Mar 24]. JAMA. 2020;10.1001/jama.2020.4742. https://doi.org/10.1001/jama.2020.4742
19. Habibi R, Burci GL, de Campos TC, Chirwa D, Cinà M, Dagron S, et al. Do not violate the International Health Regulations during the COVID-19 outbreak. Lancet. 2020;395(10225):664-666. https://doi.org/10.1016/S0140-6736(20)30373-1

J Bras Pneumol. 2020;46(3):e20200191
https://dx.doi.org/10.36416/1806-3756/e20200191

Yes, there really are individuals with severe asthma: the importance and limitations of data obtained from specialized centers

Vanessa Carvalho do Lago[1], Simone Alves do Vale[1], Irma de Godoy[1]

Asthma is a chronic disease that affects approximately 300 million people worldwide, with a prevalence of 1-16%. Despite a downward trend, asthma mortality in Brazil is high; between 1980 and 2012, asthma was responsible for approximately 2,339 deaths annually.[1] Lack of asthma control affects patient quality of life significantly and overburdens health care systems worldwide.[2] Therefore, lines of care that are organized and targeted at patients with asthma, especially those with severe forms of the disease, are essential.

Between 3% and 10% of adults with asthma have the severe form of the disease, defined as that which requires treatment with a high-dose inhaled corticosteroid combined with a second drug to prevent it from being uncontrolled or which remains uncontrolled despite optimal treatment in accordance with the European Respiratory Society/American Thoracic Society guidelines.[3] In Brazil, the number of patients with severe asthma and their characteristics remain unknown.

New forms of treatment, including the use of biologic agents, have revolutionized the outcomes of severe asthma in highly selected patients with defined phenotypes. However, the use of such therapies, which are not yet available via the Brazilian public health care system, requires that the treatment of individuals with asthma be organized to allow a structured diagnostic assessment, determination of disease severity/phenotype, access to a multidisciplinary team, and well-designed models of care.

In an article published in this issue of the *Jornal Brasileiro de Pneumologia*, Alves et al.[4] describe the clinical characteristics and factors associated with greater asthma severity in a sample of patients followed in the Bahia State Program for the Control of Asthma and Allergic Rhinitis, in the city of Salvador, Brazil. In this cross-sectional study, the authors included 473 adults with asthma who were systematically reevaluated between 2013 and 2015. The study used an appropriate methodology, validated questionnaires being administered in order to assess treatment adherence and quality of life. In the aforementioned sample, 88 patients (18%) met the criteria for severe asthma in accordance with the European Respiratory Society/American Thoracic Society guidelines.[3] The results showed that there was a predominance of women (87%), of overweight/obese patients, of patients with symptoms of chronic rhinitis, and of patients with symptoms of gastroesophageal reflux. Worthy of note are the absence of active smokers and the high proportion of patients that were adherent to treatment (77%), as well as of those who used their inhalers correctly. An increased number of eosinophils was associated with a 42% lower chance of severe asthma. There were no reports of oral corticosteroid use at the time of assessment, although most of the patients (71%) showed a lack of asthma control and impaired quality of life.

Diagnosing patients with severe asthma can be challenging. For example, it can be hard to distinguish between difficult-to-treat asthma and treatment-refractory asthma. Alves et al.[4] also demonstrated the importance of diagnosing and treating modifiable associated factors, such as obesity and gastroesophageal reflux disease, which increase the burden of disease and were common in the population studied. Other key elements in severe asthma include vocal cord dysfunction/breathing pattern disorder (a respiratory condition characterized by abnormal breathing and dyspnea that can occur in the absence of identifiable diseases) and sleep apnea, neither of which were addressed in the Alves et al. study.[4] Those elements are usually associated with the inappropriate use of medications and should be included in the diagnostic protocol for and assessment of severe asthma.[5]

Determination of blood eosinophil numbers and assessment of airway inflammation (measurement of sputum eosinophils and of exhaled nitric oxide), as well as assessment of small airway function, are unavailable in most health care facilities in Brazil. There is a need to develop recommendations regarding which measures are a priority (i.e., are essential in the management of patients with severe asthma). Patient care models should prioritize patient outcomes, the pursuit of equity, and the provision of adequate care to patients in all regions of the country.

We recommend caution in interpreting the results of the Alves et al. study.[4] The study was conducted at a single, specialized referral center for the treatment of patients with difficult-to-treat asthma. Therefore, it does not represent the majority of health care facilities where individuals with asthma are treated. Although most of the findings are in agreement with those described in the literature, some data require careful consideration. The proportion of individuals with severe asthma in the study sample, for instance, was much higher than that reported in the 2019 update of the Global Initiative for Asthma for patients with good treatment adherence and good inhaler technique (3.7%).[6]

In the management of individuals with asthma, it is essential to rule out problems related to treatment adherence and inhaler use before classifying an individual as having severe asthma.[6] The high rates of treatment adherence and correct inhaler use observed in the study conducted by Alves et al.[4] reveal the positive impact of

1. Departamento de Clínica Médica, Disciplina de Pneumologia, Universidade Estadual Paulista, Faculdade de Medicina de Botucatu, Botucatu (SP) Brasil.

continuing education provided by a good multidisciplinary team. Such results should constantly be pursued in the treatment of individuals with asthma at all levels of health care.[7,8] Alves et al.[4] reported that the rate of self-reported treatment adherence was 77%, compared with a rate of 57% based on data obtained from pharmacy records. That finding indicates that, during some periods, patients have to pay the costs of treatment because of drug shortages at public facilities, which makes treatment adherence difficult, given that the costs of managing severe asthma may account for as much as 24% of the budget of vulnerable families.[9]

Another factor associated with asthma severity is active smoking, which also negatively affects asthma control and the efficacy of the proposed therapy. Therefore, all patients with asthma of any severity should be included in smoking cessation programs.

In summary, data from specialized asthma treatment centers are essential for the dissemination of knowledge about the characteristics of individuals with severe asthma. Such data underscore the fact that, at facilities treating individuals with asthma, at all levels of care, it is necessary to carry out basic general assessments, monitor inhaler use, and determine treatment adherence, as well as to rule out exposure to allergens and treat comorbidities. Patients with a working diagnosis of severe asthma should be referred to centers that have the appropriate instruments to manage the disease; that is, to referral centers.[10]

REFERENCES

1. Brito TS, Luiz RR, Silva JRLE, Campos HDS. Asthma mortality in Brazil, 1980-2012: a regional perspective. J Bras Pneumol. 2018;44(5):354-360. https://doi.org/10.1590/s1806-37562017000000235
2. Cardoso TA, Roncada C, Silva ERD, Pinto LA, Jones MH, Stein RT, et al. The impact of asthma in Brazil: a longitudinal analysis of data from a Brazilian national database system. J Bras Pneumol. 2017;43(3):163-168. https://doi.org/10.1590/s1806-37562016000000352
3. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma [published correction appears in Eur Respir J. 2014 Apr;43(4):1216. Dosage error in article text] [published correction appears in Eur Respir J. 2018 Jul 27;52(1):]. Eur Respir J. 2014;43(2):343-373.
4. Alves AM, Mello LM, Matos ASL, Cruz ÁA. Clinical features and associated factors with severe asthma in Salvador, Brazil. J Bras Pneumol. 2020;46(3):e20180341.
5. McDonald VM, Gibson PG. Treatable traits and their application in high-, middle- and low-income countries. Respirology. 2019;24(10):942-943. https://doi.org/10.1111/resp.13626
6. Global Initiative for Asthma [homepage on the Internet]. Bethesda: Global Initiative for Asthma; [cited 2020 Apr 1]. Global Strategy for Asthma Management and Prevention (2019 update). Available from: http://www.ginasthma.org
7. Marchioro J, Gazzotti MR, Nascimento OA, Montealegre F, Fish J, Jardim JR. Level of asthma control and its relationship with medication use in asthma patients in Brazil. J Bras Pneumol. 2014;40(5):487-494. https://doi.org/10.1590/S1806-37132014000500004
8. Israel E, Reddel HK. Severe and Difficult-to-Treat Asthma in Adults. N Engl J Med. 2017;377(10):965-976. https://doi.org/10.1056/NEJMra1608969
9. Costa E, Caetano R, Werneck GL, Bregman M, Araújo DV, Rufino R. Estimated cost of asthma in outpatient treatment: a real-world study. Rev Saude Publica. 2018;52:27. https://doi.org/10.11606/S1518-8787.2018052000153
10. Sociedade Brasileira de Pneumologia e Tisiologia (SBPT) [homepage on the Internet]. Brasília: SBPT; c2020 [cited 2020 Apr 1]. Centros de diagnóstico e tratamento de asma. [Adobe Acrobat document, 14p.]. Available from: https://sbpt.org.br/portal/wp-content/uploads/2019/08/Centros-de-Referencia-em-Asma-Brasil.pdf

J Bras Pneumol. 2020;46(3):e20200285
https://dx.doi.org/10.36416/1806-3756/e20200285

EDITORIAL

Azithromycin in acute bronchiolitis

Dirceu Solé[1], Fausto Matsumoto[1], Gustavo Falbo Wandalsen[1]

Acute bronchiolitis is a leading cause of hospitalization due to respiratory problems in infants and young children. Among the possible etiologic agents, viruses predominate, the most common being respiratory syncytial virus (RSV) and rhinovirus.[1]

In humans and in animal models, RSV infection is followed by the production of interleukins, such as IL-12 and IL-18, and chemokines, such as IL-8, IL-10, CCL5, macrophage inflammatory protein-1α, CCL2, and eotaxin,[2] all of which are potent inflammatory mediators. Host factors, as well as genetic factors (polymorphisms) and environmental factors, can be critical in determining the severity of RSV-induced disease, even when they are related to age, recent infection, pollution, and exposure to allergens. In addition, studies indicate that individuals who had acute RSV- or rhinovirus-related bronchiolitis in the first years of life are at an increased risk of developing asthma later in childhood.[3]

Although viral etiology is responsible for the majority of cases of acute bronchiolitis, treatment with antimicrobials might be indicated, either because of a suspected bacterial coinfection or simply because of their anti-inflammatory effects. The use of antimicrobials has been widespread, especially in hospitalized patients. However, the use of antibiotics in early life has been associated with the development of recurrent wheezing or asthma later in life.[4] A study using the Taiwanese National Health Insurance Research Database 2010 (from 2005 to 2010) documented the relationship between the risk of new-onset asthma and the use of antibiotics in hospitalized patients with bronchiolitis, specifically azithromycin (adjusted OR = 2.87; 95% CI: 1.99-4.16).[5]

Macrolides, especially azithromycin, have been used as adjuvant therapy in the treatment of some lung diseases and viral bronchiolitis; in addition to their bactericidal effect, their use is justified because of their anti-inflammatory, antineutrophil, and antiviral effects.[6]

Studies evaluating the effect of treatment with azithromycin in hospitalized patients with acute viral bronchiolitis have produced different results.[7-9] That might be explained, in part, by the different variables considered in those studies (e.g., age, dose, duration of treatment, etiologic agent, presence of atopy, and clinical outcomes).

A systematic review and meta-analysis[7] evaluated the clinical effects of the treatment with azithromycin in hospitalized patients with bronchiolitis. That study included 14 double-blind, placebo-controlled studies, collectively involving 667 children receiving active treatment and 661 controls. The global analysis of the data revealed no significant differences between the groups in terms of the length of hospital stay or use of supplemental oxygen; however, there was a significant reduction in the time to relief of wheezing and cough in the treatment group, as well as in the nasopharyngeal colonization by *Streptococcus pneumoniae*, *Haemophilus* sp., and *Moraxella catarrhalis*.[7]

The importance and participation of the airway microbiome in the integrity and health of the airways is increasingly evident. The development of this microbiome starts in the first moments of life and is influenced by the type of delivery (vaginal or not), breastfeeding, environmental exposures, and the environment in which the child lives during the first days of life.

At birth, most children are colonized by *Staphylococcus* sp. or *Corynebacterium* sp. prior to a more stable colonization with *Alloiococcus* sp. or *Moraxella* sp. An imbalance in this microbiome is probably closely related to the development of respiratory diseases, such as wheezing in infancy and asthma. Lower abundances of bacteria of the phyla Bacteroidetes and Firmicutes, as well as a predominance of bacteria of the phylum Proteobacteria, have been documented in patients with asthma.[8]

Another systematic review and meta-analysis[9] evaluated the effects of macrolides on the airway microbiome and the production of cytokines in children with bronchiolitis. After treatment with macrolides, there was a significant reduction in the isolation of *S. pneumoniae*, *Haemophilus influenza*, and *M. catarrhalis* in the nasopharyngeal samples, although there was no reduction in that of *Staphylococcus aureus*. There was also a significant decrease in serum levels of IL-8, IL-4, and eotaxin three weeks after the treatment with clarithromycin.[9] Macrolides can reduce the levels of IL-8 in plasma and in the airways but have failed to demonstrate an antiviral effect in children with bronchiolitis.[9]

In this issue of the *Jornal Brasileiro de Pneumologia*, Luisi et al.[10] analyzed secondary data of a randomized, double-blind, placebo-controlled study involving infants (< 12 months of age) hospitalized for acute viral bronchiolitis (clinical diagnosis) and treated with oral azithromycin (10 mg/kg per day) or placebo for seven days. During the first phase of the study, 184 patients admitted to university hospitals were randomized to treatment with azithromycin or placebo. All treatment protocols for acute viral bronchiolitis were followed at those hospitals. The variables studied at the end of hospitalization were length of hospital stay and the need for supplemental oxygen.[11] The two groups were similar regarding clinical parameters

1. Disciplina de Alergia, Imunologia Clínica e Reumatologia, Departamento de Pediatria, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo (SP) Brasil.

ISSN 1806-3713

at admission, and approximately 15% of the children had a family history of asthma. A virus was isolated in 63% of the sample, RSV being isolated in 94% of those cases. There were no differences between the groups regarding the two variables under study.[11]

In a secondary analysis, Luisi et al.[10] contacted the parents or guardians of those children via telephone three and six months after hospital discharge in order to complete a standardized questionnaire to identify the presence of recurrent wheezing and hospital readmissions.[10] Of the initial sample of patients, 67% of the parents/guardians participated. Among those patients, 54.3% had had RSV-related bronchiolitis. The rate of recurrent wheezing was significantly lower (approximately 50%) among those treated with azithromycin three months after discharge, which was not true at six months after discharge. There were no differences regarding the rate of readmissions.[10]

The possibility of reducing recurrent wheezing with the use of azithromycin is encouraging, although various aspects still need to be better clarified before it can be recommended for the treatment of bronchiolitis. As pointed out by Luisi et al.,[10] the number of children followed was relatively small and further studies are needed in order to confirm these findings. The identification of clinical markers that provide better preventive responses after the use of azithromycin is desirable, aiming to reduce possible adverse events and antimicrobial resistance associated with the indiscriminate use of the medication.

REFERENCES

1. Paul SP, Mukherjee A, McAllister T, Harvey MJ, Clayton BA, Turner PC. Respiratory-syncytial-virus- and rhinovirus-related bronchiolitis in children aged <2 years in an English district general hospital. J Hosp Infect. 2017;96(4):360-365. https://doi.org/10.1016/j.jhin.2017.04.023
2. Welliver RC, Garofalo RP, Ogra PL. Beta-chemokines, but neither T helper type 1 nor T helper type 2 cytokines, correlate with severity of illness during respiratory syncytial virus infection. Pediatr Infect Dis J. 2002;21(5):457-461. https://doi.org/10.1097/00006454-200205000-00033
3. Sigurs N, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. Thorax. 2010;65(12):1045-1052. https://doi.org/10.1136/thx.2009.121582
4. Ahmadizar F, Vijverberg SJH, Arets HGM, de Boer A, Turner S, Devereux G, et al. Early life antibiotic use and the risk of asthma and asthma exacerbations in children. Pediatr Allergy Immunol. 2017;28(5):430-437. https://doi.org/10.1111/pai.12725
5. Chen IL, Huang HC, Chang YH, Huang HY, Yeh WJ, Wu TY, et al. Effect of antibiotic use for acute bronchiolitis on new-onset asthma in children. Sci Rep. 2018;8(1):6090. https://doi.org/10.1038/s41598-018-24348-5
6. Schögler A, Kopf BS, Edwards MR, Johnston SL, Casaulta C, Kieninger E, et al. Novel antiviral properties of azithromycin in cystic fibrosis airway epithelial cells. Eur Respir J. 2015;45(2):428-439. https://doi.org/10.1183/09031936.00102014
7. Che SY, He H, Deng Y, Liu EM. Clinical effect of azithromycin adjuvant therapy in children with bronchiolitis: a systematic review and meta analysis [Article in Chinese]. Zhongguo Dang Dai Er Ke Za Zhi. 2019;21(8):812-819.
8. Lynch SV. The Lung Microbiome and Airway Disease. Ann Am Thorac Soc. 2016;13 Suppl 2(Suppl 5):S462-S465. https://doi.org/10.1513/AnnalsATS.201605-356AW
9. Zhang Y, Dai J, Jian H, Lin J. Effects of macrolides on airway microbiome and cytokine of children with bronchiolitis: A systematic review and meta-analysis of randomized controlled trials. Microbiol Immunol. 2019;63(9):343-349. https://doi.org/10.1111/1348-0421.12726
10. Luisi F, Roza CA, Silveira VD, Machado CC, da Rosa KM, Pitrez PM, et al. Azithromycin administered for acute bronchiolitis may have a protective effect on subsequent wheezing. J Bras Pneumol. 2020;46(3):e20180376. https://doi.org/10.36416/1806-3756/e20180376
11. Pinto LA, Pitrez PM, Luisi F, de Mello PP, Gerhardt M, Ferlini R, et al. Azithromycin therapy in hospitalized infants with acute bronchiolitis is not associated with better clinical outcomes: a randomized, double-blinded, and placebo-controlled clinical trial. J Pediatr. 2012;161(6):1104-1108. https://doi.org/10.1016/j.jpeds.2012.05.053

J Bras Pneumol. 2020;46(3):e20200299
https://dx.doi.org/10.36416/1806-3756/e20200299

A new spirometry reference equation for 3- to 12-year-old children in Brazil

Diego Djones Brandenburg[1], Marina Buarque de Almeida[2,3], Paulo José Cauduro Marostica[1,4]

The importance of determining spirometric values is indisputable, not only for the individual and longitudinal monitoring of patients but also for the assessment of populations, which can even influence public and collective health care measures.[1] In addition, due to the enormous advances in medicine and the interaction among diverse pediatric subspecialties, the data obtained at pulmonary function laboratories—where spirometry is undoubtedly the most popular exam, because it is easily accessible and feasible for use in preschoolers and older chidren—can assist in the standard of care of these patients. Therefore, it is very important to have reference values for spirometry in a healthy population in order to allow the distinction between health and disease, measure the impact of diseases on lung function, diagnose pathologies correctly, maximize care for patients with chronic lung disease, and monitor the growth and the development of the lungs and airways in healthy children or in those with different pathologies.[2]

Pulmonary function laboratories must follow strict quality criteria to ensure that their pulmonary function results are accurate.[1] For this purpose, there is an indispensable tool that ensures whether the data obtained are considered normal or not: the reference values in use. Knowing the distribution of the normal curve is a concept that is deeply rooted in the routine and practice of pediatrics and childcare, and we know that the development of reference models or of parameters of normality requires herculean work, which involves the collection of data from a representative sample of the selected population that guarantees the lowest possible risk of selection bias, excluding individuals who may not be actually representative of the healthy population.

Because of the improvement in pediatric research on respiratory function, the use of spirometry, following internationally established criteria, has increased in preschoolers.[3] Therefore, reference equations that include 3- to 6-year-old children are necessary in Brazil. It is worth noting that the success rate of spirometry in 3- to 5-year-old preschoolers is higher than 70%-80% when spirometry is performed by qualified professionals following adequate acceptability criteria for this population.[4] This demonstrates the feasibility of spirometry and reinforces the importance of performing it more frequently; having specific prediction equations for this age group avoids biases, such as the simple extrapolation of reference values for older children to this age group.

In 2012, the multi-ethnic global equation by Quanjer et al.[5] for different age groups was published. Since then, those reference values have been used in the most diverse studies regarding pediatric subjects, because it covers a broad age group (from 3 to 95 years of age). However, depending on the characteristics of the pediatric population, those values proved to be adequate in some specific populations,[6,7] but not as effective in other populations in different regions.[8,9]

Ideally, each population should have their own local standards of normality, because there are various factors that might interfere with the determination of normality criteria, such as age, sex, ethnicity, and chest size, the latter not always being well represented by the height when it is used as a means of extrapolating the size of the rib cage because, depending on the various types of body build, the chest size/height ratio can considerably vary.[10,11]

The inherent characteristics of the Brazilian population with regard to the enormous plurality and miscegenation among the various ethnic groups make the challenge of creating a national prediction equation even more complex. According to data from the *Instituto Brasileiro de Geografia e Estatística* (Brazilian Institute of Geography and Statistics) in 2016,[12] about half of the Brazilian population is black or brown. In the present issue of the *Jornal Brasileiro de Pneumologia*, the study by Jones et al.[13] takes into account the ethnic characteristics of the vast majority of the Brazilian pediatric population between 3 and 12 years of age, because it covers the predicted values for individuals of white and black/brown ethnicity. Their large and representative sample totaled 1,990 subjects from different Brazilian regions; however, because there was a predominance of subjects from the southern and southeastern regions, there was a proportional inclusion of a greater number of white individuals. We know that the normal limits of pulmonary function variables show great variability among individuals, and the most modern equations can include lower limits of normality and results in Z scores, providing more robust data and facilitating longitudinal monitoring of the individual during diagnosis, treatment, and follow-up, as well as allowing the evaluation of larger groups, such as in population studies. In addition, the study by Jones et al.[13] had a strict quality control both in the compilation of the data and in the measurements performed. Moreover, all spirometric curves were reviewed by two researchers

1. Unidade de Pneumologia Infantil, Departamento de Pediatria, Hospital de Clínicas de Porto Alegre, Porto Alegre (RS) Brasil.
2. Hospital Sírio-Libanês, São Paulo (SP) Brasil.
3. Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
4. Departamento de Pediatria, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.

before their inclusion in the database. Furthermore, spirometric data that had more than four standard deviations were excluded. Finally, the study shows that the predicted values currently used for the Brazilian pediatric population,[1] similarly to those from the global equations,[5] underestimate the values of FVC and FEV_1, especially for the black population. This highlights the importance of using the new predicted values by Jones et al.[13] from now on; however, these equations should be revisited and updated periodically. We welcome the study by Jones et al.,[13] and we believe that these prediction equations for spirometry for 3- to 12-year-old children will be soon incorporated into the routine at pulmonary function laboratories in Brazil.

REFERENCES

1. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes para testes de função pulmonar. J Pneumol. 2002;28(Suppl 3):S1-S82.
2. Gray D, Zar HJ. Lung Function in Children from Sub-Saharan Africa and the Global Lung Initiative 2012 Reference Equations. Am J Respir Crit Care Med. 2017;195(2):157-158. https://doi.org/10.1164/rccm.201609-1800ED
3. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med. 2007;175(12):1304-1345. https://doi.org/10.1164/rccm.200605-642ST
4. Veras TN, Pinto LA. Feasibility of spirometry in preschool children. J Bras Pneumol. 2011;37(1):69-74. https://doi.org/10.1590/S1806-37132011000100011
5. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-1343. https://doi.org/10.1183/09031936.00080312
6. Madanhire T, Ferrand RA, Attia EF, Sibanda EN, Rusakaniko S, Rehman AM. Validation of the global lung initiative 2012 multi-ethnic spirometric reference equations in healthy urban Zimbabwean 7-13year-old school children: a cross-sectional observational study. BMC Pulm Med. 2020;20(1):56. https://doi.org/10.1186/s12890-020-1091-4
7. Busi LE, Sly PD. Validation of the GLI-2012 spirometry reference equations in Argentinian children. Pediatr Pulmonol. 2018;53(2):204-208. https://doi.org/10.1002/ppul.23923
8. Hüls A, Krämer U, Gappa M, Müller-Brandes C, Schikowski T, von Berg A, et al. Age Dependency of GLI Reference Values Compared with Paediatric Lung Function Data in Two German Studies (GINIplus and LUNOKID). PLoS One. 2016;11(7):e0159678. https://doi.org/10.1371/journal.pone.0159678
9. Arigliani M, Canciani MC, Mottini G, Altomare M, Magnolato A, Loa Clemente SV, et al. Evaluation of the Global Lung Initiative 2012 Reference Values for Spirometry in African Children. Am J Respir Crit Care Med. 2017;195(2):229-236. https://doi.org/10.1164/rccm.201604-0693OC
10. Takase M, Sakata H, Shikada M, Tatara K, Fukushima T, Miyakawa T. Development of reference equations for spirometry in Japanese children aged 6-18 years. Pediatr Pulmonol. 2013;48(1):35-44. https://doi.org/10.1002/ppul.22536
11. Haynes JM, Kaminsky DA, Stanojevic S, Ruppel GL. Pulmonary Function Reference Equations: A Brief History to Explain All the Confusion [published online ahead of print, 2020 Mar 10]. Respir Care. 2020;respcare.07188. https://doi.org/10.4187/respcare.07188
12. Instituto Brasileiro de Geografia e Estatística (IBGE). Coordenação de Trabalho e Rendimento [homepage on the Internet]. Rio de Janeiro: IBGE; [cited 2018 Sep 27]. Pesquisa nacional por amostra de domicílios 2016. Available from: http://www.ibge.gov.br
13. Jones MH, Vidal PCV, Lanza FC, Silva DCFMF, Pitrez PM, Olmedo APBF, et al. Reference values for spirometry in Brazilian children. J Bras Pneumol. 2020;46(3):e20190138. https://doi.org/10.36416/1806-3756/e20190138

J Bras Pneumol. 2020;46(3):e20200004
https://dx.doi.org/10.36416/1806-3756/e20200004

Hypodense consolidation

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

A 72-year-old male patient with advanced Alzheimer's disease presented with chronic cough and dyspnea. Chest CT showed extensive areas of consolidation in the lower lobes (Figure 1).

Pulmonary consolidation is a common imaging finding, with a broad differential diagnosis, given that airspace filling can be caused by the accumulation of various endogenous materials, such as exudates, transudates, blood, and neoplastic cells, as well as of exogenous materials, such as fat (in lipoid pneumonia) and calcium (in pulmonary alveolar microlithiasis).

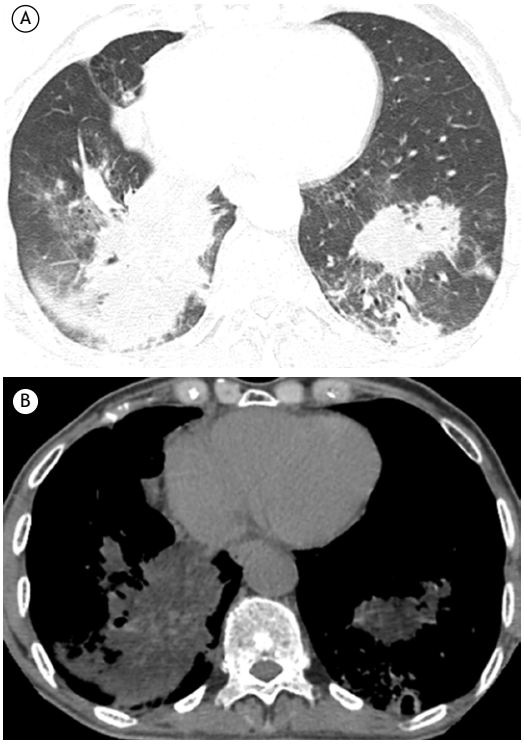


Figure 1. Axial CT scans at the level of the lower lobes, with lung and mediastinal window settings (A and B, respectively), showing bilateral areas of consolidation. Note that the density of the consolidation is lower than the density of the heart, with negative values ranging from −13 to −86 Hounsfield units.

The differential diagnosis of pulmonary consolidation can be narrowed by taking the density of consolidation, as measured in Hounsfield units (HU), into account. In most cases, the consolidation has soft-tissue density similar to that of the heart or liver. In addition, the consolidation can be hyperdense or hypodense relative to these structures. Low density within the consolidation can be due to areas of necrosis or fat.[1]

Within areas of pulmonary consolidation, necrotic portions show low density, although the values are usually positive, whereas fatty areas show negative density values, ranging from −30 HU to −150 HU. Among lung lesions, negative density can be seen within nodules, masses, or areas of consolidation. Areas of consolidation with fat density are usually indicative of lipoid pneumonia.

Exogenous lipoid pneumonia is an uncommon condition resulting from inhalation or aspiration of oils, most commonly mineral oil. In adults, the most common cause of exogenous lipoid pneumonia is the use of mineral oil for the treatment of constipation. In the elderly, exogenous lipoid pneumonia usually develops chronically and progressively, presenting with chronic cough and dyspnea. In addition, the clinical presentation may mimic that of bacterial pneumonia, with fever and cough.[2-4]

The diagnosis of exogenous lipoid pneumonia is based on a history of exposure to oil and characteristic imaging findings, and/or lipid-laden macrophages in sputum or BAL samples. Although a history of ingestion or inhalation of oil is an extremely important piece of information, rarely is it provided spontaneously by the patient, which makes diagnosis difficult. Often, that information is obtained only retrospectively, after focused history taking. On imaging, the most characteristic finding is lung consolidation with fat attenuation (i.e., negative attenuation values). Negative density values, between −30 HU and −150 HU, are highly suggestive of intrapulmonary fat.[2-4]

Our patient showed negative density values, ranging from −13 to −86 HU, and reported having used mineral oil for the treatment of chronic constipation. The final diagnosis was lipoid pneumonia.

REFERENCES

1. Marchiori E, Zanetti G, Hochhegger B. Dense consolidations. J Bras Pneumol. 2015;41(4):388. https://doi.org/10.1590/S1806-37132015000000076
2. Marchiori E, Zanetti G, Mano CM, Irion KL, Daltro PA, Hochhegger B. Lipoid pneumonia in 53 patients after aspiration of mineral oil: comparison of high-resolution computed tomography findings in adults and children. J Comput Assist Tomogr. 2010;34(1):9–12. https://doi.org/10.1097/RCT.0b013e3181a9ec9f
3. Marchiori E, Zanetti G, Mano CM, Hochhegger B. Exogenous lipoid pneumonia. Clinical and radiological manifestations. Respir Med. 2011;105(5):659–666. https://doi.org/10.1016/j.rmed.2010.12.001
4. Marchiori E, Zanetti G, Escuissato DL, Souza Jr AS, Araújo Neto C, Nobre LF, et al. Lipoid pneumonia in adults: findings on high-resolution computed tomography Radiol Bras. 2007;40(5):315-319. https://doi.org/10.1590/S0100-39842007000500007

1. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
2. Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre (RS) Brasil.

Measures of frequency: calculating prevalence and incidence in the era of COVID-19

Marcia Margaret Menezes Pizzichini[1,2], Cecilia Maria Patino[1,3], Juliana Carvalho Ferreira[1,4]

PRACTICAL SCENARIO

Coronavirus disease 2019 (COVID-19), caused by the coronavirus designated SARS-CoV-2, has become a pandemic despite global efforts to prevent its spread. The first confirmed case of COVID-19 in Brazil was reported on February 26 of 2020. Until May 11 of 2020, a total of 168,331 Brazilians had a confirmed diagnosis of COVID-19, of whom 89,429 (53.1%) were still infected, 67,384 (40%) had been cured, and 11,519 (6.8%) had died. The number of new cases on May 11th was 5,632, and the reported incidence was 80.1/100.000 population.[1]

MEASURES OF MORBIDITY AND MORTALITY OF COVID-19

Counting mild-to-severe and asymptomatic cases of COVID-19 is essential to describe and interpret local epidemic responses. In this scenario, repeated estimates of prevalence and incidence inform trajectory trends of the disease and guide the decision-making process related to control measures and resource allocation.[2]

Prevalence is defined as the proportion of a population who has the disease at one time point (Table 1). Cross-sectional studies are commonly used in order to conduct prevalence studies because they examine the disease at one particular time point. The prevalence of confirmed COVID-19 cases on May 11th was 0.08%, estimated as the number of cases of COVID-19 on that day divided by the population at risk (the Brazilian population).[1] Because measures of prevalence include both new and existing cases, they do not provide a complete picture of the natural history of the disease. In addition, the calculation of COVID-19 prevalence in Brazil on May 11th might not be accurate, because the data reported by the Brazilian Ministry of Health did not include extensive testing for SARS-CoV-2 across the full spectrum of the disease severity; therefore, the number of reported cases were likely to represent the more severe ones (because most tests were performed in symptomatic individuals and not in the general population) and, as a consequence, underestimating the actual disease prevalence.

Incidence is a measure of the occurrence of new cases during a specified period in a population at risk for the disease. Prevalence focuses on new and existing cases of the disease, whereas incidence focuses only on new cases (Table 1). To estimate incidence, all individuals in the denominator (population at risk) must have the potential to be in the numerator (those who develop the disease). Estimates of incidence require longitudinal follow-up (e.g., hours, days, or years). The study design of choice is cohort studies involving individuals at risk but without the disease at baseline who are followed through time and are evaluated if they develop the disease. Finally, the incidence also depends on the frequency of the disease, the definition of cases, and the population at risk. In the Brazilian scenario, the incidence of confirmed cases of COVID-19 on May 11th was 2.7/100,000 population at risk (Table 1).

KEY POINTS TO INTERPRET PREVALENCE AND INCIDENCE ESTIMATES

1. Accurate definitions of cases and noncases are critical to defining prevalence and incidence.
2. Both prevalence and incidence estimates can be misleading if the number of cases is underestimated due to barriers in accessing information regarding diagnosis and health care practices or if only patients with severe disease are submitted to diagnostic tests.
3. The timing of the estimates of prevalence and incidence must be taken into account when interpreting these measures. For example, the estimates might be lower in the beginning of an outbreak when compared with the epidemic later.

Table 1. Incidence and prevalence of COVID-19 on May 11 of 2020 in Brazil.[1]

Measure	Definition	How to calculate	Equation	Result
Prevalence	Existing cases of a disease at a point in time divided by the population at risk of having the disease	Cases of COVID-19 on May 11th ÷ Population at risk	168,331 ÷ 210 mi	0.08%
Incidence	New cases of a disease in a defined population over a period of time (a day, for example) divided by the population at risk	New cases of COVID-19 within a day ÷ Population at risk on May 11th[a]	5,632 ÷ 209,837,301	2.7/100,000

mi: million (Brazilian population). [a]Brazilian population minus the total number of confirmed cases on May 11th.

REFERENCES

1. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde [homepage on the Internet]. Brasília: Ministério da Saúde; c2020 [cited 2020 May 11]. COVID-19 Painel Coronavírus. Available from: https://covid.saude.gov.br
2. Lipsitch M, Hayden FG, Cowling BJ, Leung GM. How to maintain surveillance for novel influenza A H1N1 when there are too many cases to count. Lancet. 2009;374(9696):1209-1211. https://doi.org/10.1016/S0140-6736(09)61377-5

1. Methods in Epidemiologic, Clinical, and Operations Research–MECOR–program, American Thoracic Society/Asociación Latinoamericana del Tórax, Montevideo, Uruguay.
2. Programa de Pós-Graduação em Ciências Médicas, Universidade Federal de Santa Catarina – UFSC – Florianópolis (SC) Brasil.
3. Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA.
4. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ISSN 1806-3713

Obesity: how pulmonary function tests may let us down

José Alberto Neder[1], Danilo Cortozi Berton[2], Denis E. O'Donnell[1]

BACKGROUND

There has been an exponential increase in the prevalence of obesity worldwide.[1] Consequently, there has been an increase in the number of obese individuals referred for pulmonary function tests (PFTs) prior to bariatric surgery, for example, as well as because of chronic wheezing, chronic breathlessness, and multiple comorbidities potentially explaining disproportionate dyspnea.[2] The pulmonologist in charge of interpreting the results of a PFT, as well as the physician requesting the test, should be acquainted with the peculiar effects that obesity has on lung function.

OVERVIEW

A 72-year-old male—smoking history = 32 pack-years; height = 159 cm; and body mass index (BMI) = 48.2 kg/m^2—was referred for a full PFT in a tertiary health care facility due to worsening dyspnea despite maximal therapy for suspected COPD. Office spirometry was, according to the referral note, "unremarkable". In fact, spirometry, whole-body plethysmography, and DLCO were all within the normal range. However, because the patient experienced severe dyspnea and distress after the tests, he was referred to the emergency department by the respiratory therapist. Upon arrival in the emergency

Chart 1. A non-exhaustive list of challenges and pitfalls in the interpretation of pulmonary function tests in obese patients. Note that these sources of confusion increase as does the body mass index, but they are also negatively affected by male sex, height, and abdominal obesity for a given body mass index.

Directional change	Putative mechanism(s)	Common misinterpretation and potential consequences
Spirometry		
↔ FEV_1/FVC in the presence of airway disease	↓ FVC due to early closure of small airways and/or due to ↓ TLC and/or ↑ RV/TLC	No airway disease is present. If the patient is a smoker, false reassurance; if he/she has asthma, undertreatment
↓ FEV_1/FVC in the absence of airway disease	Compression of central airways in the forced maneuver	Excessive pharmacological treatment (usually for asthma) of a patient who, fundamentally, should lose weight
↓ $FEF_{25-75\%}$ due to low FVC in the absence of airway disease	Flows commensurate with volumes	As above
Plethysmography		
↓ TLC in the absence of intraparenchymal restriction	↑ elastic recoil, including the chest wall; common if BMI > 50 kg/m^2, very common if BMI > 60 kg/m^2	Unfounded alert for ILD or another cause of restriction; underestimation of lung overdistension caused by obstruction
↓ FRC in the absence of intraparenchymal restriction	Downward displacement of the chest wall-parenchymal equilibrium point plus mass load effect	As above
↔ IC in the presence of expiratory flow limitation	↓ FRC but ↔ TLC	The effects of air trapping and lung hyperinflation on operating lung volumes are counterbalanced.
Gas exchange		
↔ DLCO in the presence of gas exchange impairment	↑ blood flow in areas of preserved ventilation-perfusion	No impairment in gas exchange
↔ K_{CO} in the presence of gas exchange impairment	K_{CO} ↑ exponentially as V_A ↓	As above
↓ SpO_2 on the six-minute walk test	↑ perfusion of poorly ventilated (dependent) airways with poorly oxygenated mixed venous blood	Overestimation of the impairment caused by any underlying respiratory disease

↔: preserved; ↑: high/increased; ↓: low/decreased; $FEF_{25-75\%}$: forced expiratory flow at 25-75% of FVC; BMI: body mass index; ILD: interstitial lung disease; FRC: functional residual capacity; IC: inspiratory capacity; K_{CO}: carbon monoxide transfer coefficient; and V_A: alveolar volume.

1. Pulmonary Function Laboratory and Respiratory Investigation Unit, Division of Respirology and Sleep Medicine, Kingston Health Science Center & Queen's University, Kingston (ON) Canada.
2. Unidade de Fisiologia Pulmonar, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.

department, the patient had a respiratory arrest. After endotracheal intubation, chest CT angiography showed bilateral massive pulmonary thromboembolism, as well as severe emphysema and diffuse airway plugging. After a prolonged stay in the ICU, the patient eventually died of ventilator-associated pneumonia. How could such dramatic, life-threatening abnormalities be missed by the PFTs?

Obesity may increase the expiratory flows due to increased lung/chest wall elastic recoil. FVC may underestimate slow VC because FVC is precociously "amputated" by early small airway closure in the forced maneuver, i.e., the FEV_1/FVC ratio tends to increase.[3] Although functional residual capacity decreases in comparison with that in the earlier stages of obesity,[4] volume "extremities"—RV and TLC—are only mildly affected (unless obesity is massive). It follows that expiratory reserve volume decreases and inspiratory capacity increases in tandem with BMI.[4] These changes are in opposite direction to those caused by obstruction with air trapping, leading to underestimation of or a false negative for airway disease. DLCO increases for a given alveolar volume (V_A) because lung perfusion and intrathoracic blood volume increase; moreover, V_A decreases more than does DLCO as the lung deflates. Therefore, carbon monoxide transfer coefficient (K_{CO} = DLCO/V_A) increases exponentially as V_A decreases.[5] Consequently, signs of impaired gas exchange efficiency (low DLCO and K_{CO}) might be obscured. A short height and abdominal obesity, as in our patient, tend to potentiate these effects of obesity. Chart 1 provides a non-exhaustive list of the most common pitfalls in the interpretation of PFTs in obese patients.

CLINICAL MESSAGE

BMI must be available in every PFT report: it is the third variable to look at (after age and sex) before any attempt to interpret the tests. This case illustrates that PFTs in obese patients can be relatively unaltered even in the presence of life-threatening conditions in the airways, lung parenchyma, or both. Special caution is advisable if little is known about the pre-test probability of abnormality (as is frequently the case). The final report should acknowledge these "shades of gray" rather than giving a rigid dichotomous "verdict": recognizing uncertainty always meets the best interests of the patient.

REFERENCES

1. Finkelstein EA, Khavjou OA, Thompson H, Trogdon JG, Pan L, Sherryet B, et al. Obesity and severe obesity forecasts through 2030. Am J Prev Med. 2012;42(6):563–570. https://doi.org/10.1016/j.amepre.2011.10.026
2. O'Donnell DE, Milne KM, Vincent SG, Neder JA. Unraveling the Causes of Unexplained Dyspnea: The Value of Exercise Testing. Clin Chest Med. 2019;40(2):471–499. https://doi.org/10.1016/j.ccm.2019.02.014
3. Saint-Pierre M, Ladha J, Berton DC, Reimao G, Castelli G, Marillier M, et al. Is the Slow Vital Capacity Clinically Useful to Uncover Airflow Limitation in Subjects With Preserved FEV1/FVC Ratio? Chest. 2019;156(3):497–506. https://doi.org/10.1016/j.chest.2019.02.001
4. O'Donnell DE, Deesomchok A, Lam YM, Guenette JA, Amornputtisathaporn N, Forkert L, et al. Effects of BMI on static lung volumes in patients with airway obstruction. Chest. 2011;140(2):461–468. https://doi.org/10.1378/chest.10-2582
5. Neder JA, Berton DC, Muller PT, O'Donnell DE. Incorporating Lung Diffusing Capacity for Carbon Monoxide in Clinical Decision Making in Chest Medicine. Clin Chest Med. 2019;40(2):285–305. https://doi.org/10.1016/j.ccm.2019.02.005

J Bras Pneumol. 2020;46(3):e20180341
http://dx.doi.org/10.36416/1806-3756/e20180341

Clinical features and associated factors with severe asthma in Salvador, Brazil

Alexssandra Maia Alves[1], Luane Marques de Mello[2], Aline Silva Lima Matos[3], Álvaro Augusto Cruz[4]

1. Programa de Pós-Graduação em Ciências da Saúde, Universidade Federal da Bahia, Salvador (BA) Brasil.
2. Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto (SP) Brasil.
3. Núcleo de Excelência em Asma, Programa para o Controle da Asma na Bahia, Universidade Federal da Bahia, Salvador (BA) Brasil.
4. Faculdade de Medicina, Universidade Federal da Bahia, Salvador (BA) Brasil.

Submitted: 06 November 2018.
Accepted: 01 April 2019.

Study carried out in the Núcleo de Excelência em Asma, Programa para o Controle da Asma na Bahia, Salvador (BA) Brasil.

ABSTRACT

Objective: To describe the clinical features and to identify factors associated with significant severe asthma in samples of patients followed in a reference center in Salvador. **Methods:** A cross-sectional study of 473 adults, regularly followed in the "Asthma Control Program" in Bahia (*Programa de Controle da Asma e da Rinite Alérgica na Bahia* (ProAR)), reassessed systematically between 2013 and 2015. The patients were admitted for meeting previous criteria of severe asthma and were reclassified according to the most current definition proposed by a joint document of the "European Respiratory Society/American Thoracic Society" (ERS/ATS) (ERS/ATS 2014). **Results:** Only 88/473 (18%) were reclassified as having severe asthma by ERS/ATS criteria (SA-ERS/ATS). Among these patients, 87% were women, 48% obese, with a median Body Mass Index (BMI) of 29 kg·m^2 (IQ 26-34), furthermore, 99% had symptoms of chronic rhinitis and 83% had symptoms of Gastroesophageal Reflux Disease (GERD). None of the 88 patients claimed to be current smokers. The most frequently corticosteroids were beclomethasone dipropionate (BDP) (88%) and budesonide (BUD) (69%). The majority of the evaluations reported adequate adherence (77%), however, the minority (0,6%) detected serious errors in inhalation techniques. The median Forced Expiratory Volume (FEV_1) associated with post-bronchodilator test (post-BD) was 67% predicted (IQ 55-80). The median number of eosinophils in the peripheral blood was lower in patients with SA-ERS/ATS (258 cells/mm^3 (IQ 116-321) than in the other patients studied [258 cells/mm^3 (IQ 154-403)]. Gastroesophageal reflux symptoms were associated with a higher severity [OR = 2.2 95% CI (1.2-4.2)]. **Conclusion:** In this group of patients, symptoms of GERD were associated with SA-ERS/ATS and eosinophil count > 260 cells/mm^3 were associated 42% with less chance SA-ERS/ATS

Keywords: Asthma; Gastroesophageal reflux disease (GERD); Eosinophils; Biomarkers.

INTRODUCTION

Most asthmatics can achieve adequate control of symptoms with inhaled corticosteroids, but approximately 5% are unsuccessful, even with adequate treatment and good adherence.[1] In addition to high morbidity, this group is responsible for most health expenditures, which are higher than those of other chronic diseases such as diabetes and kidney disease.[2] In Brazil, the annual cost of severe asthma is estimated to exceed a thousand dollars/patient/year.[3]

Despite some recognized phenotypes, there is great variability in clinical presentation and biomarkers associated with asthma severity. The studies conducted by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) in Severe Asthma Research Program (SARP III) found that with advancing age, patients with severe asthma became more obese and less sensitive to allergens.[4] The study from the European Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes (U-BIOPRED) found a higher frequency of nasal polyps and Gastroesophageal Reflux Disease (GERD)[5] in patients with severe asthma.

In Brazil, some studies have described the clinical and sociodemographic profile of adults and severe asthmatic children in different regions.[6-9] More recently, Kuschnir et al.[10] found a significant association between asthma severity and metabolic syndrome in a study on cardiovascular risk in adolescents.

Given the wide diversity of clinical manifestations of this disease, the negative impact on patients' quality of life and the high health costs, there is still a need to better understand the factors related to severe asthma in specific regions.

There has been no uniformity in the definition of severe asthma. A World Health Organization (WHO) expert meeting in 2009 proposed a classification that included three categories: untreated severe asthma; difficult to treat severe asthma and treatment-resistant severe

Correspondence to:
Alexssandra Maia Alves. Programa para o Controle da Asma na Bahia, Rua Carlos Gomes, 270, Centro de Saúde Carlos Gomes, 7º andar, Dois de Julho, CEP 40060-330, Salvador, BA, Brasil.
Tel.: 55 71 3013-8462. E-mail: alexssandra.maia@yahoo.com

Financial support: This study used data from a larger line of research entitled "Fatores de risco, biomarcadores e endofenótipos de asma grave" which receives financial support from Programa de Apoio a Núcleos de Excelência (PRONEX) of the Fundação de Amparo à Pesquisa do Estado da Bahia (FAPESB) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), no. 6353, Edital 020/2009 (Núcleo de Excelência em Asma da Universidade Federal da Bahia). This study received financial support from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (Process: 471057/2014-2) and GlaxoSmithKline, Trust in Science program, *investigator initiated grant* (2012-2015).

asthma.[11] In the Program for the Control of Asthma in Bahia, described in Portuguese as ProAR, there is a cohort of patients with severe asthma established from 2003,[12] using the severity criteria of that time, which coincide with the untreated severe asthma category proposed by WHO. In a study started in 2013, it was observed that most patients in this cohort can be considered as belonging to the severe asthma category that is difficult to treat.[13]

The aim of this study was to describe clinical, laboratory and functional characteristics of severe asthma, to assess the level of control and to identify factors associated with an expressive asthma severity in a group of patients, users of the Unified Health System (in Portuguese *Sistema Único de Saúde* (SUS)), followed at the ProAR referral outpatient clinic. These patients were also reclassified retrospectively according to the current criteria of the European Respiratory Society/American Thoracic Society (ERS/ATS) in 2014 (AG-ERS/ATS),[14] which were not known when the original study was started.

METHODS

This was a cross-sectional study, which was conducted through the analysis of secondary data from a larger project entitled "Risk factors, biomarkers and endophenotypes of severe asthma".

The study population consisted of adult patients, followed regularly since 2003 at the ProAR from the *Universidade Federal da Bahia* (UFBA) at Central Referral Outpatient Clinic for patients with severe asthma in Salvador. For admission to this outpatient clinic, the patients should meet at least one of the following severity criteria, based on the NIH-NHBLI Guidelines for Diagnosis and Management of Asthma[15] and Global Initiative for Asthma (GINA),[16] such as: daily symptoms; limitation of daily activities (symptoms with minimal effort); nocturnal symptoms > twice a week; use of bronchodilators > twice a day; Peak Expiratory Flow/Forced Expiratory Volume 1 (PEF/FEV1) < 60% of predicted.

At the beginning of the main study, each patient had their diagnosis confirmed and validated by two specialists, through a review of the medical records, when the presence of typical asthma and spirometry symptoms was verified, demonstrating significant reversible obstructive ventilatory disorder (increase of 12% and 200 ml in post-bronchodilator (post-BD FEV1). When there was a divergence in validation among experts, a third party was consulted.

For "inclusion" in this study, the following criteria were used: age ≥ 18 years; residency in Salvador or Lauro de Freitas in the state of Bahia (BA); validation of asthma diagnosis and a follow-up program for at least six months. Patients with conditions that could interfere with the interpretation of results, such as Chronic Obstructive Pulmonary Disease (COPD), sequelae in patients associated with extensive tuberculosis, structural changes in the lungs and pregnancy, were excluded.

After the selection of eligible individuals, telephone contact and invitation to participate in the study were made. On the scheduled date, the Informed Consent Form (ICF) was read and those who agreed and signed, were systematically evaluated in "face-to-face" visits, which were conducted between January 2013 and July 2015. A properly trained multidisciplinary team, composed of doctors, nurses, pharmacists, physiotherapists, nutritionists and psychologists, performed the research evaluations and procedures.

Blood collection and anthropometric measurements were performed with the fasting patient. Individuals with Body Mass Index (BMI) ≥ 30 kg/m^2 (WHO norm[17]) were considered obese.

Immediate-reading skin test was performed according to Global Allergy and Asthma European Network/ Allergic Rhinitis and its Impact on Asthma (GA2LEN/ARIA)[18] guidelines and evaluated the hypersensitivity to aeroallergens: *Dermatophagoides pteronyssinus*, *D. farinae*, *Aspergillus flavus*, *A. fumigatus*, *Alternaria alternata*, *Cladosporium herium*, *C. herio cat*, *Blatella germanica*, *Periplaneta americana*, *Paspalum notatum* Fluegge (Bahia *grass*), *Cynodon dactylon* (L.) Pers (Bermuda *grass*) *(GREER®)* and *Blomia tropicalis (FDA allergenics*. Positive responses were considered, papules ≥ 3mm when compared to the papule of the negative control. Testicle readings were interpreted by allergist.

Spirometry was performed by a trained technician or physiotherapist certified by the Brazilian Society of Pulmonology and Physiology (SBPT) using a Koko® spirometer (PDS Instrumentation Inc., Louisville, CO, USA) following the 1995 American Thoracic Society protocol.[19] Spirometer software was updated with Brazilian normal values.[20]

Stool samples were evaluated by the spontaneous sedimentation method to verify the presence of parasites.

The blood count was obtained by the automated Cell-Dyn Ruby method and the total IgE by the chemiluminescence method. For the evaluation of eosinophilia, the cutoff point was the peripheral blood eosinophil count of 260 cells/mm3, based on the work of Zhang et al.,[21] who found this value through Receiver Operating Characteristics (ROV) curve (ROC curve) analysis in a population with similar characteristics to the population of the present study.

The inhalation technique was systematically verified with each patient using the devices: pressurized inhaler with and without spacer; aerolizer; turbuhaler and diskus. Serious errors considered the absence of one of the following steps: "put between the lips"; inhale; hold the breath (all devices); trigger (pressurized inhaler); open the compartment and place the capsule inside; press the inhaler buttons (aerolizer) and rotate the device (turbuhaler). It is noteworthy that most patients used more than one device, which is why the number of evaluations was much larger than the sample size.

Adequate adherence was considered by subjective/self-reported assessment when the patient reported consumption of at least 70% of doses in the evaluation week. For objective evaluation, pharmaceutical dispensation records were used and adherence was considered adequate when the drug was withdrawn monthly by the patient within the last six months of the evaluation.

The Asthma Control Questionnaire-6 (ACQ-6) questionnaires for control,[22] Asthma Quality of Life Questionnaire (AQLQ) for quality of life[23] and QS-GERD questionnaires were also used to evaluate symptoms of GERD.[24] All questionnaires were translated into Brazilian Portuguese and validated in our population. In addition,the GINA classification was used to evaluate symptom control.[25]

The selection of ERS/ATS 2014[14] criteria for reclassification is justified as the most recent and widely accepted severity definition criteria. These criteria define severe asthma as requiring treatment according to GINA step 4 or 5 (high dose of inhaled corticosteroid associated with long-acting beta-agonist and/or leukotriene and/or theophylline modifier) in the last year, or corticosteroid ≥ 50% of the year in the last year to prevent it from becoming uncontrolled or remaining uncontrolled despite treatment.

The final sample, therefore, consisted of patients who used high doses of corticosteroids (equal to or greater than 1600 µg budesonide (BUD) or equivalent) associated with another controller (long acting bronchodilator) and/or systemic corticosteroids for 50% or more of the last year of the assessment.

Statistical Package for Social Sciences for Windows version 20.0 (SPSS Inc., Chicago, IL, USA) was used. Variables were described using the median and interquartile range. The tests used in the statistical analysis were Chi-square and Fisher's Exact for categorical variables and Mann-Withney for numerical variables. Binary logistic regression was performed for multivariate analysis to identify possible predictors for severity classification.

This study was approved by the *Comissão Nacional de Ética em Seres Humanos* (CONEP) statement no. 450/10.

RESULTS

Clinical features

Secondary data from 473 patients followed in ProAR were reclassified and analyzed. Eighty-eight were considered to have AG-ERS/ATS (Figure 1). The median age was 53 years (Intelligence Quotient (IQ) 45-62) and the age at onset of symptoms was nine years (IQ 1-25). Most of the sample, 77 (87%) were women. No patient declared as current smoker and 22 (25%) reported previous smoking history. Almost half of those studied patients [43 (49%)] were obese. The median BMI was 29 kg/m^2 (IQ 26-34). Most patients [73 (83%)] admitted GERD symptoms, with median QS-GERD scores of nine (IQ 4-15). Almost all cases [87 (99%)] had rhinitis symptoms. We found a significantly higher proportion of patients with obesity, GERD and rhinitis in the AG-ERS/ATS group than in the group without AG-ERS/ATS (Table 1).

Treatment features

The main inhaled corticosteroids used as control medication were beclomethasone dipropionate 78 (88%), budesonide (BUD) 69 (78%), fluticasone propionate 17 (19%), mometasone furoate monohydrate 1 (1%), nevertheless, the long-acting bronchodilators were formoterol 69 (78%) and salmeterol 17 (19%). Many patients used a combination of inhaled corticosteroids for maintaining a higher dose. Most patients had adequate adherence according to self-report [68 (77%)], but this proportion was lower when assessed through pharmacy records [50 (57%)]. A total of 977 inhalation device technique evaluations were performed, and only six (0.6%) cases showed severe errors involving the inhalation technique.

Functional features

The median absolute values and percentages of FEV_1 and Forced Expiratory Flow $(FEF)_{25-75}$ post-BD were slightly lower in patients with AG-ERS/ATS [$FEV_{1post-BD}$ = 1.7L (IQ 1.3-2.0) and $FEV_{1\ post-BD}$ = 67% (IQ 55-80); FEF_{25-75} = 0.9L/s (IQ 0.6-1.5) and FEF25-75 37% (IQ 26-64)] compared to those without AG-ERS/ATS [$FEV_{1\ post-BD}$ = 1.8L (1, 4-2.3) and $FEV_{1\ post-BD}$ = 69% (IQ 58-81) and FEF_{25-75} = 1.1L/s (IQ 0.7-1.8) and FEF_{25-75} = 41% (30-63) with statistically significant difference only in relation to the absolute value of FEV1 (Table 1).

Laboratory features

Absolute and relative peripheral blood eosinophil counts [209 cells/mm3 (IQ 16-321) and 3% [(IQ 1-5), respectively]) were significantly lower in AG-ERS/ATS patients compared to patients without AG-ERS/ATS [258 cells/mm3 (IQ154-403) and 4% (IQ3-7)]. The opposite was true for absolute and relative neutrophil count values [3988 cells/mm3 (IQ 2958-5191) and 58% (IQ 51-65), respectively], which was significantly higher in patients with ER-ERS./ATS, compared to those without severe asthma [3481 cells/mm3 (IQ 2409-4548) and 55% (48-61)].

The median total IgE concentration was 276 IU/mL (IQ 117-423) and 52 (69%) patients had positive skin test for aeroallergens (Table 1) among patients with AG-ERS/ATS.

A parasitological stool examination was performed on 446 patients. Only 10 (2%) presented parasites associated with eosinophilia (four infected with strongyloidiasis, three with ascariasis and three with schistosomiasis). Only two patients with AG-ERS/ATS had positive samples for stool parasitology and only one of these had peripheral blood eosinophil count > 260 cells/mm3. The low proportion of patients with positive samples for stool parasitology in this category rule out the influence of parasitosis on eosinophil count results.

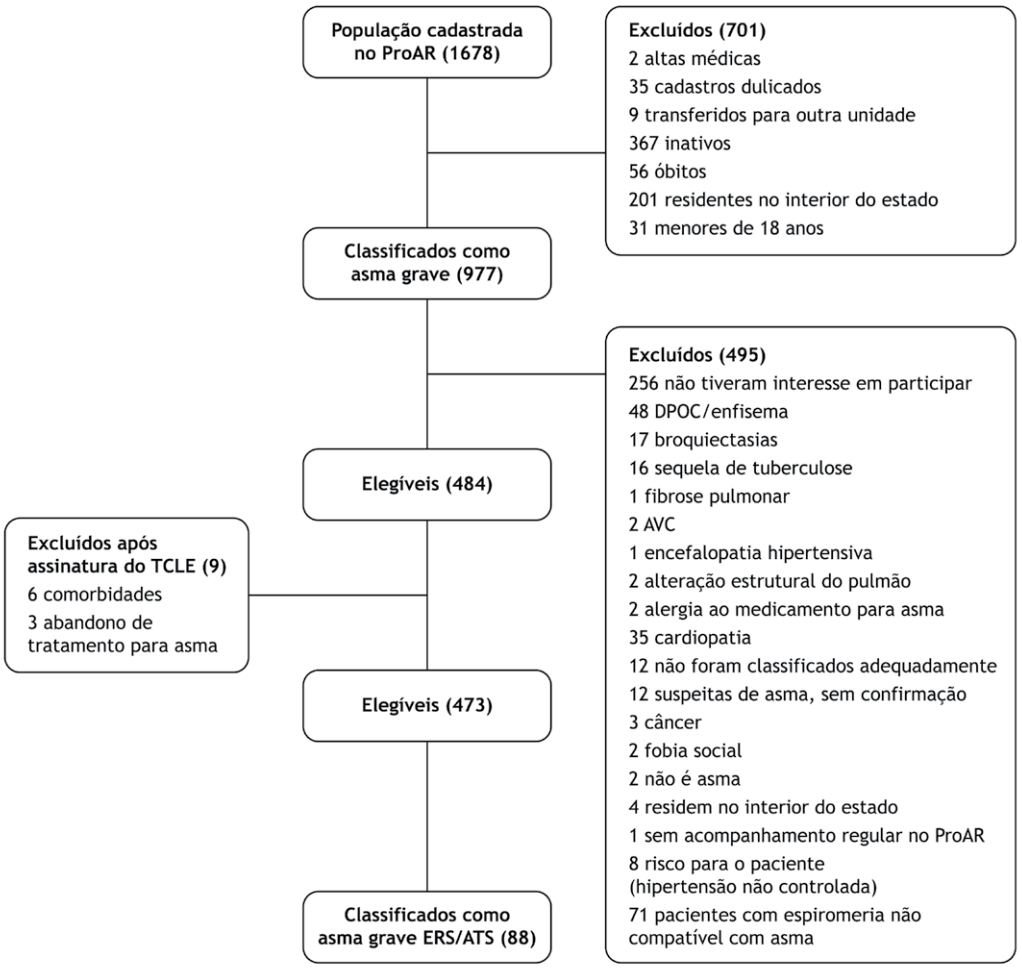


Figure 1. Inclusion and evaluation in the study. The eligibility criteria mentioned were in relation to the main study. The reclassification of patients according to the 2014 ERS/ATS criteria resulted in the final sample of 88 patients considered to have severe asthma (AG-ERS/ATS).

Adjusted analysis

Factors associated with AG-ERS/ATS were verified by multivariate logistic regression. Age, age at onset of symptoms, gender, obesity (BMI > 30 kg/m^2), rhinitis, GERD and eosinophil count > 260 cells/mm^3 were included in the model.

Analysis showed that patients with GERD symptoms were 2.28 times more likely to have AG-ERS/ATS than those without these complaints. Patients with eosinophil counts > 260 cells/mm^3 were 42% less likely to have AG-ERS/ATS than those with eosinophil counts ≤ 260 cells/mm^3 (Table 2).

Exacerbations in the last year

Patients with AG-ERS/ATS had significantly higher morbidity [sought emergency 1.5 times more (95% CI 1.09-2.32) and used oral corticosteroids last year 3.8 times (95% CI 2.40-6,16) when compared to patients without AG-ERS/ATS] (Table 3).

Control evaluation

In patients with AG-ERS/ATS, the median ACQ-6 score was 1.5 (IQ 0.8-2.3) and AQLQ was 3.4 (IQ 2.5-4.7) showing poor control and poor quality of life, respectively, with a statistically significant difference when compared to the scores of patients without severe asthma. By GINA categorical classification, 24 (27%) patients were controlled, 35 (39%) were partially controlled, and 29 (32%) were uncontrolled (Table 4).

DISCUSSION

In our study, the proportion of AG-ERS/ATS was higher than that presented in the general literature, in samples obtained from specialized services. This

Table 1. Sociodemographic, clinical, functional and laboratory features of patients with severe asthma according to the criteria of the ERS/ATS 2014 (AG-ERS/ATS) compared to the group without AG-ERS/ATS[a].

Feature	With AG-ERS/ATS n = 88	Without AG-ERS/ATS n = 385	*p* value
Female gender - n (%)	77(87)	303 (78)	0.61 [¥]
Age/Years - Md (IQ)	53 (45-62)	51 (42-61)	0.21 [T]
Asthma onset > 18 years - n (%)	39(44)	137 (35)	0.12 [¥]
Age at onset of symptoms (years) Md (IQ)	9 (1-25)	10 (2-25)	0.73 [T]
Current smoking - n (%)	0	5 (1)	0.53 [Ω]
Obesity (BMI ≥30 kg/m^2) - n (%)	43 (48)	140(36)	0.03 [¥]
BMI kg/m^2 - Md (IQ)	29 (26-34)	28 (24-31)	0.01 [T]
GERD symptoms - n (%)	73(83)	252 (65)	<0.01 [¥]
QS DRGE * in scores - Md (IQ)	9 (4-15)	7 (1-12)	0.01 [T]
Symptoms of chronic rhinitis - n (%)	87(99)	359 (93)	0.04 [¥]
Beclomethasone use - n (%)	78(88)	111(28)	<0.01 [¥]
Budesonide (BUD) use - n (%)	88(69)	299(77)	0.26 [¥]
Fluticasone use - n (%)	17(19)	67(17)	0.67 [¥]
Formoterol use - n (%)	69(78)	301(78)	0.14 [¥]
Salmeterol use - n (%)	17(19)	68(17)	0.71 [¥]
Treatment adherence (pharmacy records) - n (%)	50(57) [#]	178(46) [##]	0.07 [¥]
Treatment adherence (self-report) - n (%)	68(77)	310(80) [###]	0.46 [¥]
FEV1 $_{post\ BD}$ <60% - n (%)	41(46) [#]	163(42)	0.46 [¥]
FEV1 $_{post\ BD}$ L - Md (IQ)	1.7(1.3-2.0)	1.8(1.4-2.3)	0.32 [T]
FEV1 $_{post\ BD}$ % predicted - Md (IQ)	67(55-80)	69 (58-81)	0.22 [T]
Neutrophils % - Md (IQ)	58(51- 65)	55(48-61) [⊥]	<0.01[T]
Neutrophils cells/mm^3 - Md (IQ)	3988(2958-5191)	3481(2409-4548) [⊥]	<0.01[T]
Eosinophils % - Md (IQ)	3 (1-5)	4(3-7) [⊥]	<0.01[T]
Eosinophils cells/mm3 - Md (IQ)	209(116-321)	258(154-403) [⊥]	0.01[T]
Eosinophils> 260 cells/mm^3	32 (36) [⊥]	189(49) [⊥]	0.02 [¥]
IgE IU/ml - Md (IQ)	276 (117-423)	346 (149-517)	0.10 [T]
Positive skin test - n (%)	52 (69) [⊥⊥]	224 (63) [⊥⊥⊥]	0.34 [¥]

[a]Values expressed as *n* (%) for categorical variables and median (Md)/interquartile range (IQ) for continuous variables; [¥]Chi-square test; [Ω]Fisher Fisher's exact test; [T]Mann-Withney test; *QS GERD: Questionnaire on the severity of symptoms of Gastroesophageal Reflux Disease; [#]n: 87 patients; [##]n: 380 patients; [###]n: 384 patients; [⊥]n: 381 patients; [⊥⊥]n: 75 patients; [⊥⊥⊥]n: 352 patients. n (%): number of cases in absolute values and percentage; p: probability of significance.

Table 2. Multivariate logistic regression analysis model for the evaluation of possible factors associated with severe asthma by the criteria of the ERS/ATS 2014 (AG-ERS/ATS).

Variable	Gross effect (OR; CI95%)	Adjusted effect* (OR; CI95%)
Feminine gender	1.89 (0.96-3.73)	1.41 (0.71-2.59)
Age in years		1.00 (0.98-1.02)
Onset of asthma symptoms> 18 years	1.44 (0.90-2.3)	1.50 (0.89-2.52)
Obesity*	1.67 (1.05-2.67)	1.46 (0.89-2.39)
GERD symptoms	2.57 (1.42-4.65)	2.28 (1.22-4.23)
Rhinitis Symptoms	6.30 (0.84-47.7)	4.55 (0.58-35.4)
Eosinophils > 260 cells/mm3	0.58 (0.36-0.94)	0.58 (0.35-0.96)

*BMI> 30 (WHO). ERS: European Respiratory Society; ATS: American Thoracic Society; AG: Severe Asthma; OR: Odds Ratio; 95% CI: 95% Confidence Interval; GERD: Gastroesophageal Reflux Disease.

Table 3. Comparison between the proportion of patients with exacerbations in the last year according to the presence or absence of severe asthma concerning the ATS/ERS 2014 classification (AG-ERS/ATS)[12].

Feature	AG-ERS/ATS YES n = 88	AG-ERS/ATS NO n = 385	*p* value	PR (CI95%)
Visits to emergency services n (%)	35 (39)	104 (27)	<0.01[¥]	1.59 (1.09-2.32)
Oral corticosteroid use	68 (77)	198 (51)	0.01[¥]	3.85 (2.40-6.16)
n (%)	6 (6)	16 (4)	<0.28[¥]	1.50 (0.74-3.05)

Values expressed in n (%). [¥]Chi-square test; PR= Prevalence Ratio. CI95%: Confidence interval 95%; n (%): number of cases in absolute values and percentage; p: probability of significance.

Table 4. Evaluation of asthma symptom control among patients with severe asthma according to ATS/ERS 2014 classification (AG-ERS/ATS) and comparison with patients without AG-ERS/ATS[12].

Features	AG-ERS/ATS YES n = 88	AG-ERS/ATS NO n = 385	*p* value
ACQ-6 score - Md (IQ)	1.5 (0.8-2.3)	0.8 (0.3-1.6)	<0.01[T]
AQLQ score - Md (IQ)	3.4 (2.5-4.7)	4 .6 (3.5-5.6)	<0.01[T]
GINA Control Level - n (%)			<0.01[¥]
Controlled	24 (29)	184 (47)	
Partially Controlled	35 (39)	136 (35)	
Uncontrolled	29(32)	65 (16)	

Values expressed as median Md (IQ) and interquartile range. [¥]Chi-square test; [T]Mann-Withney test. n (%): number of cases in absolute values and percentage; p: probability of significance; ACQ-6: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; GINA: Global Initiative for Asthma; ERS: European Respiratory Society; ATS: American Thoracic Society.

result is justified because they are patients followed in a specific outpatient clinic for severe asthma. To be admitted to the program in the past, such patients would initially have to meet the current severity criteria from 2003 and have been reclassified to the most current severity criteria from 2015.

No patient claimed to be a smoker. Smoking is an exclusion condition for dispensing formoterol + budesonide according to a decree of the Ministry of Health. Some patients may have omitted this information during the interview. Some studies, using indirect measures of smoking such as urinary cotinine test, showed an omission of smoking among asthmatic patients. Pinheiro et al.,[26] in a study of 1341 individuals in Salvador-BA, including the sample evaluated in the present study, observed elevated urinary cotinine levels among some self-reported non-smokers and past smokers, especially in patients with severe asthma. Stelmach found 38% omission among asthmatic patients and patients with COPD in a study conducted at a referral outpatient clinic in São Paulo.[27]

Regarding treatment, patients received free of charge the drugs listed in *Relação Nacional de Medicamentos Essenciais* (RENAME) and/or the list of specialized components of the "Bahia State Health Department", standardized by SUS. The discrepancy between adherence declared and obtained by the pharmacy is explained, in part, by the shortage of public pharmacies that occurred in some periods throughout the main study, causing patients to purchase them with their own resources. Considering self-report, our rates are higher than those described in the literature.[28] The extremely low proportion of errors in inhalation technique results from the multiprofessional approach and continuing education applied to ProAR patients.

As for comorbidities, the patients with AG-ERS/ATS studied had more obesity, symptoms of GERD and rhinitis when compared to patients without severe asthma (Table 1).

The proportion of obese patients in this study was high, especially in the group with severe asthma. Studies show a higher prevalence of asthma among obese,[29] who tend to have worse control and greater impairment of lung function.[30] Heaney et al.[31] observed a median BMI similar to our study in patients with refractory asthma in a multicenter study in the United Kingdom (UK). Several pathophysiological mechanisms have been proposed to justify this association[32] but the causal relationship has not yet been clearly established.

The GERD symptoms were more frequent in AG-ERS/ATS patients, according to the median QS-GERD score. In addition, the association between severe asthma and GERD symptoms was found in both crude and adjusted analysis. The prevalence of GERD in the general population ranges from 8-33%[33] and in asthmatics, it exceeds 50%.[34] The "reflux and reflex theory"[35] proposes that both "reflux leads to asthma and asthma leads to reflux". Although the current study was based on self-report, the validated QS-DRGE[24] questionnaire was used, increasing the reliability of this information.

Our results also corroborated the "single airway disease" hypothesis.[36] The North American multicenter study TENOR II identified allergic rhinitis as the most common comorbidity among patients with severe/difficult to treat asthma.[37]

The inverse relationship between eosinophil count > 260 cells/mm^3 and higher asthma severity can be explained by the profile of our sample. The AG-ERS/ATS by definition, includes the need for high doses of corticosteroids, which are known to induce eosinophil apoptosis and inhibit neutrophil apoptosis.[38] Ortega et al.[39] observed in a real-life study a decrease in blood eosinophil count following corticosteroid use in patients with severe or persistent asthma. In addition, our sample consisted of mostly female and largely obese, a phenotype that may be associated with the non-TH2 profile. Furthermore, it is known that patients with eosinophilic asthma tend to respond better to corticosteroids, which would not generally qualify them for the AG-ERS/ATS criteria. It is important to highlight the study by Lima-Matos et al.,[13] which found an association between number of eosinophils in the blood > 260 cells/mm^3, lack of control and significant asthma severity. The authors evaluated a population from the same referral center and included the sample of patients with severe asthma used in our study. Patients

without asthma, from mild to moderate asthma and severe asthma were included, and in this last group, previous criteria of severity were used, which are included in the standardization proposal presented to the WHO.[11] The difference between the results of the two studies reflects how much the choice of severity criterion may influence the identification of groups with distinct clinical characteristics.

Patients with AG-ERS/ATS also had more visits to emergency services, poorer control and poorer quality of life. This, our results are as expected and agree with similar studies.[40]

In conclusion, the present study, by re-evaluating 473 patients classified as severe asthma according to previous criteria, found that only 88 (18%) patients fell into the severe asthma category according to the 2014 ERS/ATS classification. Gastroesophageal reflux symptoms were associated with AG-ERS/ATS and eosinophil count > 260 cells/mm^3, in contrast, was inversely associated with AG-ERS/ATS.

REFERENCES

1. Hekking PW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. J Allergy Clin Immunol. 2015;135(4):896-902. http://dx.doi.org/10.1016/j.jaci.2014.08.042. PMid:25441637.
2. O'Neill S, Sweeney J, Patterson CC, Menzies-Gow A, Niven R, Mansur AH, et al. The coast of treating severe refractory asthma in the UK: an economic analysis from British Thoracic Society Difficult Asthma Registry. Thorax. 2015;70(4):376-8. http://dx.doi.org/10.1136/thoraxjnl-2013-204114. PMid:24917087.
3. Franco R, Santos AC, Nascimento HF, Souza-Machado C, Ponte E, Souza-Machado A, et al. Cost-effectiveness analysis of a state funded programme for control of severe asthma. BMC Public Health. 2007;7(1):82. http://dx.doi.org/10.1186/1471-2458-7-82. PMid:17509137.
4. Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, et al. Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: differences with Age. J Allergy Clin Immunol Pract. 2018;6(2):545-54. http://dx.doi.org/10.1016/j.jaip.2017.05.032. PMid:28866107.
5. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. Eur Respir J. 2015;46(5):1308-21. http://dx.doi.org/10.1183/13993003.00779-2015. PMid:26357963.
6. Pereira ED, Cavalcante AG, Pereira EN, Lucas P, Holanda MA. Controle da asma e qualidade de vida em pacientes com asma moderada ou grave. J Bras Pneumol. 2011;37(6):705-11. http://dx.doi.org/10.1590/S1806-37132011000600002. PMid:22241026.
7. Athanazio R, Carvalho-Pinto R, Fernandes FL, Rached S, Rabe K, Cukier A, et al. Can severe asthmatic patients achieve asthma control? A systematic approach in patients with difficult to control asthma followed in a specialized clinic. BMC Pulm Med. 2016;16(1):153. http://dx.doi.org/10.1186/s12890-016-0314-1. PMid:27852260.
8. Andrade WCC, Lasmar LMLBF, Ricci CAT, Camargos PAM, Cruz AA. Phenotypes of severe asthma among children and adolescents in Brazil: a prospective study. BMC Pulm Med. 2015;15(1):36. http://dx.doi.org/10.1186/s12890-015-0029-8. PMid:25912047.
9. Rodrigues AM, Roncada C, Santos G, Heinzmann-Filho JP, Souza RG, Vargas MHM, et al. Clinical characteristics of children and adolescents with severe therapy-resistant asthma in Brazil. J Bras Pneumol. 2015;41(4):343-50. http://dx.doi.org/10.1590/S1806-37132015000004462. PMid:26398754.
10. Kuschnir FC, Felix MMR, Kuschnir MCC, Bloch KV, Azevedo E, Solé D. LedoAJ.Severe asthma is associated with metabolic syndrome in Brazilian adolescents. J Allergy Clin Immunol. 2018;141(5):1947-9. http://dx.doi.org/10.1016/j.jaci.2018.01.026. PMid:29427644.
11. Bousquet J, Mantzouranis E, Cruz A, Aït-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol. 2010;126(5):926-38. http://dx.doi.org/10.1016/j.jaci.2010.07.019. PMid:20926125.
12. Cruz AA, Souza-Machado A, Franco R, Souza-Machado C, Ponte EV, Santos PM, et al. The impact of a program for control of asthma in a low-income setting. World Allergy Organ J. 2010;3(4):167-74. http://dx.doi.org/10.1097/WOX.0b013e3181dc3383. PMid:23268428.
13. Lima-Matos A, Ponte EV, Jesus JPV, Almeida PCA, Lima VB, Kwon N, et al. Eosinophilic asthma, according to a blood eosinophilcriterion, is associated with disease severity and lack of control among underprivileged urban Brazilians. Respir Med. 2018;145:95-100. http://dx.doi.org/10.1016/j.rmed.2018.10.025. PMid:30509723.
14. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343-73. http://dx.doi.org/10.1183/09031936.00202013. PMid:24337046.
15. NAEPP: National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol. 2007;120(5, Suppl.):S94-138. PMid:17983880. http://dx.doi.org/10.1016/j.jaci.2007.09.029
16. GINA: Global Initiative for Asthma. Global strategy for asthma management and prevention. Fontana, WI; 2002.
17. WHO: World Health Organization. Obesity: preventing and managing the global epidemic. Report of WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1-253. PMid:11234459.
18. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, et al. Practical guide to skin prick tests in allergy to aeroallergens. Allergy. 2012;67(1):18-24. http://dx.doi.org/10.1111/j.1398-9995.2011.02728.x. PMid:22050279.
19. ATS: American Thoracic Society. Standardization of Spirometry, 1994 Update. Am J Respir Crit Care Med. 1995;152(3):1107-36. http://dx.doi.org/10.1164/ajrccm.152.3.7663792. PMid:7663792.
20. Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. J Bras Pneumol. 2007;33(4):397-406. http://dx.doi.org/10.1590/S1806-37132007000400008. PMid:17982531.
21. Zhang XY, Simpson JL, Powell H, Yang IA, Upham JW, Reynolds PN, et al. Full blood count parameters for the detection of asthma inflammatory phenotypes. Clin Exp Allergy. 2014;44(9):1137-45. http://dx.doi.org/10.1111/cea.12345. PMid:24849076.
22. Leite M, Ponte EV, Petroni J, D'Oliveira Júnior A, Pizzichini E, Cruz AA. Avaliação do questionário de controle da asma validado para uso no Brasil. J Bras Pneumol. 2008;34(10):756-63. http://dx.doi.org/10.1590/S1806-37132008001000002. PMid:19009207.
23. Silva LMC, Silva LCC. Validação do questionário de qualidade de vida em asma (Juniper) para o português brasileiro. Rev Assoc Med Rio Grande do Sul. 2007;51(1):31-7.
24. Fornari F, Gruber AC, Lopes AB, Cecchetti D, Barros SG. Questionário de sintomas na doença do refluxo gastroesofágico. Arq Gastroenterol. 2004;41(4):263-7. http://dx.doi.org/10.1590/S0004-28032004000400012. PMid:15806272.
25. GINA: Global Initiative for Asthma. Global strategy for asthma management and prevention. NHLB/Who Report. 2014;63(7):932-8.
26. Pinheiro GP, Souza-Machado C, Fernandes AGO, Mota RCL, Lima LL, Vasconcellos DS, et al. Tabagismo entre asmáticos: avaliação por autorrelato e dosagem de cotinina urinária. J Bras Pneumol. 2018;44(6):477-85. http://dx.doi.org/10.1590/s1806-37562017000000018. PMid:30304204.
27. Stelmach R, Fernandes FL, Carvalho-Pinto RM, Athanazio RA, Rached SZ, Prado GF, et al. Comparison between objective measures of smoking and self-reported smoking status in patients with asthma or COPD: are our patients telling us the truth? J Bras Pneumol. 2015;41(2):124-32. http://dx.doi.org/10.1590/S1806-37132015000004526. PMid:25972966.
28. Bårnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. Respir Care. 2015;60(3):455-68. http://dx.doi.org/10.4187/respcare.03200. PMid:25118311.
29. Akinbami LJ, Fryar CD. Current asthma prevalence by weight status among adults: United States, 2001-2014 [Internet]. [cited 2017 Mar 13]. Atlanta: CDC; 2016. Available from: https://www.cdc.gov/nchs/products/databriefs/db239.htm
30. Jesus JPV, Lima-Matos AS, Almeida PCA, Lima VB, Mello LM, Souza-Machado A, et al. Obesidade e asma: caracterização clínica elaboratorial

de uma associação frequente. J Bras Pneumol. 2018;44(3):207-12. http://dx.doi.org/10.1590/s1806-37562017000000034. PMid:30043887.

31. Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. Thorax. 2010;65(9):787-94. http://dx.doi.org/10.1136/thx.2010.137414. PMid:20805172.
32. Peters U, Dixon AE, Forno E. Obesity and asthma. J Allergy Clin Immunol. 2018;141(4):1169-79. http://dx.doi.org/10.1016/j.jaci.2018.02.004. PMid:29627041.
33. El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2014;63(6):871-80. http://dx.doi.org/10.1136/gutjnl-2012-304269. PMid:23853213.
34. Havemann BD, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. Gut. 2007;56(12):1654-64. http://dx.doi.org/10.1136/gut.2007.122465. PMid:17682001.
35. Ates F, Vaezi MF. Insight into the relationship between gastroesophageal reflux disease and asthma. Gastroenterol Hepatol. 2014;10(11):729-36. PMid:28435409.
36. Giavina-Bianchi P, Aun MV, Takejima P, Kalil J, Agondi RC. United airway disease: current perspectives. J Asthma Allergy. 2016;2016:93-100. http://dx.doi.org/10.2147/JAA.S81541. PMid:27257389.
37. Chipps BE, Haselkorn T, Paknis B, Ortiz B, Bleecker ER, Kianifard F, et al. More than a decade follow-up in patients with severe or difficult-to-treat asthma: the epidemiology and natural history of asthma: outcomes and Treatment Regimens (TENOR) II. J Allergy Clin Immunol. 2018;141(5):1590-7. http://dx.doi.org/10.1016/j.jaci.2017.07.014. PMid:28797732.
38. Dunican EM, Fahy JV. Asthma and corticosteroids: time for a more precise approach to treatment. Eur Respir J. 2017;49(6):1701167. http://dx.doi.org/10.1183/13993003.01167-2017. PMid:28663322.
39. Ortega H, Llanos JP, Lafeuille MH, Duh MS, Germain G, Lejeune D, et al. Effects of systemic corticosteroids on blood eosinophil counts in asthma: real-world data. J Asthma. 2018;16:1-8. http://dx.doi.org/10.1080/02770903.2018.1502301. PMid:30130418.
40. Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. BMC Pulm Med. 2017;17(1):74. http://dx.doi.org/10.1186/s12890-017-0409-3. PMid:28449686.

J Bras Pneumol. 2020;46(3):e20190102
http://dx.doi.org/10.36416/1806-3756/e20190102

ORIGINAL ARTICLE

Assessment of asthma control among different measures and evaluation of functional exercise capacity in children and adolescents with asthma

Natasha Yumi Matsunaga[1,2], Caio de Oliveira[2], Livea Gianfrancesco[1,2], Marina Simões Oliveira[1,2], Maria Cristina Ribeiro dos Santos Simões[2], André Moreno Morcillo[3], José Dirceu Ribeiro[2,3], Maria Angela Gonçalves de Oliveira Ribeiro[2,3], Adyléia Aparecida Dalbo Contrera Toro[2,3]

1. Programa de Pós-Graduação em Saúde da Criança e do Adolescente, Universidade Estadual de Campinas, Campinas (SP) Brasil.
2. Laboratório de Fisiologia Pulmonar, Universidade Estadual de Campinas, Campinas (SP) Brasil.
3. Departamento de Pediatria, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas (SP) Brasil.

Submitted: 10 April 2019.
Accepted: 13 June 2019.

Study carried out in the Ambulatório de Pediatria, Setor de Pneumologia Pediátrica Hospital das Clinicas, Faculdade de Ciências Médicas, Universidade Estadual de Campinas e no Laboratório de Fisiologia Pulmonar, Centro de Investigação em Pediatria, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas (SP) Brasil.

ABSTRACT

Objective: To assess the agreement among asthma control measures and functional exercise capacity in children and adolescents with uncontrolled and controlled asthma. **Methods:** Children and adolescents with asthma from 7-17 years old were selected, and they were attended in the "Pediatric Pulmonology Outpatient Clinic of State University of Campinas", in Brazil. All patients had asthma control level assessed by Global Initiative for Asthma questionnaire (GINAq), Asthma Control Test (ACT), spirometry and six-minute-walk-test (6MWT). Patients were classified as uncontrolled or controlled asthma in each test and agreement among measures was assessed by kappa statistics. The ROC curve was calculated for the 6MWT. The spirometric index obtained from spirometry was composed by FEV1, FEV1/FVC and FEF25-75%. Spirometry and 6MWT results were compared between uncontrolled and controlled asthma group by GINAq. **Results:** Of the 138 subjects included, 78 (56.5%) were male with median age of 11 (7-17) years old. GINAq detected 68.8% of patients with uncontrolled asthma. Moderate agreement ($\rho < 0.001$; $k = 0.56$) and high specificity (100%) was observed between GINAq and ACT. In 6MWT, the cut-off point of 82.03% of predicted distance was able to distinguish patients with controlled and uncontrolled asthma. Spirometric index presented 73.4% of sensitivity according to GINAq. The results for 6MWT in patients with uncontrolled asthma were the worst of all. **Conclusion:** This study highlights the importance of assessing more than one measure to differentiate asthma control level. GINAq identified more patients with uncontrolled asthma and presented moderate agreement with ACT. Spirometric index was associated with uncontrolled asthma according to GINAq. 6MWT was a suitable measure to distinguish patients with controlled and uncontrolled asthma.

Keywords: Asthma; Asthma control; Spirometry; Walk test; Children.

INTRODUCTION

Asthma control is defined by the extent to which the manifestations of asthma are reduced, decreased or removed with treatment.[1] It is determined by association among individual genetic factors, phenotypic expression, appropriate treatment, adherence, inhaler technique, response to therapy, environment control, trigger exposure, psychosocial and socioeconomic factors.[1-3]

The assessment of asthma control is important to guide the treatment, to provide information about the disease progression and its underestimation, seeing that it is a risk for increasing morbidity and mortality of asthmatic patients.[1,4,5] Asthma control level can be assessed by history of symptoms control by including the analysis of future risks of adverse outcome, physical examination and Pulmonary Function Tests (PFT) (spirometry measures).[1,5]

Studies have assessed asthma control according to the conventional clinical assessment by pediatrician, standardized questionnaires, lung function and inflammatory markers to establish the most appropriate measure for asthma evaluation, but there is a disagreement between these results.[5-8] Moreover, there is a lack of studies

Correspondence to:
Adyléia Aparecida Dalbo Contrera Toro. Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Rua Tessália Vieira de Camargo, 126, Cidade Universitária Zeferino Vaz, CEP 13083-887, Campinas, SP, Brasil.
Tel.: 55 19 3521-8983/55 19 3521-8958. E-mail: dalbotoro@terra.com.br
Financial support: Process nº 2016/22102-8, Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).

which assessed asthma control using cardiorespiratory tests, such as six-minute walk test (6MWT) in pediatric age groups, and that evaluated differences in 6MWT between asthma control groups.

The objective of this study was to assess the agreement among asthma control measures, as GINAq, ACT, spirometry and 6MWT. Furthermore, it was also important to compare pulmonary lung function and functional exercise capacity between controlled and uncontrolled patients, classified by GINAq.

METHODS

Participants and study protocol

This was a prospective, observational, cross-sectional and analytical clinical study performed at the "Pulmonary Physiology Laboratory of the Pediatric Research Center" of the State University of Campinas – *Universidade Estadual de Campinas* (Unicamp).

Children and adolescents diagnosed with asthma from 7-17 years old were selected, and they were attended in the "Pediatric Pulmonology Outpatient Clinic" of Unicamp, in Brazil. The excluding criteria were: patients who presented cardiac comorbidities; other respiratory diseases; cognitive or motor limitations that could compromise their performance in any of the tests; who had exacerbated asthma on the day of test or those who could not perform all tests in the same day.

This study was approved by the "Research Ethics Committee" of the "Unicamp School of Medical Sciences" (Ruling no.438.481/2013). Parents or legal guardians of all children and adolescents signed a written informed consent (IC) document.

Measures of asthma control

In this study, asthma control was assessed through Global Initiative for Asthma questionnaire (GINAq), Asthma Control Test (ACT), spirometry and six-minute-walk-test (6MWT).

Step 1: GINAq is made by internationally renowned specialists to assess asthma control based on history of symptom control.[1] In this questionnaire, asthmatics must answer four questions about the past four weeks: a) presence of daytime asthma symptom more than twice a week; b) presence of any night waking due to asthma; c) needed to use relief medication for asthma symptoms more than twice a week; d) presence of any activity limitation due to asthma.[1] In this study, patients were classified as controlled asthma if they answered "no" to all questions and uncontrolled asthma when they answered "yes" to at least one question.[9]

Step 2: ACT consists in five questions regarding to daytime and nocturnal symptoms, presence of activity limitation, needed to use relief medication and self-evaluation of asthma control in the last four weeks.[10,11] The final score ranges from 5 to 25 points. Patients with 20 points or more were classified as controlled asthma and scores up to 19 points were considered uncontrolled asthma.[10]

Step 3: Spirometry was performed with spirometer CPFS/D model (Medical Graphics Corporation, St. Paul, MN, USA) according to the recommendations of European Respiratory Society (ERS) and American Thoracic Society (ATS).[11] Parameters were expressed as a percentage of predicted value reference and were evaluated before and after using four jets of 100 mcg each of salbutamol.[12]

For spirometry, patients were considered as controlled asthma if they presented: a) Tiffeneau index (FEV1/FVC) > 0.8 in adolescents with 12 years old or more and > 0.9 in children with 7-11 years old; b) forced expiratory volume in the first second (FEV1) pre-bronchodilator ≥ 80% of predicted; c) an increase on FEV1 post-bronchodilator < 12% and 200 mL from baseline in adolescents with 12 years old or more and < 12% in children with 7-11 years old; d) forced expiratory flow between 25% and 75% of Forced Vital Capacity (FEF 25-75%) pre-bronchodilator > 70% of predicted; e) an increase on FEF 25-75% post-bronchodilator < 30%;[1,13,14] f) normal spirometric index, which is developed from parameters of FEV1, FEV1/FVC and FEF25-75% regarding interpretation according to previously mentioned criteria. In spirometric index, the patient was classified as uncontrolled asthma if he/she had one altered parameter in spirometry.

If the patient does not fulfill any of the parameters from "a" to "f", he or she was classified as uncontrolled asthma. The classification in controlled and uncontrolled asthma was made in each parameter of spirometry. Spirometric parameters were also compared between groups of uncontrolled and controlled asthma classified by GINAq.

Six-Minute-Walk-Test (6MWT)

The 6MWT is a submaximal test, performed according recommendations of the American Thoracic Society (ATS).[15] The patient was asked to walk as far as possible in a flat floor, without running or jogging for 6 minutes.

The cardiorespiratory parameters were measured for heart rate, respiratory rate, systemic blood pressure, oxygen saturation and also for Borg scale for dyspnea and overall fatigue at baseline and immediately after the test.[15] During the test, standard phrases of encouragement were used and heart rate, oxygen saturation and Borg scale for dyspnea and overall fatigue were measured in 2, 4 and 6 minutes.[15] The 6MWT was immediately stopped if patient presented chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.[15]

To analyze the cardiorespiratory parameters in 6MWT, the variation between post-test and pre-test values were calculated. Total distance walked and percent of predicted distance was calculated in meters by using reference formulas for the Brazilian population.[16,17]

Patients with asthma were considered controlled if they: a) completed and finished the test regardless distance walked; b) presented values of percent-predicted distance above the cut-off point established by ROC curve. Otherwise, the patient was classified as uncontrolled asthma. The classification of controlled and uncontrolled asthma was made in both items of 6MWT.

6MWT variables were also compared between groups of uncontrolled and controlled asthma classified by GINAq.

Statistical analysis

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

Categorical variables were presented in a descriptive form and the differences were analyzed using the Chi-square test.

To calculate the cut-off point in 6MWT to classify in uncontrolled and controlled asthma, the classification by GINAq and created the ROC curve in MedCalc program were used, and the better value was defined by Youden index.

The outcome for each test was coded as uncontrolled (1) or controlled (2) asthma. Agreement among measures was assessed by cross-tabulation and kappa statistics (poor agreement ≤ 0.4; moderate agreement between 0.4 and 0.75; excellent agreement ≥ 0.75).[18]

GINAq was considered the gold-standard test, and affected by this disease (asthma) if the patient was classified as uncontrolled asthma. The sensitivity, specificity, positive and negative predictive values and accuracy with other measures were calculated by using the Openepi program version 3 - Diagnostic test.

To compare the distributions of nonparametric quantitative variables among two groups, the Mann-Whitney test was used. In all cases, the level of significance was set at 5%.

RESULTS

It could be evaluated all patients with asthma who were followed up in our Outpatient Clinic during the study period. Out of 261 patients selected based on inclusion criteria, 21 were excluded by presence of cardiac comorbidities, 63 for other respiratory diseases, 14 for cognitive limitations, three for motor limitations, nine by presence of immunodeficiency disease, three by presence of anaphylaxis history and 10 did not want to participate in this study.

Of the 138 children and adolescents included, 78 (56.5%) were male and the median age was 11 (7-17) years. According to GINAq, 43 (31.2%) children and adolescents were classified as controlled asthma, and 95 (68.8%) as uncontrolled asthma. The comparison of general characteristics of uncontrolled and controlled asthmatic patients are shown in Table 1.

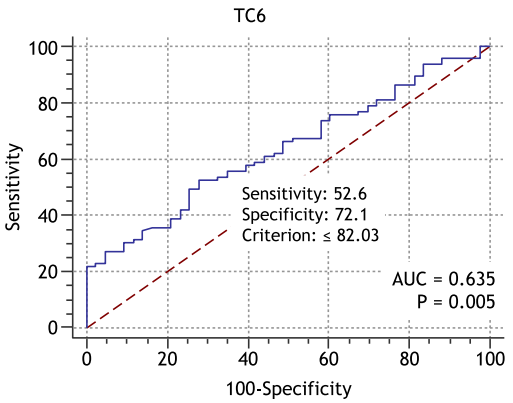


Figure 1. ROC-curve and cut-off point of controlled and uncontrolled asthma using percentage-predicted distance in 6MWT.

Table 1. General characteristics of asthmatic children and adolescents of this study.

Variable	Uncontrolled asthma by GINAq	Controlled asthma by GINAq	p
Demographics characteristics			
Male gender	*55 (70.5)*	23 (29.5)	0.629*
Caucasian race	*48 (75.0)*	16 (25.0)	0.223*
Anthropometric characteristics			
Age (years)	10 (7-17)	11 (7-17)	0.256**
Weight (kg)	38.3 (20.9-91.6)	40.65 (22.3-79.3)	0.168**
Height (m)	1.42 (1.19-1.72)	1.44 (1.20-1.71)	0.346**
BMI	19.39 (13.6-35.96)	18.87 (15.04-33.64)	0.279**

GINAq: Global Initiative for Asthma questionnaire; kg: kilograms; m: meters; BMI: Body Mass Index; p≤0.005. Statistic test: *Chi-square Test; **Mann-Whitney Test.

In 6MWT, the better cut-off to distingue patients in controlled and uncontrolled asthma using the predicted distance was 82.03%, with 52% of sensitivity and 72.1% of specificity (Figure 1).

GINAq identified more patients with uncontrolled asthma (68.8%). In contrast, 6MWT analyzed when patients finished the test, in other words, the measure that detected the lowest number of patients with uncontrolled asthma, 13% of cases.

The number and percentage of cases with uncontrolled and controlled asthma based on cut-off points described in "Methods" section, as GINAq, ACT, spirometry and 6MWT are shown in Table 2.

Table 2. Number of cases with uncontrolled and controlled asthma among different measures in children and adolescents.

	Uncontrolled asthma N (%)	Controlled asthma N (%)
GINAq	95 (68.8)	43 (31.2)
ACT	64 (46.4)	74 (53.6)
FEV1/FVC	84 (60.9)	54 (39.1)
FEV1%	53 (38.4)	85 (61.6)
FEV1 BD	53 (38.4)	85 (61.6)
FEF 25-75%	65 (47.1)	73 (52.9)
FEF 25-75% BD	70 (50.7)	68 (49.3)
Spirometric index	94 (68.1)	44 (31.9)
Completed 6MWT	18 (13.0)	120 (86.9)
6MWT % ROC-curve	61 (44.2)	77 (55.8)

N: Number of cases; %: percentage of cases; GINAq: Global Initiative for Asthma questionnaire; ACT: Asthma Control Test; FEV1/FVC: Tiffennau index; FEV1%: Forced Expiratory Volume in the first second pre-bronchodilator; FEV1 BD: Increase in FEV1 post-bronchodilator; FEF25-75%: Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity pre-bronchodilator; FEF25-75% BD: Increase in FEF25-75% post-bronchodilator; Spirometric index: composed by VEF1, VEF1/FVC and FEF25-75%; Completed 6MWT: Completed Six-minute-walk-test regardless of the distance walked; 6MWT % Receiver Operating Characteristic (ROC)-curve: classification based on ROC-curve values of percentage-predicted distance walked in 6MWT.

All tests were compared with each other and the proportion of agreement expressed by *k* statistic are shown in Table 3. A moderate agreement was observed between GINAq and ACT ($p < 0.001$; $k = 0.56$), both measures based on history of symptoms, however, it could be observed a poor agreement between GINAq and both measures of 6MWT. The spirometric index did not show any agreement with others measures of asthma control. Most of the spirometric parameters presented moderate agreement between their own parameters.

Considering GINAq as gold-standard test, the sensitivity, specificity, positive and negative predictive values and accuracy were calculated with ACT, spirometric parameters and 6MWT (Table 4).

When analyzing GINAq and ACT, which presented moderate agreement in kappa statistic, 100% of specificity and positive predictive value could be observed. All patients, being classified as uncontrolled asthma in ACT, were classified as uncontrolled asthma in GINAq.

Spirometric index presented higher sensitivity (72,6%) regarding GINAq. Of all patients, who presented altered spirometric index, 73.4% were classified with uncontrolled asthma by GINAq. Complete 6MWT presented 100% of specificity with GINAq. In 6MWT, 18 patients did not finish the test and all these cases were classified as uncontrolled asthma by GINAq (Table 4).

Regarding asthma control assessed by GINAq and 6MWT, it could be observed statistically a significant increase of dyspnea evaluated by Borg scale in patients with uncontrolled asthma after test ($p = 0.001$). In addition, patients with uncontrolled asthma presented a lower distance walked ($p = 0.001$) and percent of predicted distance ($p = 0.014$) when compared to children and adolescents with controlled asthma. No differences between spirometric parameters and groups of asthma control were observed.

The 6MWT measures and variation of cardiorespiratory parameters between baseline and post-test and spirometric parameters are shown in Table 5.

Table 3. Proportion of agreement, expressed by *k* statistic different measures of asthma control in children and adolescents.

	ACT	Spirometric index	Completed 6MWT	6MWT%ROC-curve
GINA	k= 0.563	k= 0.144	k= 0.127	k= 0.67
	p<0.001	p= 0.091	p= 0.002	p= 0.026
	ACT	k= 0.096	k= 0.234	k= 0.196
		p= 0.212	p<0.001	p= 0.021
		Spirometric index	k= 0.017	k= 0.015
			p= 0.689	p= 0.839
			Completed 6MWT	k= 0.318
				p<0.001

GINA: Global Initiative for Asthma questionnaire; ACT: Asthma Control Test; Spirometric index: composed by VEF1, VEF1/FVC and FEF25-75%; Completed 6MWT: Completed Six-minute-walk-test regardless of the distance walked; 6MWT % Receiver Operating Characteristic (ROC)- curve: classification based on ROC-curve values of percentage-predicted distance walked in 6MWT.

Table 4. Sensitivity, specificity, positive and negative predictive values and accuracy between GINA questionnaire (GINAq) and others measures of asthma control.

	Sensitivity	Specificity	Positive PV	Negative PV	Accuracy
ACT	67.4%	100%	100%	58.1%	77.5%
FEV1/FVC	66.3%	51.2%	75.0%	40.7%	61.6%
FEV1%	36.8%	58.1%	66.0%	29.4%	43.5%
FEV1 BD increase	38.9%	62.8%	69.8%	31.8%	46.4%
FEF25-75%	49.5%	58.1%	72.3%	34.2%	52.2%
FEF25-75% BD increase	51.6%	51.2%	70.0%	32.3%	51.4%
Spirometric index	72.6%	41.9%	73.4%	40.9%	63.0%
Completed 6MWT	18.9%	100%	100%	35.8%	44.2%
6MWT %ROC-curve	50.5%	69.8%	78.7%	39.0%	56.5%

PV: Predicted values; GINAq: Global Initiative for Asthma questionnaire; ACT: Asthma Control Test; FEV1/FVC: Tifennau index; FEV1%: Forced Expiratory Volume in the First Second pre-bronchodilator; FEV1 BD increase: Increase in FEV1 post-bronchodilator; FEF25-75%: Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity pre-bronchodilator; FEF25-75% BD increase: Increase in FEF25-75% post-bronchodilator; Spirometric index: composed by VEF1, VEF1/FVC and FEF25-75%; Completed 6MWT: Completed Six-minute walk test regardless of the distance walked; 6MWT % Receiver Operating Characteristic (ROC)-curve: classification based on ROC-curve values of percentage-predicted distance walked in 6MWT.

Table 5. Comparison of 6MWT results and spirometric parameters between groups of uncontrolled and controlled asthma by GINA questionnaire (GINAq).

Variable	Uncontrolled asthma by GINAq	Controlled asthma by GINAq	p
6MWT			
Total distance walked (m)	481.0 (40.0 - 625.8)	520.0 (362.7 - 700.0)	0.001
Predicted distance (%)	81.6 (7.0 - 106.1)	85.5 (65.5 - 107.2)	0.014
Δ Heart rate	45 (9 - 92)	36 (4 - 121)	0.517
Δ Respiratory rate	5 (-8 - +19)	3 (-7 - +17)	0.099
Δ Oxygen saturation	-2 (-15 - +2)	-1 (-6 - +1)	0.216
Δ Systolic blood pressure	5 (-10 - +26)	5 (-5 - +30)	0.732
Δ Diastolic blood pressure	5 (-10 - +30)	5 (-10 - +30)	0.857
Δ Borg scale for dyspnea	1 (-0.5 - +10)	0 (0 - 6)	0.001
Δ Borg scale for overall fatigue	0.5 (-0.5 - +8)	0 (0 - 8)	0.070
Spirometric parameters			
FEV1/FVC	81 (49 - 100)	82 (59 - 96)	0.256
FEV1%	84 (45 - 116)	83 (60 - 112)	0.966
FEV1 BD increase	7 (-11 - +51)	7 (-19 - +51)	0.439
FEF 25-75%	70 (20 - 131)	71 (27 - 124)	0.490
FEF 25-75% BD increase	30 (-39 - +109)	29 (-46 - +72)	0.290

GINAq: Global Initiative for Asthma questionnaire; 6MWT: Six-minute-walk-test; m: meters; Δ: Variation (final value – baseline value); FEV1/FVC: Tifennau index; FEV1%: Forced Expiratory Volume in the First Second pre-bronchodilator; FEV1 BD increase: Increase in FEV1 post-bronchodilator; FEF25-75%: Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity pre-bronchodilator; FEF25-75% BD increase: Increase in FEF25-75% post-bronchodilator.

DISCUSSION

All asthma guidelines suggest that asthma control should be assessed, whenever possible, to verify and guide the disease management and adequate treatment.[1,19] However, there are many measures available to assess asthma control and each of them analyze different aspects regarding the asthmatic patient. In the current study, it could be assessed the history of symptoms by GINAq and ACT, lung function by spirometry and functional exercise capacity by 6MWT.

As well as in other studies, GINAq as gold-standard test was used.[20] In this study, GINAq was able to identify more patients with uncontrolled asthma and presented moderate agreement, and 100% of specificity with ACT. Although GINAq uses a categorical scale for classification and ACT uses multiple choice, both questionnaires are based on history of symptoms.[1,21]

According to our study, Koolen et al.[22] showed that c-ACT or ACT demonstrated good agreement with GINAq in children and adolescents and demonstrated the use of "19" as a cut-off point for ACT results in 66% of sensitivity and 100% of specificity. Waibel et al.[7] also verified a moderate agreement between GINAq and c-ACT and concluded that c-ACT was useful for monitoring children with asthma. In adults with asthma, Vermeulen et al.,[8] studied five measures of asthma

control assessment and found moderate agreement between GINAq and ACT, with higher percentage of patients with uncontrolled asthma classified by GINAq.

In contrast, other authors found a significant disagreement between c-ACT and GINAq and between c-ACT and pediatrician's assessment.[23,24] They concluded that the use of only one measure for determining asthma control level does not seem to be consistent and accurate and the assessment of asthma control should include analysis of symptoms and lung function.[23,24]

The GINA guideline emphasizes the importance of development of other asthma control measures to help in clinical practice, to distinguish levels of symptoms control and to provide more information on disease progress.[1,25]

The assessment of spirometry should be included on evaluation of children with asthma at least once a year for a better measure on lung function and asthma control and progression.[1,11,13,25] Many authors corroborated our results and related a disagreement between asthma control level evaluated by symptoms and spirometric parameters analyzed individually.[5,25,26] However, we found that spirometric index presented higher sensitivity with GINAq, therefore, presence of at least one alteration in spirometry is associated with classification as uncontrolled asthma by GINAq.

Salviano et al., assessed Brazilian asthmatic children and adolescents and found an association between FEV1 and asthma control level according to GINAq, reinforcing the importance of spirometry in clinical follow-up of these patients.[27] Some authors highlighted that VEF1 should be used as a risk factor for the worst asthma outcome, and failure to include spirometry a measure of asthma control index can underestimate future risk of exacerbations.[28,29]

Then again, some studies demonstrated that despite asthmatic children were classified as controlled by GINAq or c-ACT, their lung function might not be normal, and they may have persistent abnormal lung function or airway reversibility.[25,26]

We found a moderate agreement between spirometric parameters such as FEV1 and FEF25-75%. Green et al. also found an agreement when comparing spirometric parameters, however, they found a poor agreement between FEV1 and FEF25-75%.[5] Some authors have shown that altered FEF25-75% values are associated with worse asthma control, increase of severity, exacerbations, morbidity and use of systemic corticosteroids.[15,30,31] In contrast, other study reported that FEF25-75% is not a good parameter to be used in the evaluation of spirometry in children and adults.[32]

Although there are no recommendations in current guidelines about the usefulness of FEF 25-75% for asthma diagnosis and management, we suggest the use of this parameter in association with FEV1 and FEV1/FVC in evaluation of children and adolescents with asthma, once it may provide important information regarding changes and presence of hyperresponsiveness in small airways.[14,33,34]

In order to classify patients with controlled and uncontrolled asthma according to predicted distance in 6MWT, we need to calculate the cut-off point, since there are no studies with this information on asthmatic children and adolescents. The cut-off point of 82,03% was able to differentiate patients with controlled and uncontrolled asthma.

Despite being a simple and highly applicable test, there are few studies that uses 6MWT in children and adolescents with asthma and none of them associated this test and asthma control level.[15,35-37] In our study, subjects with uncontrolled asthma presented higher presence of dyspnea, lower total distance walked and percent of predicted distance in 6MWT. Andrade et al., assessed physical performance and cardiorespiratory responses in asthmatic children using 6MWT and concluded that the distance walked is significantly lower than the predicted values for healthy children, and it is directly influenced by sedentary lifestyle.[35] Basso et al., compared physical performance in 6MWT between asthmatic and healthy adolescents and verify that asthmatic adolescents had positive correlations between walked distance and duration of intense activity.[36] Gonzalez-Dias et al., compared children with and without asthma and found no significant difference in distance walked between two groups.[37]

The 6MWT is a submaximal test, used to assess presence of dyspnea and desaturation during physical activity, to evaluate the aerobic capacity for practicing exercises, to verify response to therapeutic or rehabilitation programs and to assess the disease evaluation.[15] In addition, a review that studied the 6MWT as a tool for assessing pulmonary impairment concluded that the application of this test was recommended as a complementary exam in evaluation of patients with pulmonary and cardiovascular diseases.[38] Therefore, we emphasize the importance of this study, once it was able to establish a cut-off point to distinguish controlled and uncontrolled asthma in children and adolescents using predicted distance in 6MWT and demonstrate a correlation between asthma control level and application of this test in clinical practice. Furthermore, most activities done by children and adolescents with asthma in daily living are performed at submaximal levels, nevertheless, the 6MWT may reflect the functional exercise level required for these activities.[15]

The whole evaluation of history of symptoms, cardiopulmonary function, aerobic capacity and analysis of inflammatory biomarkers to assess asthma control would be ideal, but unfortunately this does not happen nowadays in all healthcare centers of asthma management.[39,40] In many cases, measures such as spirometry or 6MWT are not available or the healthcare center does not have trained professionals to do it. In this

situation, GINAq can be a good measure to use, since it is a simple and standardized questionnaire, which does not require special equipment to be applied.[1,21] Besides this, our study demonstrated that GINAq was able to distinguish more patients with uncontrolled asthma when compared to other measures.

We consider that a measure which assess asthma phenotypes by inflammatory markers would contribute even more to our findings, therefore its absence is a limitation of our study.

In conclusion, GINAq was the measure that identified more patients with uncontrolled asthma and presented moderate agreement with ACT. A disagreement was found between GINAq, spirometry and 6MWT. In spirometry assessment, the spirometric index did not show agreement with GINAq and ACT. However, there was a 72.6% sensitivity between spirometric index and GINAq. Regarding 6MWT and asthma control, we established a cut-off point to distinguish controlled and uncontrolled asthma in children and adolescents using predicted distance. In addition, we highlight the importance of 6MWT in the assessment of daily living activities, cardiorespiratory parameters and aerobic capacity in this population.

Therefore, to avoid the indiscriminate use of medications and underestimate asthma severity, we emphasize that the assessment of asthma control should be done with caution, regardless of the measure used in, physician evaluation, questionnaires, lung function measures, cardiorespiratory parameters or biormarkers.[4,5] It is important to state that the use of more than one measure to assess asthma control will provide the healthcare team a better information regarding the disease control and progression and therefore enable a better management of treatment.[23] It is important to notice that before changing medication, the physician must evaluate the diagnosis, adherence to treatment and adequate inhalation technique.[1]

REFERENCES

1. GINAQ: Global Initiative for Asthma. 2019 GINA report: global strategy for asthma management and prevention. Bethesda: Global Strategy for Asthma Management and Prevention; 2018.
2. Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, et al. A new perspective on concepts of asthma severity and control. Eur Respir J. 2008;32(3):545-54. http://dx.doi.org/10.1183/09031936.00155307. PMid:18757695.
3. Yawn BP, Bertram S, Kurland M, Wollan P, Graham D, Littlefield D, et al. Protocol for the asthma tools study: a pragmatic practice-based research network trial. Pragmat Obs Res. 2013;31(4):7-18. http://dx.doi.org/10.2147/POR.S43161. PMid:27774020.
4. Bush A, Fleming L, Saglani S. Severe asthma in children. Respirology. 2017;22(5):886-97. http://dx.doi.org/10.1111/resp.13085. PMid:28543931.
5. Green RJ, Klein M, Becker P, Halkas A, Lewis H, Kitchin O, et al. Disagreement among common measures of asthma control in children. Chest. 2013;143(1):117-22. http://dx.doi.org/10.1378/chest.12-1070. PMid:22878380.
6. Lee CC, Holder-Niles FF, Haynes L, Chan Yuen J, Rea CJ, Conroy K, et al. Associations between patient-reported outcome measures of asthma control and psychosocial symptoms. Clin Pediatr. 2018. No prelo. PMid:30461298.
7. Waibel V, Ulmer H, Horak E. Assessing asthma control: symptom scores, GINAQ levels of asthma control, lung function, and exhaled nitric oxide. Pediatr Pulmonol. 2012;47(2):113-8. http://dx.doi.org/10.1002/ppul.21529. PMid:22241569.
8. Vermeulen F, de Meulder I, Paesmans M, Muylle I, Bruyneel M, Ninane V. Asthma control measurement using five different questionnaires: a prospective study. Respir Med. 2013;107(9):1314-21. http://dx.doi.org/10.1016/j.rmed.2013.07.003. PMid:23890766.
9. Andrade WCC, Lasmar LMLBF, Ricci CAT, Camargos PAM, Cruz AA. Phenotypes of severe asthma among children and adolescents in Brazil: a prospective study. BMC Pulm Med. 2015;15(1):36. http://dx.doi.org/10.1186/s12890-015-0029-8. PMid:25912047.
10. Roxo JPF, Ponte EV, Ramos DCB, Pimentel L, D'Oliveira A Jr, Cruz AA. Portuguese-language version of the Asthma Control Test: validation for use in Brazil. J Bras Pneumol. 2010;36(2):159-66. http://dx.doi.org/10.1590/S1806-37132010000200002. PMid:20485935.
11. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. ATS/ERS Task Force: standardisation of lung function testing: standardisation of spirometry. Eur Respir J. 2005;26(2):319-38. http://dx.doi.org/10.1183/09031936.05.00034805. PMid:16055882.
12. Polgar G, Promadhat V. Pulmonary function testing in children: techniques and standards. Philadelphia: WB Saunders Company; 1971.
13. Pereira CAC. Guidelines for Pulmonary Function Test - Spirometry. J Bras Pneumol. 2002;28(3):1-82.
14. Rao DR, Gaffin JM, Baxi SN, Sheehan WJ, Hoffman EB, Phipatanakul W. The utility of forced expiratory flow between 25% and 75% of vital capacity in predicting childhood asthma morbidity and severity. J Asthma. 2012;49(6):586-92. http://dx.doi.org/10.3109/02770903.2012.690481. PMid:22742446.
15. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7. http://dx.doi.org/10.1164/ajrccm.166.1.at1102. PMid:12091180.
16. Priesnitz CV, Rodrigues CH, Stumpf CS, Viapiana G, Cabral CP, Stein RT, et al. Reference values for the 6 minute walk test in healthy children age 6-12. Pediatr Pulmonol. 2009;44(12):1174-9. http://dx.doi.org/10.1002/ppul.21062. PMid:19911357.
17. Iwama AM, Andrade GN, Shima P, Tanni SE, Godoy I, Dourado VZ. The six minute walk test and body weight walk distance product in healthy brazilian subjects. Braz J Med Biol Res. 2009;42(11):1080-5. http://dx.doi.org/10.1590/S0100-879X2009005000032. PMid:19802464.
18. Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: John Wiley & Sons; 1981. p. 212-18.
19. Becker AB, Abrams EM. Asthma guidelines: the Global Initiative for Asthma in relation to national guidelines. Curr Opin Allergy Clin Immunol. 2017;17(2):99-103. http://dx.doi.org/10.1097/ACI.0000000000000346. PMid:28118238.
20. Leung TF, Ko FW, Sy HY, Wong E, Li CY, Yung E, et al. Identifying uncontrolled asthma in young children: clinical scores or objective variables? J Asthma. 2009;46(2):130-5. http://dx.doi.org/10.1080/02770900802468533. PMid:19253117.
21. O'Byrne PM, Reddel HK, Eriksson G, Ostlund O, Peterson S, Sears MR, et al. Measuring asthma control: a comparison of three classification systems. Eur Respir J. 2010;36(2):269-76. http://dx.doi.org/10.1183/09031936.00124009. PMid:20110397.
22. Koolen BB, Pijnenburg MWH, Brackel HJL, Landstra AM, Van den Berg NJ, Merkus PJFM, et al. Comparing Global Initiative for Asthma (GINAQ) criteria with the Childhood Asthma Control Test (C-ACT) and Asthma Control Test (ACT). Eur Respir J. 2011;38(3):561-6. http://dx.doi.org/10.1183/09031936.00173710. PMid:21406508.
23. Erkoçoğlu M, Akan A, Civelek E, Kan R, Azkur D, Kocabaş CN. Consistency of GINAQ criteria and childhood asthma control test on the determination of asthma control. Pediatr Allergy Immunol. 2012;23(1):34-9. http://dx.doi.org/10.1111/j.1399-3038.2011.01232.x. PMid:22136557.
24. Deschildre A, Pin I, El Abd K, Belmin-Larrar S, El Mourad S, Thumerelle C, et al. Asthma control assessment in a pediatric population: comparison between GINAQ/NAEPP guidelines, Childhood Asthma Control Test (C-ACT), and physician's rating. Allergy. 2014;69(6):784-90. http://dx.doi.org/10.1111/all.12402. PMid:24725204.

25. Pijnenburg MW, Baraldi E, Brand PLP, Carlsen KH, Eber E, Frischer T, et al. Monitoring asthma in children. Task Force Report. ERS Statement. ERJ Express. 2015. Eur Respir J. 2015;45(4):906-25. http://dx.doi.org/10.1183/09031936.00088814. PMid:25745042.
26. Uppala R, Kaenpugdee P, Srisutthikamol S, Teeratakulpisarn J. Assessment of small airway function and reversibility in symptom-controlled asthma in pediatric patients. Asian Pac J Allergy Immunol. 2018. No prelo. PMid:29549701.
27. Salviano LDDS, Taglia-Ferre KD, Lisboa S, Costa ACCD, Campos HDS, March MFP. Association between fraction of exhaled nitric oxide and spirometry data and clinical control of asthma in children and adolescents. Rev Paul Pediatr. 2018;36(1):8. PMid:29412429.
28. Dostaler SM, Olajos-Clow JG, Sands TW, Licskai CJ, Minard JP, Lougheed MD. Comparison of asthma control criteria: importance of spirometry. J Asthma. 2011;48(10):1069-75. http://dx.doi.org/10.3109/02770903.2011.631243. PMid:22091743.
29. Schuler M, Faller H, Wittmann M, Schultz K. Asthma Control Test and Asthma Control Questionnaire: factorial validity, reliability and correspondence in assessing status and change in asthma control. J Asthma. 2016;53(4):438-45. http://dx.doi.org/10.3109/02770903.2015.1101134. PMid:26539757.
30. Ciprandi G, Gallo F, Cirillo I. FEF25-75 and asthma in clinical practice. Iran J Allergy Asthma Immunol. 2018;17(3):295-7. PMid:29908548.
31. Siroux V, Boudier A, Dolgopoloff M, Chanoine S, Bousquet J, Gormand F, et al. Forced midexpiratory flow between 25% and 75% of forced vital capacity is associated with long-term persistence of asthma and poor asthma outcomes. J Allergy Clin Immunol. 2016;137(6):1709-16. http://dx.doi.org/10.1016/j.jaci.2015.10.029. PMid:26688518.
32. Quanjer PH, Weiner DJ, Pretto JJ, Brazzale DJ, Boros PW. Measurement of FEF25-75% and FEF75% does not contribute to clinical decision making. Eur Respir J. 2014;43(4):1051-8. http://dx.doi.org/10.1183/09031936.00128113. PMid:24072211.
33. Kong JK, Lee SH, Jung JY, Eom SY, Hahn YS. Clinical implications of the FEF25-75 variability in childhood asthma. Ann Allergy Asthma Immunol. 2018;121(4):496-7. http://dx.doi.org/10.1016/j.anai.2018.05.034. PMid:29894728.
34. Piccioni P, Tassinari R, Carosso A, Carena C, Bugiani M, Bono R. Lung function changes from childhood to adolescence: a seven-year follow-up study. BMC Pulm Med. 2015;15(1):31. http://dx.doi.org/10.1186/s12890-015-0028-9. PMid:25885675.
35. Andrade LB, Silva DA, Salgado TL, Figueroa JN, Lucena-Silva N, Britto MC. Comparison of six-minute walk test in children with moderate/severe asthma with reference values for healthy children. J Pediatr. 2014;90(3):250-7. http://dx.doi.org/10.1016/j.jped.2013.08.006. PMid:24184268.
36. Basso RP, Jamami M, Pessoa BV, Labadessa IG, Regueiro EM, Di Lorenzo VA. Assessment of exercise capacity among asthmatic and healthy adolescents. Rev Bras Fisioter. 2010;14(3):252-8. http://dx.doi.org/10.1590/S1413-35552010000300005. PMid:20730371.
37. González-Díaz SN, Partida-Ortega AB, Macías-Weinmann A, Arias-Cruz A, Galindo-Rodríguez G, Hernández-Robles M, et al. Evaluación de la capacidad funcional mediante prueba de marcha de 6 minutos en niños con asma. Rev Alerg Mex. 2017;64(4):415-29. http://dx.doi.org/10.29262/ram.v64i4.224. PMid:29249104.
38. Morales-Blanhir JE, Vidal CDP, Romero MJR, Castro MMG, Villegas AL, Zamboni M. Six-minute walk test: a valuable tool for assessing pulmonary impairment. J Bras Pneumol. 2011;37(1):110-7. http://dx.doi.org/10.1590/S1806-37132011000100016. PMid:21390439.
39. Chipps BE, Parikh NG, Maharaj SK. Severe asthma in children. Curr Allergy Asthma Rep. 2017;17(4):21. http://dx.doi.org/10.1007/s11882-017-0688-z. PMid:28353215.
40. Uwaezuoke SN, Ayuk AC, Eze JN. Severe bronchial asthma in children: a review of novel biomarkers used as predictors of the disease. J Asthma Allergy. 2018;11:11-8. http://dx.doi.org/10.2147/JAA.S149577. PMid:29398922.

J Bras Pneumol. 2020;46(3):e20190223
https://dx.doi.org/10.36416/1806-3756/e20190223

ORIGINAL ARTICLE

Symptom variability over the course of the day in patients with stable COPD in Brazil: a real-world observational study

Alberto Cukier[1], Irma de Godoy[2], Claudia Henrique da Costa[3], Adalberto Sperb Rubin[4], Marcelo Gervilla Gregorio[5], Aldo Agra de Albuquerque Neto[6], Marina Andrade Lima[7], Monica Corso Pereira[8], Suzana Erico Tanni[2], Rodrigo Abensur Athanazio[1], Elizabeth Jauhar Cardoso Bessa[3], Fernando Cesar Wehrmeister[9], Cristina Bassi Lourenco[10], Ana Maria Baptista Menezes[9]

1. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Disciplina de Pneumologia, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista – UNESP – Botucatu (SP) Brasil.
3. Disciplina de Pneumologia, Universidade do Estado do Rio de Janeiro – UERJ – Rio de Janeiro (RJ) Brasil.
4. Universidade Federal de Ciências da Saúde de Porto Alegre, Santa Casa de Misericórdia de Porto Alegre, Porto Alegre (RS) Brasil.
5. Clínica Médica Netspiro, São Bernardo do Campo (SP) Brasil.
6. Departamento de Pneumologia, Centro de Reabilitação Pulmonar, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil.
7. Hospital Dia do Pulmão, Blumenau (SC) Brasil.
8. Disciplina de Pneumologia, Departamento de Clínica Médica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas (SP) Brasil.
9. Programa de Pós-Graduação em Epidemiologia, Universidade Federal de Pelotas, Pelotas (RS) Brasil.
10. AstraZeneca do Brasil, São Paulo (SP) Brasil.

Submitted: 24 June 2019.
Accepted: 8 September 2019.

ABSTRACT

Objective: To analyze symptoms at different times of day in patients with COPD. **Methods:** This was a multicenter, cross-sectional observational study conducted at eight centers in Brazil. We evaluated morning, daytime, and nighttime symptoms in patients with stable COPD. **Results:** We included 593 patients under regular treatment, of whom 309 (52.1%) were male and 92 (15.5%) were active smokers. The mean age was 67.7 years, and the mean FEV_1 was 49.4% of the predicted value. In comparison with the patients who had mild or moderate symptoms, the 183 (30.8%) with severe symptoms were less physically active ($p = 0.002$), had greater airflow limitation ($p < 0.001$), had more outpatient exacerbations ($p = 0.002$) and more inpatient exacerbations ($p = 0.043$), as well as scoring worse on specific instruments. The most common morning and nighttime symptoms were dyspnea (in 45.2% and 33.1%, respectively), cough (in 37.5% and 33.3%, respectively), and wheezing (in 24.4% and 27.0%, respectively). The intensity of daytime symptoms correlated strongly with that of morning symptoms ($r = 0.65$, $p < 0.001$) and that of nighttime symptoms ($r = 0.60$, $p < 0.001$), as well as with the COPD Assessment Test score ($r = 0.62$; $p < 0.001$), although it showed only a weak correlation with FEV_1 ($r = -0.205$; $p < 0.001$). **Conclusions:** Dyspnea was more common in the morning than at night. Having morning or nighttime symptoms was associated with greater daytime symptom severity. Symptom intensity was strongly associated with poor quality of life and with the frequency of exacerbations, although it was weakly associated with airflow limitation.

Keywords: Pulmonary disease, chronic obstructive; Signs and symptoms, respiratory; Quality of life; Disease progression; Brazil.

INTRODUCTION

Classically, the management of obstructive diseases has always been based on clinical data.[1,2] In the early 21st century, in keeping with the proposal according to which spirometry became mandatory for its diagnosis,[3] the main international guidelines adopted a severity classification system of COPD based on the degree of FEV_1 reduction.[3] The intention was never to diminish the importance of clinical information; however, in practice, that is what happened. It is interesting to note that the Brazilian consensus guidelines never ceased drawing attention to clinical symptoms as part of patient care.[4]

In recent years, the importance of patient-based outcomes in clinical trials has been emphasized. This trend is reflected in the current global guideline that defines the severity of COPD based on symptoms, pulmonary function, and exacerbations.[5] In parallel, the drug arsenal has been greatly increased by the inclusion of several medications, delivered by various inhalation devices, with their own pharmacological characteristics and pharmacodynamics. Finally, the concept of personalized medicine proposes

Correspondence to:
Alberto Cukier. Avenida Enéas de Carvalho Aguiar, 44, CEP 05403-000, São Paulo, SP, Brasil.
Tel.: 55 11 2661-5695. E-mail: pnealberto@incor.usp.br
Financial support: This study received the financial support of AstraZeneca do Brasil.

identifying the pattern of symptoms and the treatment preferences of each patient.

Various articles have assessed the behavior of symptoms in COPD patients around the clock in different populations.[6-17] Most have shown that patient complaints are more common early in the morning. Other studies have drawn attention to nighttime symptoms, such as the one conducted in 2018 by Miravitlles et al.[15] in seven Latin American countries.

Given that patient behavior varies depending on multiple factors, such as cultural, motivational, and climatic factors,[18-20] it is relevant to understand the symptomatic profile of patients in Brazil. In this context, by using the same methodology applied in the study conducted by Miravitlles et al.,[15] the present proposal aims to characterize and determine the prevalence and severity of symptoms early in the morning, during the day, and at nighttime in patients with stable COPD in Brazil, as well as to evaluate the correlation of each symptom with the severity of the disease.

METHODS

The study entitled "A Study to Evaluate Symptoms Over 24 Hours in Patients With Chronic Obstructive Pulmonary Disease - LASSYC Study (LASSYC-BR)", registered with ClinicalTrials.gov (identifier: NCT03381560), was a multicenter, cross-sectional, observational, non-interventional study. The aim of the study was to characterize the prevalence and severity of symptoms from the beginning of regular daytime activities to bedtime (daytime symptoms), in the early morning (morning symptoms), and at nighttime in patients with stable COPD in Brazil. The study was conducted between November of 2017 and June of 2018, at eight research centers, distributed throughout the southeastern and southern regions of Brazil and detailed in the online Supplement (http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=71; Figure S1), with the approval of the ethics committees of each institution. All the patients gave written informed consent.

The patients were in outpatient follow-up and were included consecutively. The inclusion and exclusion criteria are detailed in the online Supplement (Methods S1).

The following information, obtained from medical records or from interviews conducted during the study visits, was collected from each patient: demographic data, lifestyle, history of smoking, comorbidities, dyspnea level, COPD severity, and the history of exacerbations in the last 12 months. Patients provided data on daytime, morning, and nighttime disease-related symptoms, as well as on health-related quality of life and level of physical activity.

Dyspnea level was measured using the modified Medical Research Council (mMRC) dyspnea scale.[21] The level of COPD severity was quantified using the **B**ody mass index, airflow **O**bstruction, **D**yspnea, and **Ex**acerbations index (BODEx).[22] Comorbidities were assessed using the COPD-specific **CO**morbidity **TE**st (COTE) score.[23] The COPD Assessment Test (CAT) was utilized to define the impact of the disease on health status.[24]

Daytime symptoms were assessed using the **EXA**cerbations of **C**OPD **T**ool (EXACT)-Respiratory Symptoms (E-RS) questionnaire, designed for use in clinical trials to assess the effectiveness of therapeutic interventions regarding symptoms.[25,26] The E-RS evaluates symptoms that have occurred on the day prior to a study visit, from the beginning of regular activities until the patient lies down to sleep.[25] The E-RS provides a total score, ranging from 0 to 40, and three subscales: RS-dyspnea (scale 0-17); RS-cough and sputum (scale 0-11); and RS-symptoms in the chest (scale 0-12). Higher scores translate to greater symptom intensity.

Morning symptoms (on the day of a study visit, from the time patients got out of bed to begin their daytime activities until they were ready for routine activities) were analyzed using the Early Morning Symptoms of COPD Instrument.[27]

Nighttime symptoms (from the time the research subject went to bed the night before until rising out of bed to begin daytime activities on the day of a study visit) were measured using the Nighttime Symptoms of COPD Instrument (online Supplement; Methods S1).[28]

The intensity of daytime symptoms was classified as mild, moderate, or severe, according to the distribution of E-RS scores in tertiles. The questionnaire has no predetermined cutoff levels.

In the study conducted by Miravitlles et al.,[15] the presence of morning symptoms was considered significant in cases of moderate, intense, or very intense dyspnea, associated with any other moderate, intense, or very intense symptoms (definition 1). To evaluate the influence of different definition criteria on the prevalence of symptoms, we also adopted a second definition: at least two of the evaluated symptoms classified as being at least moderate or one symptom perceived as being at least intense (definition 2). Similarly, for the analysis of significant nighttime symptoms, two definitions were considered: any nocturnal awakening (definition of the study conducted by Miravitlles et al.)[15]; or at least two symptoms assessed as being at least moderate or one symptom perceived as being at least severe. The level of physical activity was assessed using the International Physical Activity Questionnaire.[29]

Considering the primary outcome of the study (the occurrence of morning, daytime, and nighttime symptoms), we calculated the sample size based on the estimated prevalence of the outcome in each period. A 30-40% prevalence of the outcome was considered, with an estimated error of 5%, a confidence interval of 95%, and the addition of 5% for possible losses. Therefore, the estimated sample size required was 600 patients.

Statistical analysis

Descriptive analyses were performed to show absolute frequencies using the chi-square test for heterogeneity to describe morning, daytime, and nighttime symptoms.

Pearson's correlation test was used in order to obtain the correlation coefficient of FEV_1 symptom scores. All analyses were performed with the Stata statistical package, version 15.1 (StataCorp LP, College Station, TX, USA).

RESULTS

Patients

We included 593 patients whose demographic and clinical characteristics are shown in Table 1. The mean age was 67.7 ± 9.0 years. The mean FEV_1 was 49.4% ± 17.5% of the predicted value. In the sample, 92 patients (15.5%) were active smokers and 102 (17.2%) reported having a concomitant diagnosis of asthma. The complete results of the questionnaires concerning symptoms were available for 565 patients.

Patient characteristics according to daytime symptoms

There was a balance in the distribution of patients regarding mild, moderate, and severe daytime symptoms. Compared with the mild and moderate symptoms groups, the severe respiratory symptoms group had higher proportions of patients with a low level of physical activity ($p = 0.002$), greater dyspnea severity on the mMRC scale ($p < 0.001$), greater airflow limitation. ($p < 0.001$), worse CAT scores, and worse BODEx scores ($p < 0.001$ for both), as well as a higher prevalence of outpatient and inpatient exacerbations in the last year ($p = 0.002$ and $p = 0.043$, respectively; Table 1).

Prevalence and intensity of morning and nighttime symptoms

The most common symptoms were dyspnea, cough, and wheezing (Figure 1). The prevalence of morning and nighttime symptoms was similar, except for dyspnea. In the sample as a whole, the morning symptoms were cough, in 37.5% of the patients; wheezing, in 24.4%; dyspnea, in 45.2%; chest tightness, in 15.7%; chest congestion, in 20.6%; and difficulty expelling phlegm, in 17.5%. The nighttime symptoms were cough, in 33.3% of the patients; wheezing, in 27.0%; dyspnea, in 33.1%; chest tightness, in 18.3%; chest congestion, in 19.5%; and difficulty expelling phlegm, in 18.8%. Although most symptoms were described as mild or moderate, approximately 10% of patients rated their dyspnea as severe or very severe (in the morning, in 10.1%; and at night, in 8.5%).

Of the 593 patients in the sample, 120 (20%) reported moderate, intense, or very intense dyspnea associated with any other moderate, intense, or very intense morning symptom (definition 1). Regarding nighttime symptoms, 107 (18%) patients reported at least one nocturnal awakening due to symptoms associated with COPD.

In relation to definition 2 (at least two of the symptoms assessed as being at least moderate or one perceived as being at least intense), 182 (31%) and 171 (29%) patients had significant morning and nighttime symptoms, respectively.

Characteristics of patients with morning or nighttime symptoms

Patients who reported moderate, intense, or very intense dyspnea associated with any other moderate, intense, or very intense morning symptom (definition 1) were younger, had higher COTE, mMRC, CAT, and BODEx scores, and reported a higher number of outpatient exacerbations in the last year ($p < 0.001$ for all).

Patients who reported nocturnal awakening due to COPD (definition 1) were younger, had higher mMRC scores, and had higher CAT scores ($p < 0.001$ for all), as well as having higher BODEx scores ($p = 0.001$; Table 2).

Using the criteria of definition 2, we observed the following (online supplement; Table S1): patients with morning symptoms were younger ($p < 0.001$); were predominantly male ($p = 0.022$); had higher COTE, mMRC, CAT, and BODEx scores ($p < 0.001$ for all); had worse pulmonary function, as determined by FEV_1 ($p = 0.015$); and had a higher number of outpatient exacerbations in the past year ($p < 0.001$).

Patients with nighttime symptoms were younger ($p = 0.039$); were predominantly female ($p = 0.044$); had higher COTE and mMRC scores ($p = 0.013$ and $p < 0.001$, respectively); had worse CAT and BODEx scores ($p < 0.001$ for both); had a higher number of outpatient exacerbations in the past year ($p < 0.001$); and had a higher number of inpatient exacerbations in the past year ($p = 0.021$). Pulmonary function did not differ between the patients with and without nighttime symptoms.

Association between the intensity of daytime symptoms and the presence of morning and nighttime symptoms

We detected a strong association between the presence of morning and nighttime symptoms and the intensity of daytime symptoms using definition 1. Of the patients with morning symptoms, 76.1% reported severe daytime symptoms, compared with only 21.4% of those without morning symptoms. Similarly, 64.7% of the patients with nighttime symptoms reported severe daytime symptoms, compared with only 25.3% of those without nighttime symptoms. Among those with morning and nighttime symptoms, approximately 90% had severe daytime symptoms, compared with less than 20% of those with no morning or nighttime symptoms (Figure 2). The same level of association was detected by analyses using definition 2 (online Supplement; Figure S2).

Correlations between the intensity of daytime symptoms and the presence of morning and nighttime symptoms, as well as COPD characteristics

The correlation matrix between some COPD characteristics and the overall E-RS score is presented

Table 1. Demographic and clinical characteristics of COPD patients, according to the intensity of daytime symptoms.[a,b]

Characteristic	All patients (n = 593)	Symptom severity			p*			
		Mild (n = 216)	Moderate (n = 166)	Severe (n = 183)	Overall	Mild vs. moderate	Mild vs. severe	Severe vs. moderate
Age, years	67.7 ± 9.0	69.1 ± 9.0	67.3 ± 9.1	66.2 ± 8.4	0.003	0.133	0.003	0.707
Male	309 (52.1)	121 (56.2)	89 (53.6)	81 (44.3)	0.052	0.640	0.019	0.081
BMI, kg/m^2	26.4 ± 5.3	26.3 ± 4.8	26.3 ± 5.5	26.6 ± 5.7	0.781	1.000	1.000	1.000
Active smokers	92 (15.5)	30 (13.9)	31 (18.7)	23 (12.6)	0.243	0.206	0.699	0.115
Smoking history, pack-years	51.2 ± 32.9	50.9 ± 35.3	48.7 ± 28.8	53.8 ± 33.3	0.338	1.000	1.000	0.431
Levels of physical activity					0.002	0.040	0.001	0.172
Low	233 (39.3)	66 (30.6)	62 (37.4)	86 (47.0)				
Moderate	131 (22.1)	44 (20.4)	44 (26.5)	38 (20.8)				
High	229 (38.6)	106 (49.1)	60 (36.1)	59 (32.2)				
Diagnosis of asthma	102 (17.2)	39 (18.1)	27 (16.3)	34 (18.6)	0.839	0.646	0.893	0.570
COTE index	1.3 ± 2.3	1.0 ± 1.9	1.3 ± 2.4	1.6 ± 2.5	0.052	0.694	0.045	0.777
mMRC scale	2.1 ± 1.1	1.5 ± 0.9	2.2 ± 1.1	2.7 ± 0.9	< 0.001	< 0.001	< 0.001	< 0.001
Spirometry								
FVC, % of predicted	70.9 ± 16.4	74.9 ± 16.1	70.0 ± 16.5	67.3 ± 16.3	< 0.001	0.012	< 0.001	0.363
FEV_1, % of predicted	49.4 ± 17.5	54.3 ± 16.7	48.0 ± 17.9	44.8 ± 17.2	< 0.001	0.001	< 0.001	0.264
FEV_1/FVC	50.9 ± 11.3	53.1 ± 10.7	49.9 ± 11.4	48.7 ± 11.6	< 0.001	0.016	< 0.001	0.937
CAT score	16.8 ± 8.5	10.8 ± 5.9	17.8 ± 7.3	22.7 ± 7.5	< 0.001	< 0.001	< 0.001	< 0.001
BODEx index	2.9 ± 1.8	2.0 ± 1.4	3.1 ± 1.8	3.7 ± 1.7	< 0.001	< 0.001	< 0.001	0.001
Exacerbations								
Outpatient	0.9 ± 2.4	0.6 ± 1.1	0.8 ± 1.2	1.4 ± 3.9	0.002	1.000	0.002	0.044
Inpatient	0.2 ± 0.5	0.1 ± 0.3	0.1 ± 0.4	0.2 ± 0.5	0.043	0.905	0.037	0.526
E-RS score								
Total	8.9 ± 7.3	1.5 ± 1.4	8.9 ± 2.4	17.7 ± 4.1	< 0.001	< 0.001	< 0.001	< 0.001
Breathlessness domain	6.4 ± 6.0	0.6 ± 1.1	6.6 ± 3.9	13.3 ± 3.2	< 0.001	< 0.001	< 0.001	< 0.001
Cough and sputum domain	1.6 ± 1.9	0.7 ± 1.0	1.6 ± 1.9	2.8 ± 2.1	< 0.001	< 0.001	< 0.001	< 0.001
Chest symptoms domain	0.8 ± 1.2	0.2 ± 0.5	0.7 ± 0.9	1.6 ± 1.5	< 0.001	< 0.001	< 0.001	< 0.001
Severity of morning symptoms score	3.0 ± 3.8	0.7 ± 1.4	3.0 ± 2.9	5.7 ± 4.7	< 0.001	< 0.001	< 0.001	< 0.001
Severity of nighttime symptoms score	2.9 ± 4.0	0.7 ± 1.6	2.6 ± 3.5	5.6 ± 4.7	< 0.001	< 0.001	< 0.001	< 0.001
≥ 1 nocturnal awakening due to COPD	107 (18.0)	12 (5.6)	24 (14.5)	66 (36.1)	< 0.001	0.003	< 0.001	< 0.001

BMI: body mass index; COTE: (COPD-specific) **CO**morbidity **TE**st; mMRC: modified Medical Research Council score; CAT: COPD Assessment Test; BODEx: **B**ody mass index, airflow **O**bstruction, **D**yspnea, and **Ex**acerbations; and E-RS: **EXA**cerbations of **C**OPD **T**ool (EXACT)-Respiratory Symptoms. [a]Values expressed in n (%) or mean ± SD. [b]Complete data from 565 patients. Incomplete data from 28 patients. *ANOVA for continuous variables and the chi-square test for categorical variables.

in Table 3. All but one of the variables had a correlation close to or greater than 0.6 (moderate to high), including the global E-RS—CAT score ($r = 0.62$; $p < 0.001$), the severity score of morning symptoms ($r = 0.65$; $p < 0.001$), and the severity score of nighttime symptoms ($r = 0.60$; $p < 0.001$), the exception being pulmonary function ($r = -0.21$; $p < 0.001$). In addition, the CAT score correlated well with the severity of morning and nighttime symptoms. We also observed a very strong correlation between morning and nighttime symptom severity scores ($r = 0.83$; $p < 0.001$).

Patients with a concomitant diagnosis of asthma were younger, were mostly female, and had a higher body mass index. Except for those characteristics and the FVC in % of predicted value, there were no statistical differences in any other parameter.

DISCUSSION

We have shown that a considerable proportion of patients with stable COPD remain symptomatic. The strong association between morning and nighttime complaints, as well as the intensity of symptoms during the day, suggest that the symptoms affect the clinical behavior of the disease around the clock. Those results indicate that a focused history-taking investigating this variability may help in defining an individualized therapeutic proposal.

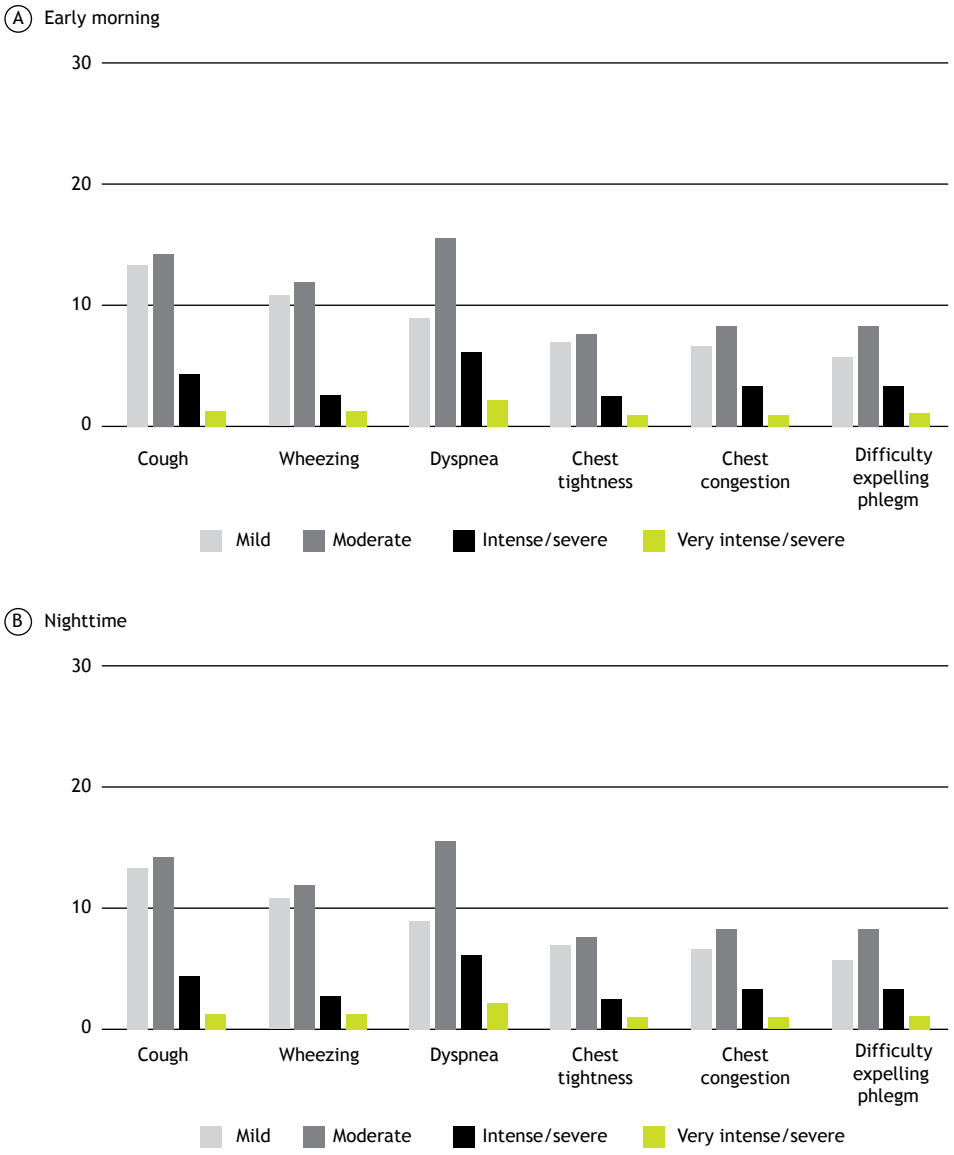


Figure 1. Prevalence and intensity of morning symptoms (in A) and nighttime symptoms (in B).

Thirty percent of patients with stable COPD undergoing regular clinical treatment reported severe daytime symptoms. A considerable number reported morning symptoms or nocturnal awakening due to respiratory complaints. Dyspnea was the most common manifestation, being 12% more common in the morning than at night, and 10% of the patients rated their dyspnea as intense or very intense.

Our results were similar to those obtained in the study conducted by Miravitlles et al.,[15] despite the predominance of men in that study (61% vs. 52%) and a higher prevalence of asthma in our population (17.2% vs. 4.5%). Recently, Soler-Cataluña et al.[14] reported that symptoms and their impact on quality of life were less pronounced among patients in Spain than among those in other European countries. The higher proportion of men in the Spanish cohort was hypothesized to be one of the possible explanations for the difference, because it has been suggested that the impact of COPD would be greater in women.[30] Regarding asthma, its symptomatic behavior in our patients did not differ in relation to the 82.8% of patients who did not have an associated diagnosis of asthma and COPD, suggesting that asthma did not influence the pattern of variability in respiratory complaints.

In recent years, several authors have published studies evaluating the variability of symptoms in patients with stable COPD in different regions.[6-17] Morning symptoms were reported by 37-81% of the patients in the samples, whereas nighttime symptoms were reported by 25-68%. There are several explanations for this disparity, such as the heterogeneity in study design,[31] the method of assessing symptoms, and

Table 2. Demographic and clinical characteristics of COPD patients, according to the presence of morning or nighttime symptoms.[a,b]

Characteristic	Morning symptoms		p*	Nighttime symptoms		p*
	No (n = 473)	Yes (n = 120)		No (n = 486)	Yes (n = 107)	
Age, years	68.3 ± 9.1	65.3 ± 8.3	< 0.001	68.3 ± 8.9	64.9 ± 9.0	< 0.001
Male	255 (53.9)	54 (45.0)	0.081	258 (53.1)	51 (47.7)	0.309
BMI, kg/m^2	26.3 ± 5.1	26.7 ± 5.9	0.475	26.4 ± 5.1	26.4 ± 6.2	0.962
Active smokers	73 (15.4)	19 (15.8)	0.914	74 (15.2)	18 (16.8)	0.680
Smoking history, pack-years	50.3 ± 33.4	54.7 ± 30.4	0.187	51.0 ± 33.4	52.1 ± 30.3	0.761
Levels of physical activity			0.633			0.314
Low	182 (38.5)	51 (42.5)		184 (37.9)	49 (45.8)	
Moderate	104 (22.0)	27 (22.5)		110 (22.6)	21 (19.6)	
High	187 (39.5)	42 (35.0)		192 (39.5)	37 (34.6)	
Diagnosis of asthma	78 (16.5)	24 (20.0)	0.363	86 (17.7)	16 (15.0)	0.496
COTE index	1.1 ± 2.1	1.9 ± 2.7	< 0.001	1.3 ± 2.2	1.4 ± 2.4	0.622
mMRC scale	2.0 ± 1.1	2.6 ± 1.0	< 0.001	2.0 ± 1.1	2.4 ± 1.0	< 0.001
Spirometry						
FVC, % of predicted	71.4 ± 16.1	69.0 ± 17.5	0.163	71.5 ± 16.4	67.9 ± 15.8	0.041
FEV_1, % of predicted	50.0 ± 17.3	47.1 ± 18.3	0.109	49.8 ± 17.4	47.3 ± 17.7	0.176
FEV_1/FVC	51.1 ± 11.5	49.7 ± 10.5	0.213	50.8 ± 11.4	50.9 ± 11.2	0.937
CAT score	14.8 ± 7.4	24.5 ± 8.0	< 0.001	15.4 ± 7.9	23.4 ± 8.0	< 0.001
BODEx index	2.7 ± 1.7	3.5 ± 1.8	< 0.001	2.8 ± 1.8	3.4 ± 1.8	0.001
Exacerbations						
Outpatient	0.7 ± 1.2	1.7 ± 0.4	< 0.001	0.8 ± 2.5	1.3 ± 1.4	0.028
Inpatient	0.1 ± 0.5	0.2 ± 0.5	0.129	0.1 ± 0.5	0.2 ± 0.6	0.248
E-RS score						
Total	6.8 ± 6.0	17.4 ± 6.1	< 0.001	7.6 ± 6.6	14.8 ± 7.5	< 0.001
Breathlessness domain	5.0 ± 5.5	12.0 ± 4.5	< 0.001	5.7 ± 5.8	9.9 ± 5.6	< 0.001
Cough and sputum domain	1.2 ± 1.6	3.2 ± 2.3	< 0.001	1.3 ± 1.7	3.0 ± 2.3	< 0.001
Chest symptoms domain	0.5 ± 0.8	2.0 ± 1.5	< 0.001	0.6 ± 0.9	1.8 ± 1.5	< 0.001
Severity of morning symptoms score	1.6 ± 2.0	8.7 ± 4.0	< 0.001	2.1 ± 2.8	7.0 ± 5.0	< 0.001
Severity of nighttime symptoms score	1.6 ± 2.5	7.6 ± 5.0	< 0.001	1.9 ± 3.0	7.4 ± 4.6	< 0.001
≥ 1 nocturnal awakening due to COPD	51 (10.8)	56 (46.7)	< 0.001	-	-	-

BMI: body mass index; COTE: (COPD-specific) **CO**morbidity **TE**st; mMRC: modified Medical Research Council score; CAT: COPD Assessment Test; BODEx: **B**ody mass index, airflow **O**bstruction, **D**yspnea, and **Ex**acerbations; and E-RS: **EXA**cerbations of **C**OPD **T**ool (EXACT)-Respiratory Symptoms. [a]Values expressed in n (%) or mean ± SD. [b]Complete data from 565 patients. Incomplete data from 28 patients. *ANOVA for continuous variables and the chi-square test for categorical variables.

behavioral differences between patients in different locations.[18,19,32]

By adopting two forms of grading symptoms, we demonstrated the importance of the assessment method in determining their prevalence. Morning dyspnea was reported by 20% of our patients when the criterion was moderate, intense, or very intense dyspnea accompanied by any other moderate, intense, or very intense symptom. This prevalence increased to 31% by simply changing the criteria to include at least two symptoms assessed as being at least moderate or one perceived as being at least intense. Similarly, the prevalence of nighttime symptoms varied between 18% and 29% due to the change of those two criteria, respectively.

Morning and nighttime symptoms were both found to correlate strongly with the intensity of symptoms around the clock. We also observed a very strong correlation between morning and nighttime symptom severity scores. However, the correlation between symptoms and the degree of airflow limitation, although statistically significant, was weak. Those data are in line with those of other publications,[6-17] which underscores the importance of assessing the symptomatology of patients and the weak association between the degree of spirometric changes and symptoms.

One of the strengths of our study was that we characterized the symptomatic behavior of COPD patients in Brazil with an adequate sample size. Regarding the methodological aspects, we emphasize that the present study is one of the few in the international literature in which validated questionnaires were used to evaluate morning and nighttime symptoms.[31]

Our study has some limitations. As with all other published studies on the variability of symptoms around the clock, we emphasize that this was a cross-sectional

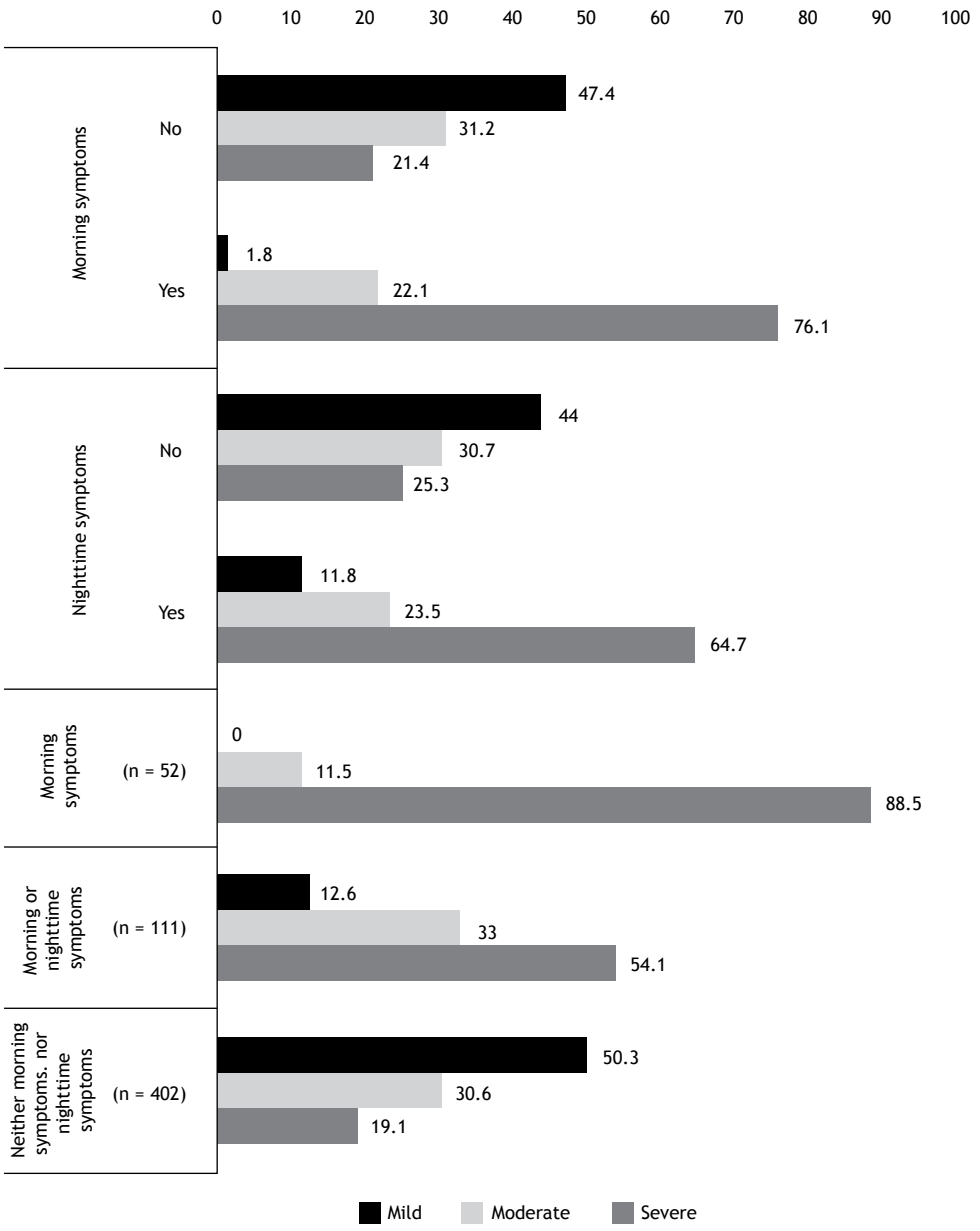


Figure 2. Associations between the intensity of daytime and nighttime symptoms and the prevalence of morning and nighttime symptoms.

observational analysis. In addition, as with other studies, we evaluated only the variability of respiratory symptoms without investigating extrapulmonary manifestations. Another limitation is related to the distribution of the participating research centers, all of which treat patients at the secondary and tertiary health care levels and are located in the southeastern or southern regions of the country, thereby limiting the generalizability of the findings. Finally, during the collection of data, there were variations in the availability of medications at most of those centers. Although the patients included in the study had not had any changes in their medication prescriptions for two months, some were not using their usual maintenance treatment regimen. However, these limitations did not influence the main study outcome, which underscores the importance of evaluating the variability of symptomatology around the clock in our population.

The mechanisms responsible for the temporal variability of respiratory symptoms are unclear. Circadian rhythms probably have an influence. In healthy individuals, it is recognized that FEV_1 is reduced by approximately 150 mL during the night,[33] and a similar reduction has been reported in patients with COPD.[34] It is speculated that these variations contribute to the onset of nighttime and morning symptoms.

Our data have obvious clinical implications. Health professionals are used to questioning COPD patients

Table 3. Correlation matrix between the total score of the global **EXA**cerbations of **C**OPD **T**ool-Respiratory Symptoms instrument, COPD Assessment Test score, FEV_1 in % of predicted, and severity scores of morning and nighttime symptoms.

Parameter	E-RS total		CAT		FEV_1, % of predicted value		Score – morning symptoms	
	r	p	r	p	r	p	r	p
CAT	0.6176	< 0.001						
FEV_1, % of predicted value	−0.2095	< 0.001	−0.1923	< 0.001				
Morning symptoms score	0.6515	< 0.001	0.5857	< 0.001	−0.0428	0.310		
Nighttime symptoms score	0.5982	< 0.001	0.5833	< 0.001	−0.0051	0.904	0.8334	< 0.001

E-RS: **EXA**cerbations of **C**OPD **T**ool (EXACT)-Respiratory Symptoms; and CAT: COPD Assessment Test.

about their symptoms. However, it is not customary to ask patients to report the period of the day during which their complaints prevail, nor is it common to inquire about the impact those complaints have on their activities and well-being. A considerable proportion of patients remain symptomatic despite receiving adequate treatment that follows the treatment guidelines. It is possible that, for some, a personalized approach to treatment that recognizes the particularities of the periods of the day during which the symptoms are at their worst will result in an improvement of symptoms.

When we treat our patients, we use a set of information. Specifically, we evaluate and quantify their symptoms, the frequency and intensity of exacerbations, the behavior of the disease over time, and the impact on activities of daily living.[35] The data presented in this study, combined with those published previously, suggest that inquiring about the variability of symptoms throughout the day and night should be an integral part of a proper history-taking.

ACKNOWLEDGMENTS

We are grateful to all of the patients and staff of the study centers who participated in the LASSYC-BR study, for their professionalism and contributions.

AUTHOR CONTRIBUTIONS

All of the authors contributed to the collection and interpretation of the data. AMBM and FCW performed the statistical analysis of the data, and all of the authors were involved in their interpretation. AC wrote the manuscript. All of the authors contributed to the critical revision of the manuscript and have approved the final version for submission to the JBP.

CONFLICTS OF INTEREST

AMBM and FCW received financial support from AstraZeneca do Brasil for the statistical analysis. AC received financial support from AstraZeneca do Brasil for the writing of the manuscript. CBL is an employee of AstraZeneca do Brasil.

REFERENCES

1. Terminology, definitions, and classification of chronic pulmonary emphysema and related conditions: a report of the conclusions of a CIBA guest symposium. Thorax. 1959;14(4):286-99. https://doi.org/10.1136/thx.14.4.286
2. Johnson MA, Woodcock AA, Rehahn M, Geddes DM. Are "pink puffers" more breathless than "blue bloaters"? Br Med J (Clin Res Ed). 1983;286(6360):179-82. https://doi.org/10.1136/bmj.286.6360.179
3. Pauwels RA, Buist SA, Calverley PMA, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001;163(5):1256-76. https://doi.org/10.1164/ajrccm.163.5.2101039
4. Sociedade Brasileira de Pneumologia e Tisiologia. II Consenso Brasileiro sobre Doença Pulmonar Obstrutiva Crônica - DPOC - 2004. J Bras Pneumol. 2004;30(Suppl 5):S1-S42.
5. Global Initiative for Chronic Obstructive Lung Disease (GOLD) [homepage on the Internet]. Bethesda: GOLD [cited 2019 Jan 10]. Global Strategy for the Diagnosis, Management, and Prevention of COPD - 2019 Report. [Adobe Acrobat document, 155p.]. Available from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf
6. Espinosa de los Monteros MJ, Peña C, Soto Hurtado EJ, Jareño J, Miravitlles M. Variability of respiratory symptoms in severe COPD. Arch Bronconeumol. 2012;48(1):3-7. https://doi.org/10.1016/j.arbres.2011.07.004
7. Kessler R, Partridge MR, Miravitlles M, Cazzola M, Vogelmeier C, Leynaud D, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. Eur Respir J. 2011;37(2):264-72. https://doi.org/10.1183/09031936.00051110
8. Kim YJ, Lee BK, Jung CY, Jeon YJ, Hyun DS, Kim KC, et al. Patient's perception of symptoms related to morning activity in chronic obstructive pulmonary disease: The SYMBOL study. Korean J Intern Med. 2012;27(4):426-35. https://doi.org/10.3904/kjim.2012.27.4.426
9. Kuyucu T, Güçlü SZ, Saylan B, Demir C, Senol T, Güner S, et al. A cross-sectional observational study to investigate daily symptom variability, effects of symptom on morning activities and therapeutic expectations of patients and physicians in COPD-SUNRISE study. Tuberk Toraks. 2011;59(4):328-39. https://doi.org/10.5578/tt.3268
10. Miravitlles M, Worth H, Soler Cataluña JJ, Price D, De Benedetto F, Roche N, et al. Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. Respir Res. 2014;15:122. https://doi.org/10.1186/s12931-014-0122-1
11. Partridge MR, Karlsson N, Small IR. Patient insight into the impact of chronic obstructive pulmonary disease in the morning: an internet survey. Curr Med Res Opin. 2009;25(8):2043-8. https://doi.org/10.1185/03007990903103006
12. Price D, Small M, Milligan G, Higgins V, Gil EG, Estruch J. Impact of night-time symptoms in COPD: a real-world study in five European countries. Int J Chron Obstruct Pulmon Dis. 2013;8:595-603. https://doi.org/10.2147/COPD.S48570
13. Roche N, Small M, Broomfield S, Higgins V, Pollard R. Real world COPD: association of morning symptoms with clinical and patient reported outcomes. COPD. 2013;10(6):679-86. https://doi.org/10.3109/15412555.2013.844784
14. Soler-Cataluña JJ, Sauleda J, Valdés L, Marín P, Agüero R, Pérez M, et al. Prevalence and Perception of 24-Hour Symptom Patterns in Patients With Stable Chronic Obstructive Pulmonary Disease in Spain. Arch Bronconeumol. 2016;52(6):308-15. https://doi.org/10.1016/j.arbres.2015.11.010

15. Miravitlles M, Menezes A, López Varela MV, Casas A, Ugaldee L, Ramirez-Venegas A, et al. Prevalence and impact of respiratory symptoms in a population of patients with COPD in Latin America: The LASSYC observational study. Respir Med. 2018;134:62-69. https://doi.org/10.1016/j.rmed.2017.11.018
16. Stephenson JJ, Cai Q, Mocarski M, Tan H, Doshi JA, Sullivan SD. Impact and factors associated with nighttime and early morning symptoms among patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2015;10:577-86. https://doi.org/10.2147/COPD.S76157
17. Tsiligianni I, Metting E, van der Molen T, Chavannes N, Kocks J. Morning and night symptoms in primary care COPD patients: a cross-sectional and longitudinal study. An UNLOCK study from the IPCRG. NPJ Prim Care Respir Med. 2016;26:16040. https://doi.org/10.1038/npjpcrm.2016.40
18. Pitta F, Breyer MK, Hernandes NA, Teixeira D, Sant'Anna TJ, Fontana AD, et al. Comparison of daily physical activity between COPD patients from Central Europe and South America. Respir Med. 2009;103(3):421-6. https://doi.org/10.1016/j.rmed.2008.09.019
19. Furlanetto KC, Demeyer H, Sant'anna T, Hernandes NA, Camillo CA, Pons IS, et al. Physical Activity of Patients with COPD from Regions with Different Climatic Variations. COPD. 2017;14(3):276-283. https://doi.org/10.1080/15412555.2017.1303039
20. Amorim PB, Stelmach R, Carvalho CR, Fernandes FL, Carvalho-Pinto RM, Cukier A. Barriers associated with reduced physical activity in COPD patients. J Bras Pneumol. 2014;40(5):504-12. https://doi.org/10.1590/S1806-37132014000500006
21. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581-6. https://doi.org/10.1136/thx.54.7.581
22. Soler-Cataluña JJ, Martínez-García MA, Sánchez LS, Tordera MP, Sánchez PR. Severe exacerbations and BODE index: two independent risk factors for death in male COPD patients. Respir Med. 2009;103(5):692-9. https://doi.org/10.1016/j.rmed.2008.12.005
23. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;186(2):155-61 https://doi.org/10.1164/rccm.201201-0034OC
24. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648-54. https://doi.org/10.1183/09031936.00102509
25. Leidy NK, Sexton CC, Jones PW, Notte SM, Monz BU, Nelsen L, et al. Measuring respiratory symptoms in clinical trials of COPD: reliability and validity of a daily diary. Thorax. 2014;69(5):443-9. https://doi.org/10.1136/thoraxjnl-2013-204428
26. Leidy NK, Murray LT, Monz BU, Nelsen L, Goldman N, Jones PW, et al. Measuring respiratory symptoms of COPD: performance of the EXACT-Respiratory Symptoms Tool (E-RS) in three clinical trials. Respir Res. 2014;15:124. https://doi.org/10.1186/s12931-014-0124-z
27. Hareendran A, Make BJ, Zaiser E, Garcia Gil E. Evaluation of the psychometric properties of the Early Morning Symptoms of COPD Instrument (EMSCI). Int J Chron Obstruct Pulmon Dis. 2018;13:1633-1645. https://doi.org/10.2147/COPD.S152087
28. Mocarski M, Zaiser E, Trundell D, Make BJ, Hareendran A. Evaluation of the psychometric properties of the Nighttime Symptoms of COPD Instrument, Int J Chron Obstruct Pulmon Dis. 2015;10:475-87. https://doi.org/10.2147/COPD.S75776
29. Ainsworth BE, Bassett DR Jr, Strath SJ, Swartz AM, O'Brien WL, Thompson RW, et al. Comparison of three methods for measuring the time spent in physical activity. Med Sci Sports Exerc. 2000;32(9 Suppl):S457-64. https://doi.org/10.1097/00005768-200009001-00004
30. Naberan K, Azpeitia A, Cantoni J, Miravitlles M. Impairment of quality of life in women with chronic obstructive pulmonary disease. Respir Med. 2012;106(3):367-73. https://doi.org/10.1016/j.rmed.2011.09.014
31. Wu M, Wang Z, Li M, Li K. Daily Symptom Variability in Patients With Stable COPD: A Narrative Review. West J Nurs Res. 2018;40(10):1543-1561. https://doi.org/10.1177/0193945917705132
32. Menezes AM, Perez-Padilla R, Jardim JR, Muiño A, Lopez MV, Valdivia G, et al. Chronic obstructive pulmonary disease in five Latin American cities: the PLATINO study: a prevalence study. Lancet. 2005;366(9500):1875-81. https://doi.org/10.1016/S0140-6736(05)67632-5
33. Borsboom GJ, van Pelt W, van Houwelingen HC, van Vianen BG, Schouten JP, Quanjer PH. Diurnal variation in lung function in subgroups from two Dutch populations: consequences for longitudinal analysis. Am J Respir Crit Care Med. 1999;159(4 Pt 1):1163-71. https://doi.org/10.1164/ajrccm.159.4.9703106
34. Calverley PM, Lee A, Towse L, van Noord J, Witek TJ, Kelsen S. Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. Thorax. 2003;58(10):855-60. https://doi.org/10.1136/thorax.58.10.855
35. Ferreira CA, Cukier A. Evaluating COPD from the perspective of the patient. J Bras Pneumol. 2006;32(2):vii-viii. https://doi.org/10.1590/S1806-37132006000200001

J Bras Pneumol. 2020;46(3):e20180422
https://dx.doi.org/10.36416/1806-3756/e20180422

ORIGINAL ARTICLE

Construct validity and reproducibility of the six-minute step test in subjects with obstructive sleep apnea treated with continuous positive airway pressure

Matheus Gustavo Silva Magalhães[1], Juliana Baptista Teixeira[1], Ana Maria Bezerra Santos[2], Danielle Cristina Silva Clímaco[3], Thayse Neves Santos Silva[4], Anna Myrna Jaguaribe de Lima[5]

1. Programa de Pós-Graduação em Fisioterapia, Universidade Federal de Pernambuco – UFPE – Recife (PE) Brasil.
2. Graduação em Bacharelado em Ciências Biológicas, Universidade Federal Rural de Pernambuco – UFRPE – Recife (PE) Brasil.
3. Setor de Pneumologia, Hospital Otávio de Freitas, Recife (PE) Brasil.
4. Setor de Reabilitação, Hospital Otávio de Freitas, Recife (PE) Brasil.
5. Departamento de Morfologia e Fisiologia Animal, Universidade Federal Rural de Pernambuco – UFRPE – Recife (PE) Brasil.

Submitted: 27 December 2018.
Accepted: 8 May 2019.

Study carried out under the auspices of the Programa de Pós-Graduação em Fisioterapia, Universidade Federal de Pernambuco – UFPE – Recife (PE) Brasil.

ABSTRACT

Objective: To evaluate the construct validity and reproducibility of the six-minute step test (6MST) in individuals with obstructive sleep apnea (OSA) treated with continuous positive airway pressure (CPAP). **Methods:** We evaluated 48 volunteers diagnosed with OSA and treated with CPAP for at least two months. The volunteers underwent the six-minute walk test (6MWT) and the 6MST, in random order and on different days, with an interval of, at most, seven days between the two tests. **Results:** A moderate positive correlation was found between the distance walked on the 6MWT and the number of steps climbed on the 6MST ($r = 0.520$; $p < 0.001$). There was no significant difference between the two 6MSTs in terms of the number of steps climbed (121.7 ± 27.1 vs. 123.6 ± 26.7). Reproducibility for performance on the 6MST and for cardiovascular variables was considered excellent (intraclass correlation coefficient > 0.8). Regarding cardiovascular responses, the 6MST produced higher values than did the 6MWT for HR at six minutes, percent predicted maximum HR, and leg fatigue at six minutes, as well as for systolic blood pressure at six minutes and at one minute of recovery. **Conclusions:** The 6MST is valid and reproducible, producing greater cardiovascular stress than does the 6MWT. However, the 6MST is also characterized as a submaximal test for the assessment of exercise tolerance in individuals with OSA treated with CPAP.

Keywords: Sleep apnea, obstructive; Reproducibility of results; Exercise test; Exercise tolerance.

INTRODUCTION

Obstructive sleep apnea (OSA) is a disease characterized by airflow obstruction during sleep due to upper airway collapse. As a consequence, repeated episodes of hypoxia, hypercapnia, and acidosis, followed by reoxygenation, affect the cellular bioenergetic function in striated muscles.[1] Therefore, there may be structural damage to muscle fibers, in association with comorbidities such as arterial hypertension, cardiac arrhythmias, and heart failure, all of which can affect functional exercise capacity (FEC) in the population with OSA.[2]

Regarding the treatment of OSA, the adoption of a better lifestyle, weight reduction, physical exercise, lateral decubitus sleep posture, use of intraoral devices, and orthodontic or surgical correction can be used. However, the gold standard in the treatment of OSA is the use of continuous positive airway pressure (CPAP), which maintains upper airway patency during sleep, reducing the tendency toward upper airway collapse and toward successive periods of hypoxia/reoxygenation, thus helping to improve sleep quality. Therefore, the systemic effects of the disease are minimized and the chances of developing comorbidities are reduced, which result in the attenuation of potential changes in FEC.[3,4]

The most reliable method for assessing FEC is cardiopulmonary exercise testing (CPET), which analyzes cardiovascular and respiratory behavior during maximal effort. However, in addition to not being widely tolerated by patients, CPET is costly and complex to perform, which makes its use difficult. Field tests, in contrast, are generally based on a submaximal assessment, which results in higher tolerability, are inexpensive, are easy to administer, and, in general, use a habitual form of effort as a form of assessment.[5,6]

Regarding the use of field tests in OSA, including after CPAP treatment, several studies have used the six-minute walk test (6MWT).[7-11] However, there have been no studies using the six-minute step test (6MST) to assess exercise tolerance in individuals with OSA. Therefore, the objective of the present study was to validate and evaluate the reproducibility of the 6MST in individuals with OSA treated with CPAP.

Correspondence to:
Anna Myrna Jaguaribe de Lima. Rua Dom Manoel de Medeiros, s/n, Dois Irmãos, CEP 52171-900, Recife, PE, Brasil.
Tel.: 55 81 3320-6391. E-mail: annamyrna@uol.com.br
Financial support: This study received financial support from the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Office for the Advancement of Higher Education).

ISSN 1806-3713

METHODS

This was a cross-sectional study approved by the Human Research Ethics Committee of the Federal University of Pernambuco, in the city of Recife, Brazil (Ruling no. 2,081,503) and registered with ClinicalTrials.gov (Identifier: NCT03334331).

The study included individuals aged 28 to 69 years who had moderate or severe OSA, had a body mass index greater than 18 kg/m^2 and less than 45 kg/m^2, and had been on CPAP for at least two consecutive months.

The study excluded pregnant women and individuals presenting with the following comorbidities: uncontrolled hypertension or diabetes; orthopedic or neurological disorders; respiratory disorders, such as COPD or asthma; or any cardiovascular or respiratory disease that prevented them from performing the tests.

Initially, all participants were informed about the study procedures and gave written informed consent. Subsequently, participants underwent history taking, in which they were interviewed regarding their personal and clinical data, and anthropometric assessment.

Some CPAP device usage data were obtained by accessing the device's memory card.

The following data were collected: proportion of CPAP use > 4 h/night; mean hours of CPAP use; titrated pressure (cmH_2O); and mean apnea-hypopnea index (events/h). Questionnaires were then completed regarding excessive daytime sleepiness (Epworth Sleepiness Scale),[12] sleep quality (Pittsburgh Sleep Quality Index),[13] and level of physical activity (International Physical Activity Questionnaire Short-Form).[14]

The 6MWT and the 6MST were performed on different days, with a minimum interval of two days and a maximum interval of seven days between the two tests, the order of which was determined by randomization (www.randomization.com). Therefore, on the first day of assessment, participants performed either the 6MWT or the 6MST, according to the randomization, twice at least 30 min apart, and, on the second day of assessment, they performed the other test under the same conditions. During the test-retest interval, participants were asked to rest in a sitting position.

The 6MWT was performed in accordance with the American Thoracic Society (ATS) guidelines,[15] along a flat, 30-m corridor with turnaround points marked with a traffic cone. Participants were instructed to walk as far as possible (walking back and forth around the cones) without running for six minutes, at a pace they could maintain.[15,16]

In order to standardize, for the purpose of reproducibility, the way the 6MST was to be performed, we followed the ATS guidelines for the 6MWT,[15] including the use of standard phrases of encouragement every minute. For the 6MST, we used a wooden step (dimensions: 20 cm in height × 80 cm in length × 40 cm in width) with an anti-slip surface. Participants were instructed to step up and down the step, maintaining a pace that would allow them to climb the step as many times as possible during the six-minute test period. Participants could use alternate legs to step up with, without the support of their arms, which remained stationary at their sides.[15,17]

Tests were conducted by two evaluators: one monitored the cardiopulmonary variables, and one kept track of the number of laps completed or steps climbed by the participant. The following physiological variables were measured at rest, immediately upon completion of the test, and at one minute of recovery: HR; systolic blood pressure (SBP); diastolic blood pressure (DBP); SpO_2; and leg fatigue. HR and SpO_2 were also monitored every minute during the tests. Tests were interrupted if the participant reached the predicted maximum HR, if SpO_2 dropped to less than 85%, or if the participant asked to stop the test. If a test was interrupted, the participant was instructed to stop and rest in a standing position; however, the timer was not stopped, because the participant could continue the test whenever able (i.e., when SpO_2 was ≥ 88% and HR was 10 beats below the maximum HR) until the end of the six-minute test period.[15]

The sample size was calculated with G*Power statistical software, version 3.1.3 (G*Power Team; Heinrich-Heine-Universität Düsseldorf, Kiel, Germany) for moderate between-test correlations (r = 0.5) related to submaximal HR values. Therefore, we assumed a type I error of 5%, a statistical power of 95%, and an effect size of 0.5, which resulted in a sample size of 45 individuals.

The data collected were initially tabulated in a Microsoft Excel 2016 spreadsheet. Statistical procedures were performed with GraphPad Prism software, version 4.0 (GraphPad Software Inc., San Diego, CA, USA), and SigmaPlot, version 12.0 (Systat Software, San Jose, CA, USA), and the level of statistical significance was set at $p < 0.05$. The Shapiro-Wilk normality test was used for data distribution analysis. Continuous variables are expressed as mean and standard deviation, as mean difference and 95% CI, or as median and interquartile range. Categorical variables are expressed as absolute and relative frequencies.

The Student's t-test or the Mann-Whitney test was used in order to compare means between the groups of men and women and between the 6MWT and the 6MST. Categorical variables were compared by using the chi-square test or Fisher's exact test.

Convergent construct validity was assessed. This type of validity assessment is made against a non-gold standard (the gold standard in this case being CPET), and validity was assessed by calculating Pearson's correlation coefficient between the number of steps climbed on the 6MST (S6MST)—the test to be validated—and the distance walked on the 6MWT (6MWD)—a test that has been validated for measurement of FEC but is not a gold standard.

The test-retest reproducibility and reliability of the 6MST were analyzed by calculating the intraclass correlation coefficient (ICC) and Pearson's correlation coefficient. Agreement between the 6MWT and the 6MST was analyzed through Bland-Altman plots with a 95% CI.

RESULTS

The study sample consisted of 48 volunteers. The anthropometric and clinical characteristics of the sample are presented in Table 1.

Regarding performance on the 6MST, 18 (37.5%) and 30 (62.5%) of the individuals performed better on the first and the second 6MST, respectively. As shown in Table 2, there were no significant differences in 6MWD or in S6MST between test and retest, and no learning effect was detected. Table 2 also shows the difference in mean S6MST, as well as in mean 6MWD, between test and retest.

Convergent construct validity showed a moderate positive correlation between 6MWD and S6MST (Figure 1).

Regarding 6MST performance, reproducibility for HR, SBP, and DBP immediately after the test and at one minute of recovery was found to be excellent (ICC > 0.8). Reproducibility for leg fatigue immediately after the test was also found to be excellent, whereas reproducibility for leg fatigue at one minute of recovery was found to be very good (0.6 < ICC < 0.8; Table 3).

Regarding cardiovascular responses, the 6MST produced higher values than did the 6MWT for HR at six minutes, percent predicted maximum HR, and leg fatigue immediately after the test, as well as for SBP immediately after the test and at one minute of recovery. There were no differences in DBP values between the 6MWT and the 6MST (Table 4). The agreement between performance on the test and retest of the 6MST is shown in Figure 2.

DISCUSSION

To our knowledge, this is the first study to validate and verify the reproducibility of the 6MST in individuals with OSA treated with CPAP. We could verify that the 6MST is a valid and reproducible test. In addition, there was no learning effect in the study population, demonstrating that only one 6MST is needed to assess exercise tolerance reliably and safely.

Convergent construct validity (6MST in patients with OSA treated with CPAP) showed a moderate positive correlation between S6MST and 6MWD, suggesting that the 6MST is valid for assessing FEC in the study population. The 6MST has been validated for use in individuals with COPD.[18] In the present study, S6MST was strongly correlated with 6MWD, being considered a good tool for identifying low exercise capacity and for making a prognosis. In addition, the 6MST has been validated for convergence for use in healthy individuals by Arcuri et al.,[19] showing a strong correlation with performance on the 6MWT. The 6MWT is a widespread and widely studied test in the literature, with well-defined criteria for assessing FEC in other populations, and can be safely used as a benchmark against which other tools can be compared and validated.[20,21]

There were no differences in 6MWD or in S6MST between test and retest. Therefore, there was no learning effect, a situation in which there is a need for the individual to get used to the effort to be performed, by means of a proper neuromuscular adaptation to the required task and a reduction of potential psychological factors, such as anxiety.[22] Thus, in this study population, we suggest that only one 6MST is needed to assess FEC. The effort required to perform the 6MST is comparable to that of a common activity of daily living, dispensing with the need for a retest and saving time in the process of assessing FEC.[19,22,23] In line with the findings of this study, Arcuri et al.[19] also found no learning effect for the 6MST in

Table 1. General characteristics of the sample.[a]

Characteristic	Total (N = 48)
Age, years	54.5 (48.0-62.8)
Weight, kg	89.7 ± 16.8
Height, m	1.6 ± 0.1
BMI, kg/m^2	33.2 ± 5.3
Abdominal circumference, cm	108.9 ± 11.5
Neck circumference, cm	41.4 ± 4.2
Comorbidities, n (%)	
Arterial hypertension	30 (62.5)
Diabetes mellitus	12 (25.0)
Drugs	
Antihypertensive agents	28 (58.3)
Hypoglycemic agents	11 (22.9)
IPAQ	
Sedentary	30 (62.5)
Active	18 (37.5)
AHI, events/h	31.7 (25.0-46.3)
15 ≥ AHI < 30 events/h	23 (47.9)
AHI ≥ 30 events/h	24 (50)
ESS	8.0 (4.3-14.8)
No sleepiness	29 (60.4)
Sleepiness	19 (39.6)
PSQI	4.0 (3.0-6.0)
Good sleep quality	25 (52.1)
Bad sleep quality	23 (47.9)
CPAP	
Use > 4 h/night, %	70.5 (51.8-87.1)
Mean number of hours of use, h	5.4 (4.3-6.2)
Pressure, cmH_2O	10.8 (9.0-13.0)
Mean AHI, events/h	1.8 (1.1-2.8)
Difficulty of adaptation	26 (54.2)

BMI: body mass index; IPAQ: International Physical Activity Questionnaire; AHI: apnea-hypopnea index; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; and CPAP: continuous positive airway pressure. [a]Data expressed as n (%) for categorical variables and as mean ± SD or median (interquartile range) for continuous variables.

Table 2. Performance on the six-minute walk test (6MWT) and on the six-minute step test (6MST).[a]

Variable	Test 1	Test 2	Best test	ΔT (Test 1 − Test 2)	p*
6MWD, m	495.1 ± 57.0	497.4 ± 58.6	509.8 ± 55.4	2.4 ± 34.4	0.638
S6MST	121.7 ± 27.1	123.6 ± 26.7	126.0 ± 26.1	1.9 ± 8.3	0.115

6MWD: distance walked on the 6MWT; and S6MST: number of steps climbed on the 6MST. [a]Data expressed as mean ± SD and as difference in means. *Paired t-test: Test 1 vs. Test 2.

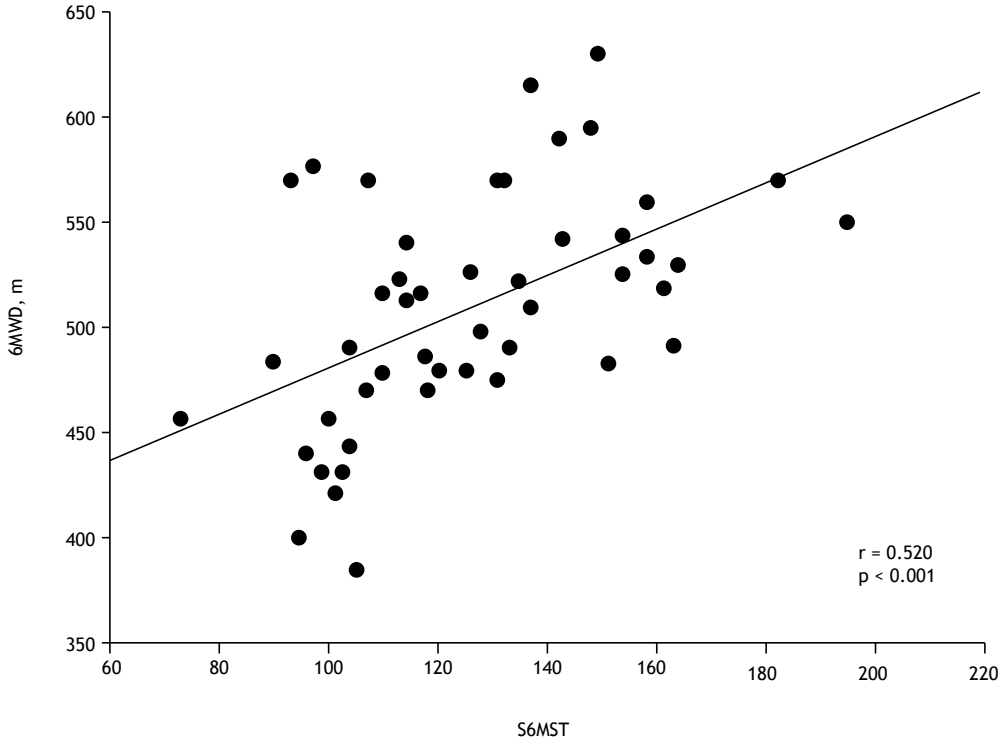


Figure 1. Correlation between the distance walked on the six-minute walk test (6MWD) and the number of steps climbed on the six-minute step test (S6MST).

Table 3. Reproducibility of the six-minute step test.

Variable	ICC (95% CI)	p
Performance on the test	0.976 (0.957-0.986)	< 0.001
HR at six minutes	0.984 (0.971-0.991)	< 0.001
HR at one minute of recovery	0.972 (0.950-0.984)	< 0.001
SBP at six minutes	0.906 (0.832-0.947)	< 0.001
SBP at one minute of recovery	0.826 (0.690-0.902)	< 0.001
DBP at six minutes	0.796 (0.636-0.886)	< 0.001
DBP at one minute of recovery	0.849 (0.730-0.915)	< 0.001
Leg fatigue at six minutes	0.927 (0.869-0.959)	< 0.001
Leg fatigue at one minute of recovery	0.646 (0.369-0.802)	< 0.001

ICC: intraclass correlation coefficient; SBP: systolic blood pressure; and DBP: diastolic blood pressure.

healthy individuals. Pessoa et al.,[18] when evaluating patients with COPD, found concurrent and predictive validity in the first 6MST, dispensing with the need for a second test.

Comparison of the behavior of physiological variables during the 6MST and during the 6MWT revealed that the 6MST produced greater cardiovascular stress. Similar results were found in a study by da Costa et al.,[24] in which healthy sedentary individuals were evaluated. However, da Silva et al.,[25] when comparing these variables in individuals who had a stroke and underwent the 6MST and the 6MWT, found no differences between the tests. The greater cardiovascular stress produced by the 6MST can be attributed to the fact that the 6MST requires greater leg muscle activity than does the 6MWT. The movement of climbing up and down steps is a vertical activity performed against the force of gravity, which that requires greater effort and metabolic demand and, consequently, greater

Table 4. Cardiovascular responses to the six-minute walk test (6MWT) and to the six-minute step test (6MST).[a]

	6MWT	6MST	Δ means	p
HR, bpm				
At rest	74.3 ± 11.9	76.0 ± 11.9	−1.7 (−6.5 to 3.1)	0.433#
At six minutes	112.8 ± 15.5	124.8 ± 21.6	−12.0 (−19.6 to −4.3)	0.002*
Recoveryb	33.6 ± 7.6	37.2 ± 11.0	−3.6 (−7.4 to 0.2)	0.064#
HRmax, % predicted	68.3 ± 8.9	74.2 ± 11.8	−5.9 (−10.2 to −1.7)	0.006*
SBP, mmHg				
At rest	120.8 ± 9.9	121.3 ± 9.1	−0.4 (−4.3 to 3.4)	0.744#
At six minutes	142.1 ± 16.9	151.9 ± 17.7	−9.8 (−16.8 to −2.8)	0.010#
At one minute of recovery	121.9 ± 10.5	127.9 ± 13.5	−5.2 (−10.1 to −0.3)	0.037*
DBP, mmHg				
At rest	81.0 ± 5.9	81.0 ± 5.6	0.0 (−2.3 to 2.3)	1.000#
At six minutes	84.0 ± 6.4	82.7 ± 7.6	1.3 (−1.6 to 4.1)	0.367#
At one minute of recovery	81.0 ± 6.9	80.2 ± 7.3	0.8 (−2.1 to 3.7)	0.551*
Leg fatigue, Borg scale				
At rest	2.1 ± 1.9	1.7 ± 1.8	0.4 (−0.3 to 1.2)	0.366#
At six minutes	4.1 ± 2.1	5.1 ± 1.9	−1.1 (−1.9 to −0.3)	0.017#
At one minute of recovery	2.5 ± 1.8	3.1 ± 1.9	−0.7 (−1.4 to 0.1)	0.084#

SBP: systolic blood pressure; and DBP: diastolic blood pressure. aData expressed as mean ± SD or as difference in means (95% CI). bRecovery = HRmax = HR at one minute of recovery. *Student's t-test: 6MWT vs. 6MST. #Mann-Whitney test: 6MWT vs. 6MST.

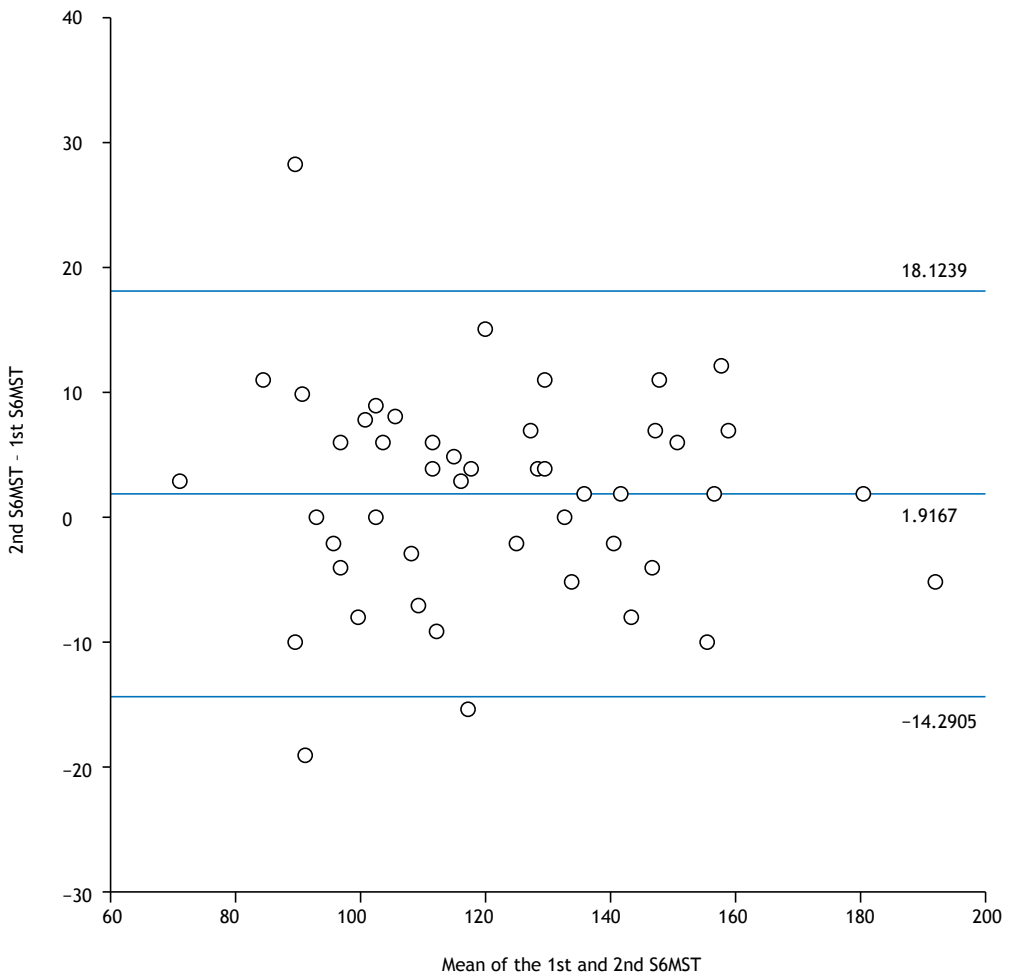


Figure 2. Bland-Altman plot for the test and retest agreement between the six-minute step test (6MST), as measured by the number of steps climbed on the 6MST (S6MST). Mean error: 1.91 steps.

cardiovascular activity, but that remains within the submaximal effort range.[24] Therefore, the 6MST can be considered more appropriate for assessing FEC, providing data that are more accurate for quantification and prescription of exercise in individuals with OSA treated with CPAP.

Assessment of submaximal exercise capacity in individuals with OSA is found in the literature mainly in studies employing the 6MWT, highlighting potential exercise intolerance accompanied by abnormal cardiovascular responses in this population,[7,8] even after CPAP treatment, with similar results to those of CPET, as well as a reduction in 6MWD when compared with the optimal 6MWD.[9,10] Another field test that has been used in this population is the shuttle test, which was able to detect changes in FEC after CPAP treatment, as well as weight reduction and excessive daytime sleepiness.[26] To our knowledge, there have been no studies on the use of the 6MST for assessing individuals with OSA treated with CPAP. In addition to having the same advantages as other field tests, the 6MST does not require a large space for it to be performed and the step can be easily transported to be used in a minimal space. Therefore, better patient monitoring is possible, because the required movement is not large or horizontal.[17,27]

In this study, the test-retest reproducibility of the 6MST was found to be excellent for the individual's performance on the test and for the cardiovascular variables analyzed. These data corroborate the results obtained by da Costa et al.[23] and Davi et al.[28] in patients with COPD and in healthy young adults, respectively. In both studies, the reproducibility of the 6MST was found to be excellent for the individual's performance on the test. Likewise, in their study involving healthy individuals, Arcuri et al.[19] obtained excellent reproducibility for physiological variables and for the individual's performance on the test. Therefore, the 6MST can be considered an evaluation strategy that uses a simple and easy-to-perform protocol, which positively contributes to its reproducibility and agreement, as well as to lower error rates.[19,23]

The present study, despite reporting relevant data, has some limitations. The data obtained from the 6MST were not compared with those obtained from CPET, which is the gold standard in the assessment of FEC. The 6MWT, however, is a consolidated tool against which data obtained from other exercise tolerance tests can be compared with and validated. We suggest that larger studies be conducted to develop prediction equations for FEC using the 6MST in patients with OSA treated with CPAP.

We concluded that the 6MST is a valid and reproducible tool to assess FEC in individuals with OSA treated with CPAP. In addition, the 6MST can produce greater cardiovascular stress when compared with the 6MWT, although the 6MST is also characterized as a submaximal test for the assessment of exercise tolerance in this population. In addition to the fact that the 6MST is easy to administer and monitor, is inexpensive, and can be performed in small areas, we found that only one 6MST is needed to assess exercise tolerance reliably in this population, given that there was no learning effect. The convergence of these factors leads to increased feasibility of using the 6MST on a large scale in routine clinical practice at public and private health care facilities.

REFERENCES

1. Beitler JR, Awad KM, Bakker JP, Edwards BA, DeYoung P, Djonlagic I, et al. Obstructive sleep apnea is associated with impaired exercise capacity: a cross-sectional study. J Clin Sleep Med. 2014;10(11):1199-1204. https://doi.org/10.5664/jcsm.4200
2. Maeder MT, Schoch OD, Rickli H. A clinical approach to obstructive sleep apnea as a risk factor for cardiovascular disease. Vasc Health Risk Manag. 2016;12:85-103. https://doi.org/10.2147/VHRM.S74703
3. Rotenberg BW, Vicini C, Pang EB, Pang KP. Reconsidering first-line treatment for obstructive sleep apnea: a systematic review of the literature. J Otolaryngol Head Neck Surg. 2016;45:23. https://doi.org/10.1186/s40463-016-0136-4
4. Litvin AY, Sukmarova ZN, Elfimova EM, Aksenova AV, Galitsin PV, Rogoza AN, et al. Effects of CPAP on "vascular" risk factors in patients with obstructive sleep apnea and arterial hypertension. Vasc Health Risk Manag. 2013;9:229-235. https://doi.org/10.2147/VHRM.S40231
5. Herdy AH, Ritt LE, Stein R, Araújo CG, Milani M, Meneghelo RS, et al. Cardiopulmonary Exercise Test: Background, Applicability and Interpretation. Arq Bras Cardiol. 2016;107(5):467-481. https://doi.org/10.5935/abc.20160171
6. Gappmaier E. The Submaximal Clinical Exercise Tolerance Test (SXTT) to Establish Safe Exercise Prescription Parameters for Patients with Chronic Disease and Disability. Cardiopulm Phys Ther J. 2012;23(2):19-29. https://doi.org/10.1097/01823246-201223020-00004
7. Pływaczewski R, Stokłosa A, Bieleń P, Bednarek M, Czerniawska J, Jonczak L, et al. Six-minute walk test in obstructive sleep apnoea. Pneumonol Alergol Pol. 2008;76(2):75-82.
8. Alameri H, Al-Kabab Y, BaHammam A. Submaximal exercise in patients with severe obstructive sleep apnea. Sleep Breath. 2010;14(2):145-151. https://doi.org/10.1007/s11325-009-0300-4
9. Cholidou KG, Manali ED, Kapsimalis F, Kostakis ID, Vougas K, Simoes D, et al. Heart rate recovery post 6-minute walking test in obstructive sleep apnea: cycle ergometry versus 6-minute walking test in OSA patients. Clin Res Cardiol. 2014;103(10):805-815. https://doi.org/10.1007/s00392-014-0721-3
10. Ben Saad H, Ben Hassen I, Ghannouchi I, Latiri I, Rouatbi S, Escourrou P, et al. 6-Min walk-test data in severe obstructive-sleep-apnea-hypopnea-syndrome (OSAHS) under continuous-positive-airway-pressure (CPAP) treatment. Respir Med. 2015;109(5):642-655. https://doi.org/10.1016/j.rmed.2015.03.001
11. Nascimento AP, Passos VM, Pedrosa RP, Brasileiro-Santos MS, Barros IM, Costa LO, et al. Sleep quality and stress tolerance in patients with obstructive sleep apnea [Article in Portuguese]. Rev Bras Med Esporte. 2014;20(2):115-118. https://doi.org/10.1590/1517-86922014200201357
12. Bertolazi AN, Fagondes SC, Hoff LS, Pedro VD, Menna Barreto SS, Johns MW. Portuguese-language version of the Epworth sleepiness scale: validation for use in Brazil. J Bras Pneumol. 2009;35(9):877-883. https://doi.org/10.1590/S1806-37132009000900009
13. Bertolazi AN, Fagondes SC, Hoff LS, Dartora EG, Miozzo IC, Barba ME, et al. Validation of the Brazilian Portuguese version of the Pittsburgh Sleep Quality Index. Sleep Med. 2011;12(1):70-75. https://doi.org/10.1016/j.sleep.2010.04.020
14. Matsudo S, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira LC, et al. Questionário Internacional de Atividade Física (IPAQ): estudo

de validade e reprodutibilidade no Brasil. Rev Bras Atividade Fisica Saude. 2001;6(2):5-18.

15. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test [published correction appears in Am J Respir Crit Care Med. 2016 May 15;193(10):1185]. Am J Respir Crit Care Med. 2002;166(1):111-117. https://doi.org/10.1164/ajrccm.166.1.at1102
16. Soaresa MR, Pereira CA. Six-minute walk test: reference values for healthy adults in Brazil. J Bras Pneumol. 2011;37(5):576-583. https://doi.org/10.12820/rbafs.v.6n2p5-18
17. Dal Corso S, Duarte SR, Neder JA, Malaguti C, Fuccio MB, de Castro Pereira CA, et al. A step test to assess exercise-related oxygen desaturation in interstitial lung disease. Eur Respir J. 2007;29(2):330-336. https://doi.org/10.1183/09031936.00094006
18. Pessoa BV, Arcuri JF, Labadessa IG, Costa JN, Sentanin AC, Di Lorenzo VA. Validity of the six-minute step test of free cadence in patients with chronic obstructive pulmonary disease. Braz J Phys Ther. 2014;18(3):228-236. https://doi.org/10.1590/bjpt-rbf.2014.0041
19. Arcuri JF, Borghi-Silva A, Labadessa IG, Sentanin AC, Candolo C, Pires Di Lorenzo VA. Validity and Reliability of the 6-Minute Step Test in Healthy Individuals: A Cross-sectional Study. Clin J Sport Med. 2016;26(1):69-75. https://doi.org/10.1097/JSM.0000000000000190
20. Mänttäri A, Suni J, Sievänen H, Husu P, Vähä-Ypyä H, Valkeinen H, et al. Six-minute walk test: a tool for predicting maximal aerobic power (VO2 max) in healthy adults. Clin Physiol Funct Imaging. 2018;10.1111/cpf.12525. https://doi.org/10.1111/cpf.12525
21. Morales-Blanhir JE, Palafox Vidal CD, Rosas Romero Mde J, García Castro MM, Londoño Villegas A, Zamboni M. Six-minute walk test: a valuable tool for assessing pulmonary impairment. J Bras Pneumol. 2011;37(1):110-117. https://doi.org/10.1590/S1806-37132011000100016
22. Rodrigues SL, Mendes HF, Viegas CA. Teste de caminhada de seis minutos: estudo do efeito do aprendizado em portadores de doença pulmonar obstrutiva crônica. J Bras Pneumol. 2004;30(2):121-125. https://doi.org/10.1590/S1806-37132004000200008
23. da Costa JN, Arcuri JF, Gonçalves IL, Davi SF, Pessoa BV, Jamami M, et al. Reproducibility of cadence-free 6-minute step test in subjects with COPD. Respir Care. 2014;59(4):538-542. https://doi.org/10.4187/respcare.02743
24. da Costa CH, da Silva KM, Maiworm A, Raphael Y, Parnayba J, Da Cal M, et al. Can we use the 6-minute step test instead of the 6-minute walking test? An observational study. Physiotherapy. 2017;103(1):48-52. https://doi.org/10.1016/j.physio.2015.11.003
25. da Silva TD, Raimundo RD, Ferreira C, Torriani-Pasin C, Monteiro CB, Theodoro Júnior OA, et al. Comparison between the six-minute walk test and the six-minute step test in post stroke patients. Int Arch Med. 2013;6:31. https://doi.org/10.1186/1755-7682-6-31
26. Billings CG, Aung T, Renshaw SA, Bianchi SM. Incremental shuttle walk test in the assessment of patients with obstructive sleep apnea-hypopnea syndrome. J Sleep Res. 2013;22(4):471-477. https://doi.org/10.1111/jsr.12037
27. Andrade CH, Cianci RG, Malaguti C, Corso SD. The use of step tests for the assessment of exercise capacity in healthy subjects and in patients with chronic lung disease. J Bras Pneumol. 2012;38(1):116-124. https://doi.org/10.1590/S1806-37132012000100016
28. Davi SF, Arcuri JF, Labadessa IG, Pessoa BV, da Costa JN, Sentanin AC, et al. Reprodutibilidade do teste de caminhada e do degrau de 6 minutos em adultos jovens saudáveis. Rev Bras Med Esporte. 2014;20(3):214-8. https://doi.org/10.1590/1517-86922014200301714

J Bras Pneumol. 2020;46(3):e20190138
https://dx.doi.org/10.36416/1806-3756/e20190138

ORIGINAL ARTICLE

Reference values for spirometry in Brazilian children

Marcus Herbert Jones[1], Paula Cristina Vasconcellos Vidal[1], Fernanda Cordoba Lanza[2], Danielle Corrêa França de Melo Franco Silva[2], Paulo Márcio Pitrez[3], Ana Paula Bigliardi de Freitas Olmedo[4], Edjane Figueiredo Burity[5], Kennedy Long Schisler[6], Leonardo Araújo Pinto[1], Aline Dill Winck[7], Edna Lúcia Santos de Souza[8], Anick Augustin Oliveira[9], Maria Ângela Gonçalves de Oliveira Ribeiro[10], Lidia Alice Gomes Monteiro Marin Torres[11], Maria de Fátima Bazhuni Pombo March[12]; Grupo de Trabalho em Função Pulmonar

1. Pontifícia Universidade Católica do Rio Grande do Sul – PUCRS – Porto Alegre (RS) Brasil.
2. Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
3. Hospital Moinhos de Vento, Porto Alegre (RS) Brasil.
4. Fundação Universidade Federal do Rio Grande – FURG – Rio Grande (RS) Brasil.
5. Universidade Federal de Pernambuco – UFPE – Recife (PE) Brasil.
6. Hospital Ministro Costa Cavalcanti, Foz do Iguaçu (PR) Brasil.
7. Universidade de Caxias do Sul – UCS – Caxias do Sul (RS) Brasil.
8. Universidade Federal da Bahia – UFBA – Salvador (BA) Brasil.
9. Hospital do Pulmão, Blumenau (SC) Brasil.
10. Universidade Estadual de Campinas – UNICAMP – Campinas (SP) Brasil.
11. Universidade de São Paulo – USP – São Paulo (SP) Brasil.
12. Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ) Brasil.

Submitted: 1 August 2019.
Accepted: 13 October 2019.

ABSTRACT

Objective: To generate reference values for spirometry in Brazilian children 3-12 years of age and to compare those values with the values employed in the equations currently in use in Brazil. **Methods:** This study involved healthy children, 3-12 years of age, recruited from 14 centers (primary data) and spirometry results from children with the same characteristics in six databases (secondary data). Reference equations by quantile regressions were generated after log transformation of the spirometric and anthropometric data. Skin color was classified as self-reported by the participants. To determine the suitability of the results obtained, they were compared with those predicted by the equations currently in use in Brazil. **Results:** We included 1,990 individuals from a total of 21 primary and secondary data sources. Of those, 1,059 (53%) were female. Equations for FEV_1, FVC, the FEV_1/FVC ratio, FEF between 25% and 75% of the FVC ($FEF_{25-75\%}$) and the $FEF_{25-75\%}$/FVC ratio were generated for white-, black-, and brown-skinned children. The logarithms for height and age, together with skin color, were the best predictors of FEV_1 and FVC. The reference values obtained were significantly higher than those employed in the equations currently in use in Brazil, for predicted values, as well as for the lower limit of normality, particularly in children with self-reported black or brown skin. **Conclusions:** New spirometric equations were generated for Brazilian children 3-12 years of age, in the three skin-color categories defined. The equations currently in use in Brazil seem to underestimate the lung function of Brazilian children 3-12 years of age and should be replaced by the equations proposed in this study.

Keywords: Spirometry; Reference values; Child; Child, preschool; Respiratory function tests.

INTRODUCTION

Spirometry is the most widely used complementary test for the assessment of respiratory function in children, and reference values are essential for its clinical application. Healthy individuals, ideally of the same ethnicity as the patients in whom the test will be used, are used in the generation of such reference values.[1]

In Brazil, reference values for spirometry in children were generated between 1989 and 1991 from a sample of individuals in the city of São Paulo. The values were then published in the 2002 *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association) Guidelines for Pulmonary Function Tests.[2] The study that generated those values included a total of 602 children (defined as individuals 6-14 years of age) and youths (defined as individuals 14-24 years of age) with self-reported skin color of white, black, or brown. However, the authors did not propose distinct equations for black and brown children; nor did they offer age- and height-adjusted values for the FEV_1/FVC ratio.[2]

In 2009, Stanojevic et al.[3] proposed international spirometric equations for white children, their sample including a small proportion of children in Brazil. In 2012, the Global Lung Function Initiative (GLI) published equations for use in White, Black, Asian, and mixed-race individuals aged 3 to 95 years.[4] However, those equations did not use spirometry data from healthy African or Latin American children and have therefore not been validated for use in Brazil. More recently, reference values for Brazilian children under 6 years of age were obtained in the cities of Recife, in the state of Pernambuco,[5] and Sete Lagoas, in the state of Minas Gerais.[6]

Correspondence to:
Marcus Herbert Jones. Hospital São Lucas, Avenida Ipiranga, 6690, CEP 90619-900, Porto Alegre, RS, Brasil.
Tel.: 55 51 99988-8524. E-mail: mhjones@pucrs.br
Financial support: This study was carried out with the financial support of the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association), the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development), the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Office for the Advancement of Higher Education), and AstraZeneca.

Given the lack of spirometry reference equations for children that have been validated for use in Brazil, the present study aimed to generate reference values for spirometry in Brazilian children 3-12 years of age, who are healthy from a respiratory standpoint, using a large, representative sample. Another objective was to compare the spirometry equations obtained in this study with those currently in use in Brazil.[2,4]

METHODS

Study design, inclusion criteria, and exclusion criteria

This was a multicenter, cross-sectional observational study involving healthy children (defined here as individuals 3-12 years of age) with a self-reported skin color of white, black, or brown. For subject selection, we used a standardized questionnaire containing specific questions about respiratory diseases, based on the American Thoracic Society/Division of Lung Diseases questionnaire for children, known as the ATS-DLD-78-C.[7] This instrument, which is formally recommended for use in epidemiological studies, has been adapted and validated for use in Brazil.[7]

The following exclusion criteria were applied: gestational age < 37 weeks, low birth weight (< 2,500 g), signs and symptoms of chronic respiratory disease, recurrent wheezing (three or more episodes), heart disease, scoliosis, history of thoracic surgery, and any disease that could prevent a forced expiratory maneuver.

Setting up the spirometry database

The data were obtained from a prospective multicenter study conducted in 16 Brazilian cities (primary data) and from spirometry databases generated in other studies of healthy children in the same age group (secondary data).

The primary database was composed of data obtained prospectively through a strict observance of the study protocol. Participants whose data were analyzed in the primary database were recruited in the following Brazilian cities (states): Belo Horizonte (Minas Gerais); Blumenau (Santa Catarina); Campinas (São Paulo); Curitiba (Paraná); Foz do Iguaçu (Paraná); Niterói (Rio de Janeiro); Porto Alegre (Rio Grande do Sul); Recife (Pernambuco); Ribeirão Preto (São Paulo); Rio de Janeiro (Rio de Janeiro); Salvador (Bahia); São Luiz Gonzaga (Rio Grande do Sul); and Sete Lagoas (Minas Gerais).

The secondary database was composed of spirometric data obtained from healthy children 3-12 years of age recruited in other studies, provided that the inclusion criteria and quality control were similar to those established in the original protocol. Those data were obtained in the city of São Paulo, as well as in three cities in the state of Rio Grande do Sul (Porto Alegre, Caxias do Sul, and Rio Grande). The collaborating researchers authorized the inclusion of their databases in the present analysis. Finally, the primary and secondary databases were combined into a single database after we confirmed, by multiple linear regression, that the data source had no significant effect on the variables FVC, FEV_1, FEV_1/FVC ratio, and $FEF_{25-75\%}$.

Spirometry and anthropometry

We collected data on gender, date of birth, birth weight, and skin color. The skin color (white, brown, or black) was self-reported by the participants.

Weight and height were measured on the day of the pulmonary function test. For the anthropometric assessment, we used digital scales with a precision of 100 g and stadiometers with a precision of 1 mm. The height was measured in triplicate, the mode of the three measurements being recorded. Maximum expiratory maneuvers were obtained with a Koko PFT Spirometer (nSpire Health Inc., Longmont, CO, USA), in accordance with the protocols of the American Thoracic Society and European Respiratory Society.[1,8] The spirometry results were registered in an electronic spreadsheet, together with the clinical and the anthropometric data.

Quality control

The flow-volume curves and the results were first analyzed by the researchers at each center at the time of collection and rejected if they did not meet the acceptance and reproducibility criteria previously described.[1] The spirometric curves were also reviewed by two researchers before inclusion in the consolidated database. Finally, spirometric data with extreme values, defined as a difference of more than four standard deviations between what was predicted by the new equations and the observed value, were excluded because of the likelihood that they were technical or typographical errors.

Statistical analysis

Demographic, anthropometric, and spirometric data were transferred to the R computing environment, where statistical calculations were performed.[9]

The lung function, height, and age variables were log transformed to correct the nonlinearity of the relationships and to stabilize the variance.

Reference equations for FVC, FEV_1, the FEV_1/FVC ratio, $FEF_{25-75\%}$, and the $FEF_{25-75\%}$/FVC ratio were generated by quantile regression so as to estimate the predicted value (50th percentile) and the lower limit of normal (5th percentile). To calculate the Z-score, we generated equations by multiple linear regression. Height, age, gender, and skin color were considered independent variables. We used multiple linear regression to compare the lung function variables of individuals by skin color. We considered lung function parameters as dependent variables, adjusted for height and age, and tested the statistical significance of skin color in the model. The same procedure was used in order to compare the primary and the secondary databases.

The results obtained were compared with the predicted values defined in the equations established in the SBPT

guidelines,[2] which propose the same equation for all children, regardless of skin color. For the comparison with the GLI equations[4], we applied the so-called "Caucasian" equations to the self-described white children, the "Black" equations to the self-described black children, and the "other/mixed" equations to the self-described brown children. The statistical analysis of the comparison between the observed and the predicted values was performed with the Mann-Whitney non-parametric test for paired samples. Descriptive statistical analyses were conducted, and linear regression models were created in the R language and environment for statistical computing.[9] The *quantreg* and *ggplot2* packages were also used in order to generate the quantile regression models and plots, respectively.

Ethics

Parents or legal guardians authorized the spirometry and gave written informed consent or assent. The study was approved by the Research Ethics Committee at the Pontifical Catholic University of Rio Grande do Sul (Reference no. 09/04787) and was later approved by the research ethics committee at each participating center. Collaborating researchers who shared their databases consented to the use of their data for generating reference values.

RESULTS

After subjects for whom there were incomplete data, nonreproducible spirometric curves, or extreme values had been excluded, the primary and secondary databases contained information on 936 subjects and 1,054 subjects, respectively. Therefore, the final database contained information on 1,990 subjects, of whom 1,059 (53%) were female and 931 (47%) were male. The various data sources are shown in Table 1. The medians (ranges) for age, height, and weight were, respectively, 9.04 years (3.0-12.9 years), 134.5 cm (85-176 cm), and 30.5 kg (11-89 kg). The age and height histograms are shown as supplementary material (Figure S1). Among the 1,990 subjects included in the analyses, the self-reported skin color was white in 1,353 (68%), black in 184 (9%), and brown in 386 (19%). The remaining 67 subjects (3%) did not report their skin color.

Comparison of lung function between the primary and secondary databases

The multiple linear regression models adjusted for age, gender, skin color, and height revealed no significant differences between the primary and secondary data for FVC, FEV_1, FEV_1/FVC ratio, and $FEF_{25-75\%}$.

Lung function by skin color

After adjusting for height and age through a multiple linear regression model, we found that the white children had significantly higher FVC and FEV_1 values than did the black and brown children. The black and brown children did not differ significantly regarding their FVC ($p = 0.582$), FEV_1 ($p = 0.561$), FEV_1/FVC ratio ($p = 0.900$), or $FEF_{25-75\%}$ ($p = 0.925$) variables. Therefore, for subsequent comparative analyses and the generation of the equations, we divided the subjects into two groups: white children; and black/brown children.

Table 1. Primary and secondary data sources: location and number of participating individuals (N = 1,990).

Data source	City, state	Individuals	
		n	%
Primary	Recife, PE	176	8.8
	Sete Lagoas, MG	164	8.2
	Porto Alegre, RS	156	7.8
	São Luis Gonzaga, RS	76	3.8
	Porto Alegre, RS	68	3.4
	Foz do Iguaçu, PR	48	2.4
	Salvador, BA	42	2.1
	Blumenau, SC	42	2.1
	Campinas, SP	34	1.7
	Ribeirão Preto, SP	32	1.6
	Rio de Janeiro, RJ	32	1.6
	Niterói, RJ	28	1.4
	Curitiba, PR	22	1.1
	Belo Horizonte, MG	16	0.8
Secondary	São Paulo, SP	266	13.4
	Porto Alegre, RS	242	12.2
	Porto Alegre, RS	220	11.1
	Rio Grande, RS	188	9.4
	Porto Alegre, RS	93	4.7
	Caxias do Sul, RS	45	2.3

PE: Pernambuco; MG: Minas Gerais; RS: Rio Grande do Sul; PR: Paraná; BA: Bahia; SC: Santa Catarina; SP: São Paulo; and RJ: Rio de Janeiro.

The black/brown children showed significantly lower FVCs in comparison with the white children, the mean differences (95% CIs) being −4.7% (−6.3% to −3.1%) for girls and −3.2% (−4.8% to −1.6%) for boys ($p < 0.001$ and $p < 0.01$, respectively). Similar differences were found for FEV_1: −4.3% (−5.8% to −2.8%) for girls and −2.2% (−3.8% to −0.7%) for boys ($p < 0.0010$ and $p < 0.050$, respectively). The differences between the two skin-color groups did not achieve statistical significance for $FEF_{25-75\%}$ or for the FEV_1/ FVC ratio. Therefore, skin color was not used as a predictor for these variables in the equations. The black/brown children had higher $FEF_{25-75\%}$/FVC ratios than did the white children ($p < 0.001$ for both genders).

Generating the predicted value equations

The equations for the predicted values and for the lower limit of normal were generated separately for female and male individuals, as shown in Table 2. The variables used in calculating the FVC and FEV_1 logarithms were the natural logarithms of height and age plus skin color, a value of 1 being assigned to the black/brown children group and a value of 0 being assigned to the white children group. For the calculation of the $FEF_{25-75\%}$ logarithm, natural logarithms of height and age were used. To calculate the predicted value for the FEV_1/FVC ratio, only the height logarithm was used, because the models did not show age or skin color to be significant. For the $FEF_{25-75\%}$/FVC ratio model, only the height and skin color logarithms were found to be significant. The adjusted correlation coefficient for the equations ranged from 0.83 to 0.85 for FVC and FEV_1, for both genders. As references, two-dimensional representations of the relationships that FEV_1 and FVC had with height, stratified by gender and skin color, can be seen in Figure 1, whereas the relationships that FEV_1/FVC ratio and $FEF_{25-75\%}$ had with height, stratified by gender, can be seen in Figure 2. The equations for calculating the Z-scores are included in the supplementary material (Table S1).

Comparisons with the SBPT and GLI equations

The comparison between the values observed in our study and those predicted by the SBPT[2] and GLI[4] equations are shown in Table 3. The values predicted by the SBPT[2] equations significantly underestimate FVC and FEV_1, when compared with those observed in our sample. For FVC, the mean amplitude of that difference was 12.5% (230 mL) and 10.2% (205 mL) in white girls and boys, respectively ($p < 0.001$ for both). For FEV_1, the difference was 9.7% (157 mL) and 5.6% (101 mL) in white girls and boys, respectively ($p < 0.001$ for both).

For black/brown children, the differences between the values predicted by the SBPT[2] and the value observed in our sample were smaller, although still considerable. The FVC values in our sample were 134 mL and 181 mL higher than those predicted by the SBPT equation.[2] For girls and boys, the differences were 132 mL and 192 mL, respectively ($p < 0.001$ for

Table 2. Equations for predicted spirometry values children 3-12 years of age in Brazil.[a]

Gender	Predicted value (50th percentile)				Lower limit of normal (5th percentile)			
Female	LN(FVC)	LN(FEV_1)	FEV_1/FVC	LN($FEF_{25-75\%}$)	$FEF_{25-75\%}$/FVC	LN(FVC)	LN(FEV_1)	FEV_1/FVC	LN($FEF_{25-75\%}$)	$FEF_{25-75\%}$/FVC
Intercept	−10.741935	−9.967740	1.437685	−7.385469	5.041747	−10.325884	−8.934018	1.313149	−7.855190	3.919387
LN(Height)	2.261976	2.088950	−0.106215	1.594033	−0.785773	2.098703	1.768038	−0.100805	1.673427	−0.642607
LN(Age)	0.156836	0.150386		0.203576		0.230220	0.290733		0.056126	
Skin color	−0.041015	−0.048582			0.046472	−0.073692	−0.054695			0.027623
Male	LN(FVC)	LN(FEV_1)	FEV_1/FVC	LN($FEF_{25-75\%}$)	$FEF_{25-75\%}$/FVC	LN(FVC)	LN(FEV_1)	FEV_1/FVC	LN($FEF_{25-75\%}$)	$FEF_{25-75\%}$/FVC
Intercept	−11.358191	−10.434226	1.760961	−6.957857	6.185501	−9.327490	−8.960184	1.942780	−5.356269	4.579022
LN(Height)	2.419817	2.207609	−0.176748	1.527303	−1.044205	1.890179	1.820202	−0.231255	1.085145	−0.786610
LN(Age)	0.115477	0.114001		0.138649		0.268924	0.208981		0.211021	
Skin color	−0.028745	−0.031836			0.093297	−0.042377	−0.026383			0.036968

NL: natural logarithm. [a]Height in centimeters; age in years; skin color: white = 0, black/brown = 1.

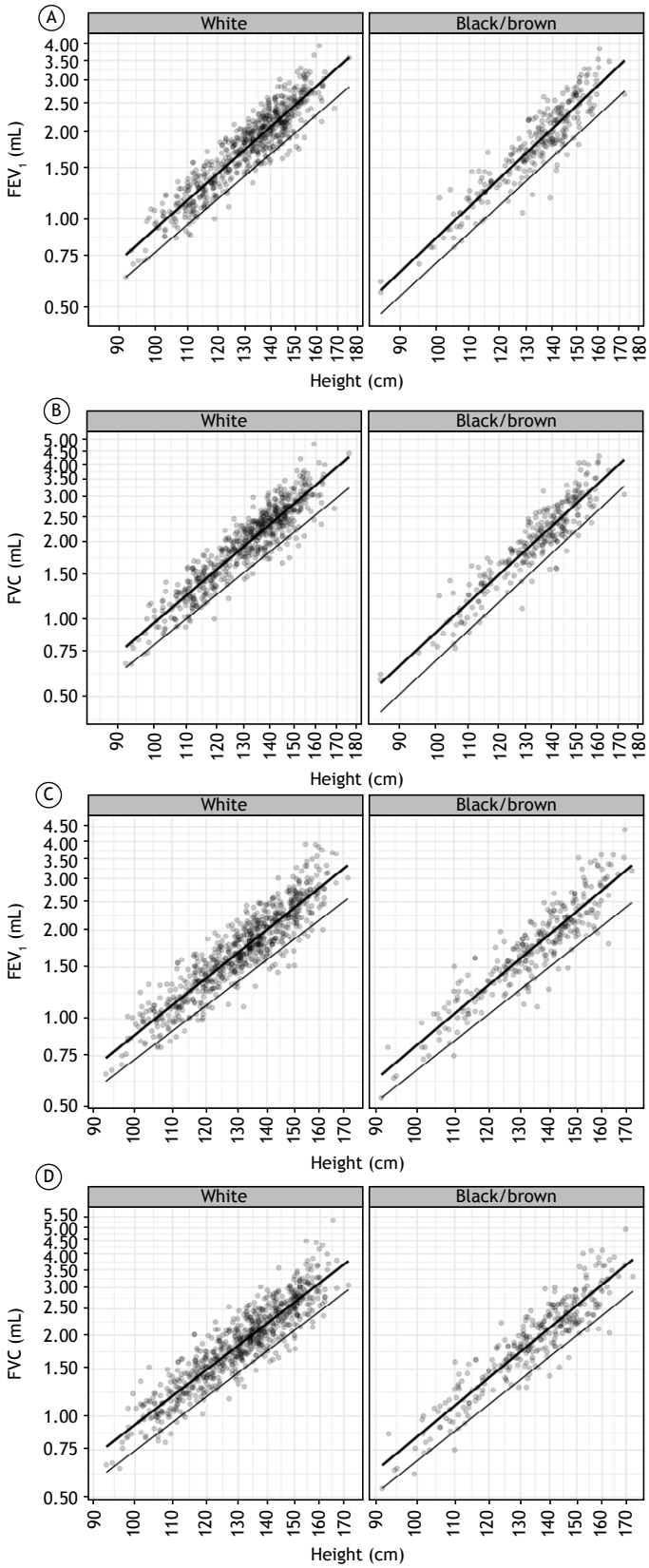


Figure 1. Lung function variables versus height in white children and in brown and black children (male: A and B, female: C and D), showing the 50th percentile (thick line) and the 5th percentile (thin line) for FEV_1 (A and C) and FVC (B and D).

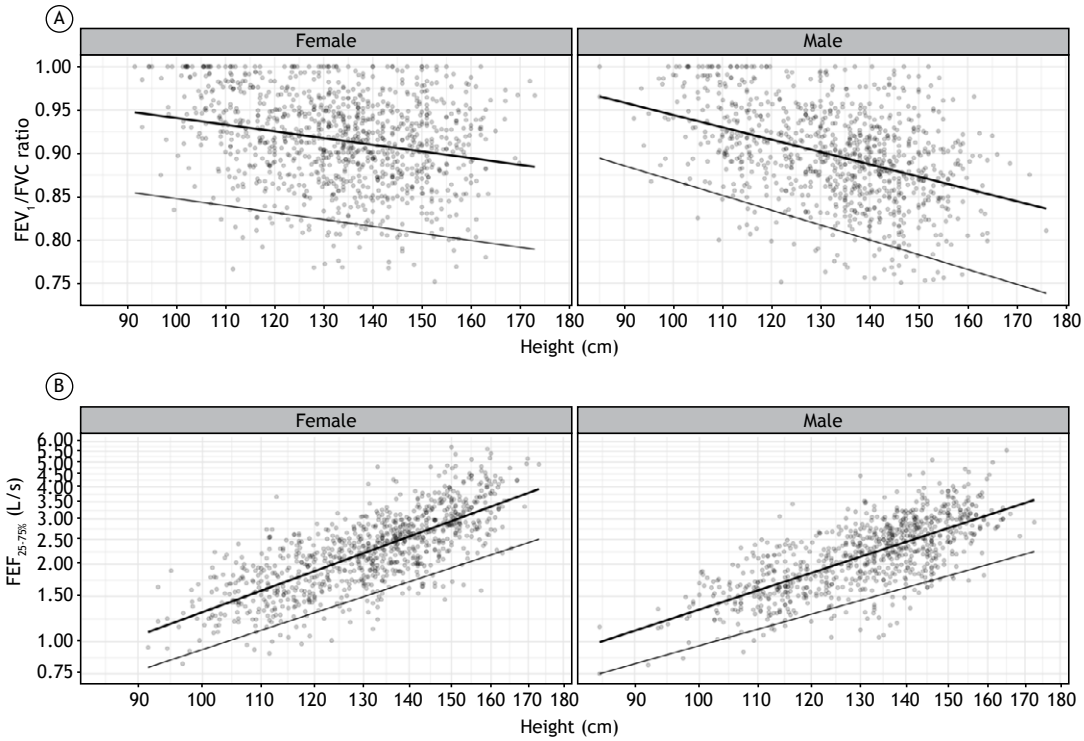


Figure 2. FEV_1/FVC ratio (A) and $FEF_{25-75\%}$ (B) versus height in white and black/brown male and female children, showing the 50th percentile (thick line) and the 5th percentile (thin line).

both). For black children, the differences between the observed FEV_1 values and those predicted by the SBPT equation[2] were smaller and not statistically significant. In our sample, the FEV_1/FVC ratio was approximately 0.04 points lower for boys and 0.02-0.03 points lower for girls when compared with the values predicted by the SBPT equation[2]. When applying the lower limits of normal of 0.83 and 0.81 to the FEV_1/FVC ratios for boys and girls, respectively, as proposed in the SBPT equation[2], 14.6% and 4.9% of the sample, respectively, were classified as "abnormal".

The international GLI equation[4] also underestimates the lung function of Brazilian children, the greatest differences being for black children, for whom the observed FEV_1 was 17.3% (262 mL) for boys and 14.9% (249 mL) for girls, higher than those predicted ($p < 0.001$ for both). Among black children, the mean FEV_1 Z-score was 1.32 for boys and 1.16 for girls. Among brown children, the FEV_1 Z-score was also quite high for boys and girls, with mean values of 0.75 and 0.60, respectively. Among white children, the mean FVC Z-score was 0.10 for boys and 0.16 for girls, compared with 1.13 and 0.61, respectively, among black children and 0.99 and 0.48, respectively, among brown children. The comparison of the FEV_1/FVC ratios found in our sample with those predicted by the GLI[4] also showed discrepancies ranging from 0.011 (not significant) to 0.017 ($p < 0.05$). The mean Z-scores in our sample were 0.32 and 0.33 for white girls and boys and 0.22 and 0.25 for black/brown girls and boys.

Table 4 shows the comparison between the lower limit of normal values proposed by the quantile equations generated in this study and those proposed by the GLI equations.[4] The differences in FVC and FEV_1 were small for white children and significantly larger for black/brown children. The lower limit of normal of the FEV_1/FVC ratio predicted by the GLI[4] was also significantly lower than that predicted by the equations proposed in this study. Those values can be found in the supplementary material (Figure S2).

DISCUSSION

In the present study, lung function data for 1,990 children in 16 Brazilian urban centers, from 21 different databases, were compiled to generate equations for predicted values and lower limits of normal. To our knowledge, this was the largest and most representative study on the lung function of children in Brazil, due to the size and geographic diversity of the sample. The data collected show that Brazilian children have significantly higher lung function values than those predicted by the equations currently used in Brazil,[2,4] emphasizing the clinical importance this study can have in the functional assessment of children in the country.

There are many possible explanations for the fact that we observed lung function values higher than those predicted by the SBPT equations.[2] First, the technological differences in the equipment used and the stricter acceptability criteria, in particular the exclusion criteria for cases of early termination and back-extrapolated

Table 3. Absolute and relative differences between the values obtained in the present study and the values predicted by the equations currently in use in Brazil.[a]

	GLI[4] (N = 1,990)			SBPT[21] (N = 1,624)		
Male	White	Black	Brown	White	Black	Brown
FEV_1 (mL)	55 (3.5%)*	262 (17.3%)*	159 (8.7%)*	101 (5.6%)*	43 (1.9%)	96 (4.8%)*
FVC (mL)	17 (1.3%)	257 (15.0%)*	147 (6.8%)*	205 (10.2%)*	132 (6.1%)*	192 (8.9%)*
FEV_1/FVC ratio	0.017*	0.011	0.012*	−0.042*	−0.043*	−0.038*
$FEF_{25-75\%}$ (mL/s)	114 (6.0%)*	419 (22.4%)*	287 (12.7%)*	17 (1.3%)	68 (2.5%)	82 (3.8%)
Female						
FEV_1 (mL)	67 (4.1%)*	249 (14.9%)*	124 (7.1%)*	156 (9.7%)*	59 (3.6%)	109 (5.8%)*
FVC (mL)	35 (2.2%)*	251 (13.3%)*	114 (5.8%)*	229 (12.5%)*	134 (6.9%)*	181 (9.1%)*
FEV_1/FVC ratio	0.013*	0.008*	0.007*	−0.019*	−0.030*	−0.022*
$FEF_{25-75\%}$ (mL/s)	131 (5.7%)*	313 (14.4%)*	192 (9.2%)*	295 (13.8%)*	165 (7.3%)*	185 (8.5%)*

GLI: Global Lung Initiative; and SBPT: *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Association). *p < 0.05. Mann-Whitney test for paired samples.

Table 4. Differences between the values predicted by the equations proposed in the present study and those predicted by the Global Lung Initiative[4] equations, for the lower limit of normal.

Lower limit of normal	Female		Male	
	White	Brown and black	White	Brown and black
FVC	0.06%	3.00%	0.21%	6.98%*
FEV_1	2.00%	7.20%*	3.34%	11.97%*
FEV_1/FVC ratio	0.028*	0.012*	0.044*	0.027*
$FEF_{25-75\%}$	9.84%*	22.34%*	10.20%*	21.51%*

*p < 0.05. Mann-Whitney test for unpaired samples.

volume, may have contributed to the higher FVC and FEV_1 values observed in the present study. In addition, the prevalence of overweight and obesity has increased considerably in the past 25 years. In children and adolescents, overweight and obesity are associated with an up to 7.5% increase in FVC and FEV_1, and that could also partially explain the differences between the studies.[10] Furthermore, secular changes in lung function may have contributed, in part, to the higher FVC, FEV_1, and $FEF_{25-75\%}$ values observed. Improvements in the general health status and, in particular, the nutritional status of the population included in this study favor changes in body proportions and final height, affecting the predicted lung function values.[11]

Regarding the differences in flows and volumes found in the comparison with the multiethnic equations proposed by the GLI,[4] we must point out that the differences for white children, although statistically significant, are small. However, the values predicted by the GLI[4] for black and brown children, who make up the majority of the Brazilian population, are very far from what was observed in our study sample. We believe this discrepancy is due to the large European genetic contribution in individuals in Brazil who self-report their skin color as black or brown.[12,13]

The quantile equations generated from this sample resulted in values significantly higher than those predicted by the GLI[4] for FVC and FEV_1, and this is particularly important for establishing the lower limit of normal. These findings are in line with the validation studies of the GLI equations[4] conducted in Brazil and in other countries, which also found significant differences between the values observed and those predicted by the GLI equations for adults and children.[14-19] These results, taken together, suggest that there are limitations to the application of international equations and that local reference values are more suitable for lung function assessment.

This study has limitations that merit further discussion. First, we evaluated a convenience sample comprising predominantly white children living in the southern and southeastern regions of Brazil. According to data from the Brazilian Institute of Geography and Statistics,[20] Brazil has a population of 206.1 million, of which 97.3 million (47.2%) self-report their skin color as brown; 90.2 million (43.8%) self-report their skin color as white; and 16.8 million (8.2%) self-report their skin color as black. Therefore, in a fully representative sample of the Brazilian population, white individuals should compose approximately half, the other half comprising black and brown individuals. The absence of individuals from the northern and central-west regions needs to be corrected in subsequent studies. Another limitation is the lack of socioeconomic data, in particular, on parental level of education and income, as well as on environmental factors, because these unquestionably influence lung development and may explain, in part, the differences observed in lung function among the white, black, and brown children in our sample.[21,22] It is also noteworthy that we employed conventional multiple linear regression, in which it is assumed that the variance is homogeneously distributed over the

height and age range. This problem was mitigated by the log transformation of the data and because a narrow age range was assessed.

In summary, this study provides reference equations for FVC, FEV_1, the FEV_1/FVC ratio, $FEF_{25-75\%}$, and the $FEF_{25-75\%}$/FVC ratio for white, brown, and black children 3-12 years of age in Brazil. These new equations differ significantly from those currently in use in Brazil,[2,4] which tend to underestimate FVC and FEV_1 values. We suggest that these equations be revised periodically, with updates that include advances in the lung assessment methodology, the evaluation of larger samples, and improvement of the mathematical model, as well as better characterization of the ancestry and socioeconomic status of the participants.

COLLABORATORS

Lung Function Working Group: Terezinha Martire, Nelson Augusto Rosario Filho, Frederico Orlando Friedrich, Jaksoel Cunha Silva, Verônica Franco Parreira, Cristian Roncada, Ana Luiza Muccillo Baisch, Maria Cristina Flores Soares, Paula Cristina Andrade Almeida, João Paulo Heinzmann-Filho, Murilo Carlos Amorim de Britto, Helen Zatti, Regina Terse Trindade Ramos, José Dirceu Ribeiro, Ana Alice Amaral Ibiapina Parente, Irmgard de Assis (in memoriam), Taisa Frescura Paim, Renato Tetelbom Stein, Paulo Augusto Moreira Camargos, Roberto Rodrigues Junior, Jussara Fittermann, and Carlos Alberto de Castro Pereira.

REFERENCES

1. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38. https://doi.org/10.1183/09031936.05.00034805
2. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes para Testes de Função Pulmonar J Bras Pneumol. 2002;28(Suppl 3):S1-S82.
3. Stanojevic S, Wade A, Cole TJ, Lum S, Custovic A, Silverman M, et al. Spirometry centile charts for young Caucasian children: the Asthma UK Collaborative Initiative. Am J Respir Crit Care Med. 2009;180(6):547-552. https://doi.org/10.1164/rccm.200903-0323OC
4. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-1343. https://doi.org/10.1183/09031936.00080312
5. Burity EF, Pereira CA, Rizzo JA, Brito MC, Sarinho ES. Reference values for spirometry in preschool children. J Pediatr (Rio J). 2013;89(4):374-380. https://doi.org/10.1016/j.jped.2013.01.002
6. França DC, Camargos PA, Jones MH, Martins JA, Vieira BS, Colosimo EA, et al. Prediction equations for spirometry in four- to six-year-old children. J Pediatr (Rio J). 2016;92(4):400-408. https://doi.org/10.1016/j.jped.2015.10.005
7. Esteves AR, Solé D, Ferraz MB. Adaptation and validity of the ATS-DLD-78-C questionnaire for asthma diagnosis in children under 13 years of age. Braz Ped News. 1999;1:3-5.
8. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HGM, Aurora P, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med. 2007;175(12):1304-1345. https://doi.org/10.1164/rccm.200605-642ST
9. The R Foundation [homepage on the Internet]. Vienna, Austria: R Foundation for Statistical Computing; [cited 2019 Apr 17] The R Project for Statistical Computing. Available from: http://www.R-project.org/
10. Jones MH, Roncada C, Fernandes MTC, Heinzmann-Filho JP, Sarria Icaza EE, Mattiello R, et al. Asthma and Obesity in Children Are Independently Associated with Airway Dysanapsis. Front Pediatr. 2017;5:270. https://doi.org/10.3389/fped.2017.00270
11. Quanjer PH, Kubota M, Kobayashi H, Omori H, Tatsumi K, Kanazawa M, et al. Secular changes in relative leg length confound height-based spirometric reference values. Chest. 2015;147(3):792-797. https://doi.org/10.1378/chest.14-1365
12. Durso DF, Bydlowski SP, Hutz MH, Suarez-Kurtz G, Magalhães TR, Pena SD. Association of genetic variants with self-assessed color categories in Brazilians. PLoS One. 2014;9(1):e83926. https://doi.org/10.1371/journal.pone.0083926
13. Moura RR, Coelho AV, Balbino Vde Q, Crovella S, Brandão LA. Meta-analysis of Brazilian genetic admixture and comparison with other Latin America countries. Am J Hum Biol. 2015;27(5):674-680. https://doi.org/10.1002/ajhb.22714
14. Backman H, Lindberg A, Sovijärvi A, Larsson K, Lundbäck B, Rönmark E. Evaluation of the global lung function initiative 2012 reference values for spirometry in a Swedish population sample. BMC Pulm Med. 2015;15:26. https://doi.org/10.1186/s12890-015-0022-2
15. Pereira CA, Duarte AA, Gimenez A, Soares MR. Comparison between reference values for FVC, FEV1, and FEV1/FVC ratio in White adults in Brazil and those suggested by the Global Lung Function Initiative 2012. J Bras Pneumol. 2014;40(4):397-402. https://doi.org/10.1590/S1806-37132014000400007
16. Ben Saad H, El Attar MN, Hadj Mabrouk K, Ben Abdelaziz A, Abdelghani A, Bousarssar M, et al. The recent multi-ethnic global lung initiative 2012 (GLI2012) reference values don't reflect contemporary adult's North African spirometry. Respir Med. 2013;107(12):2000-2008. https://doi.org/10.1016/j.rmed.2013.10.015
17. Ratomaharo J, Linares Perdomo O, Collingridge DS, Andriamihaja R, Hegewald M, Jensen RL, et al. Spirometric reference values for Malagasy adults aged 18-73 years. Eur Respir J. 2015;45(4):1046-1054. https://doi.org/10.1183/09031936.00114914
18. Kainu A, Timonen KL, Toikka J, Qaiser B, Pitkäniemi J, Kotaniemi JT, et al. Reference values of spirometry for Finnish adults. Clin Physiol Funct Imaging. 2016;36(5):346-358. https://doi.org/10.1111/cpf.12237
19. Fasola S, La Grutta S, Cibella F, Cilluffo G, Viegi G. Global Lung Function Initiative 2012 reference values for spirometry in South Italian children. Respir Med. 2017;131:11-17. https://doi.org/10.1016/j.rmed.2017.07.061
20. Instituto Brasileiro de Geografia e Estatística (IBGE). Coordenação de Trabalho e Rendimento [homepage on the Internet]. Rio de Janeiro: IBGE; [cited 2018 Sep 27]. Pesquisa nacional por amostra de domicílios 2016. Available from: http://www.ibge.gov.br
21. Braun L, Wolfgang M, Dickersin K. Defining race/ethnicity and explaining difference in research studies on lung function. Eur Respir J. 2013;41(6):1362-1370. https://doi.org/10.1183/09031936.00091612
22. Martínez-Briseño D, Fernández-Plata R, Gochicoa-Rangel L, Torres-Bouscoulet L, Rojas-Martínez R, Mendoza-Alvarado L, et al. Socioeconomic Status and Longitudinal Lung Function of Healthy Mexican Children. PLoS One. 2015;10(9):e0136935. https://doi.org/10.1371/journal.pone.0136935

J Bras Pneumol. 2020;46(3):e20180376
http://dx.doi.org/10.36416/1806-3756/e20180376

ORIGINAL ARTICLE

Azithromycin administered for acute bronchiolitis may have a protective effect on subsequent wheezing

Fernanda Luisi[1], Clarissa Aires Roza[2], Victória d'Azevedo Silveira[1], Camila Correia Machado[1], Katiana Murieli da Rosa[1], Paulo Márcio Pitrez[1], Marcus Herbert Jones[1], Renato Tetelbom Stein[1], Lidiane Alves de Azeredo Leitão[1], Talitha Comaru[1], Magáli Mocellin[1], Leonardo Araújo Pinto[1]

1. Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.
2. Universidade de Santa Cruz do Sul, Santa Cruz do Sul (RS) Brasil.

Submitted: 06 December 2018.
Accepted: 13 April 2019.

Study carried out in the Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.

ABSTRACT

Objective: A significant proportion of the infants developed recurrent wheezing after an acute bronchiolitis (AB) event. Recent studies have demonstrated protection for recurrent wheeze and lower respiratory morbidity in infants treated with azithromycin during an acute respiratory wheezing. The aim of the present study was to test the hypothesis that administration of azithromycin during an AB event reduces subsequent wheezing and hospital re-admissions. **Methods:** This is a secondary analysis of a randomized, double-blinded, placebo-controlled trial, including unpublished data of wheezing and hospitalizations during the initial 6 months following admission for acute viral bronchiolitis. The study was performed in a tertiary University hospital. Infants (<12 months of age) hospitalized with AB were randomized to receive either azithromycin or placebo, administered orally, for 7 days. Families were contacted by telephone at 3 and 6 months after the initial acute event and answered to a standardized questionnaire in order to identify recurrent wheezing and hospital readmissions. **Results:** One hundred and four patients were included (Azithromycin group, n= 50; placebo group, n=54). Considering the total of patients contacted 3 months after hospitalization (n=70), the recurrence rate of wheezing in the azithromycin group was significantly lower than in the placebo group (RR = 0.48; CI = 0.24-0.98; p = 0.038). **Conclusion:** Azithromycin significantly reduces the risk of subsequent wheezing between 0 and 3 months after hospital admission due to acute bronchiolitis irrespective of the presence of respiratory syncytial virus.

TRIAL REGISTRATION: Brazilian Clinical Trial Registry: RBR-257ZBC

Keywords: Bronchiolitis; Macrolides; Recurrent wheezing; Hospitalization.

INTRODUCTION

Acute viral bronchiolitis (AB) is the most common lower respiratory tract illness (LRTI) among infants. A previous study has shown that AB is significantly associated with subsequent development of recurrent wheezing and asthma in childhood.[1] Macrolides have a well-established antibacterial effect,[2] covering several agents, including *Mycoplasma pneumoniae* and *Bordetella pertussis*. In the past decade, additional immunomodulatory and antiviral properties of macrolides have also been described.[3-5]

Studies showed that some macrolides had a beneficial effect in the treatment of lung diseases associated with recurrent or chronic symptoms, such as cystic fibrosis (CF) and non-CF bronchiectasis.[4-6] Macrolides seem to inhibit interleukin (IL)-8 production, reducing overall neutrophilic inflammation.[7] Recurrent wheezing in young infants is characterized by a neutrophilic airway response.[8,9] Only a few trials have used the immunomodulatory rationale to test the efficacy of macrolides in recurrent wheezing. The most well-designed trials have shown negative results for acute bronchiolitis.[10,11] Instead, recent previous studies have demonstrated a prolonged protection for subsequent recurrent wheeze and lower respiratory morbidity in infants treated with azithromycin during an acute Respiratory Syncytial Virus (RSV) bronchiolitis, through the inhibition of the IL-8 inflammatory pathway.[12,13] In the present study, we have tested the hypothesis that administration of azithromycin during hospitalization for AB reduces the risk of subsequent wheezing episodes and hospital readmission, independent of the viral etiology.

METHODS

This was a randomized, double-blinded, placebo-controlled trial. Infants with a clinical diagnosis of AB were recruited from the pediatric emergency department or hospital wards of two large, tertiary hospitals during 2 years.

Correspondence to:
Leonardo Araújo Pinto. Pontifícia Universidade Católica do Rio Grande do Sul, Av. Ipiranga, 6690, Núcleo de Pediatria, 5° andar, CEP 90610-000, Porto Alegre, RS, Brasil.
Tel.: 55 51 3320-3000 (Ramal 2737). E-mail: leonardo.pinto@pucrs.br
Financial support: Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul.
TRIAL REGISTRATION: Brazilian Clinical Trial Registry: RBR-257ZBC.

Clinical data were recorded and nasopharyngeal samples for viral identification were collected at the time of enrollment. In the total of 184 initial study patients in the two centers,[10] 104 were exclusively from one center were followed by phone for a secondary analysis. After hospitalization, we tried to contact all 104 families by phone calls during the period between discharge and up to 6 months after discharge. A diagnosis of AB was confirmed if children were: (1) <12 months and admitted with prodromal viral symptoms in a first episode of wheezing or crackles with tachypnea; and (2) recruited within 48 hours of hospitalization, with a maximum of 72 hours of a history of lower respiratory tract clinical signs (wheeze and/or respiratory distress).

Main exclusion criteria were: (1) any restrictions to the use of oral macrolides; (2) prescription of macrolide therapy by the attending physician due to clinical and radiologic features consistent with a diagnosis of *Chlamydia sp.* or *Bordetella pertussis* respiratory infection; (3) a previous diagnosis of any chronic cardiopulmonary disorder, congenital/acquired immunodeficiency, or neuromuscular disease; and (4) a history of prematurity or other neonatal complications.

Infants were randomized (simple/unrestricted randomization) to receive either a daily oral dose of Azithromycin (10 mg/kg/day) or an equivalent volume of placebo for 7 days. The mechanism used to implement the random allocation sequence was a list generated using numbers 1 and 2 random selected from a sealed opaque envelope, previously to the enrollment of the patients by the first author. The azithromycin group was represented as 1 and the control group as 2. The placebo formula was produced with similar taste and smell of azithromycin. Identical medicine bottle (identified only as 1 or 2) were used. The patients were enrolled by the first author or collaborators and assigned to interventions according to the randomization list. Participants, care providers, and authors who assessed outcomes were blinded to the intervention groups. Medication was administered within 72 hours of the initial clinical symptoms and a blinded study team member supervised the interventions.

All infants were managed according to protocols routinely used by the pediatric staff in the hospital. Infants enrolled in the study could receive additional therapies (other than macrolides) prescribed by the attending pediatricians. Assessment of clinical data included length of stay in the hospital, duration of supplemental oxygen required, and identification of respiratory viruses, described in a previous publication.[10] In addition, secondary data from the initial study (but only one center) were registered in a follow-up protocol during 6 months after the AB episode in order to identify recurrent wheezing and hospital readmissions. For definition of subsequent recurrent wheezing, families were successfully contacted by telephone at 3 and 6 months after the initial acute event and answered to a standardized questionnaire. The question used was: "Did your child have wheezing again after hospital discharge?"

Statistical analysis and ethics

The outcomes were compared between groups by chi-square, Mann-Whitney tests (this latter when variables failed for normality using Kolmogorov Smirnov). In addition, relative risk (RR) with CI95% (Confidence Interval) was calculated. To detect a reduction in subsequent wheezing approximately 50% (.50 vs .22), based on data from a previous study,[12] allowing for a 2-sided 5% significance level and a power of 80%, a sample size of 45 patients per group would be required.[14] The protocol has been approved by the Human Research Ethics Committees. The parents or caregivers of all the infants included in the study signed an informed consent term. The study was registered in the Brazilian Clinical Trials Registry (Nº RBR-257ZBC), which is a joint project of the Brazilian Ministry of Health and the Pan-American Health Organization,[15] and recognized by the World Health Organization Trial Registration Data Set.

RESULTS

One hundred and four infants fulfilled all eligibility criteria (one center: N=104) and have been included in the trial that evaluated the efficacy of Azithromycin for acute bronchiolitis, as published previously.[10] In the total of patients successfully contacted in the follow-up 3 months after hospitalization (n=70/104), 52.85% (37 of 70) were in the azithromycin group. At 6 months of follow-up we were able to contact 63 subjects (Figure 1). Baseline characteristics of the patients are shown in Table 1.

Positive samples for RSV were found in 65 of the 104 (62%) of randomized patients Other viruses identified were Parainfluenza (N=10), Influenza (N=15) and Adenovirus (N=3). In the patients included in the secondary follow-up analysis, RSV was identified in 38/70 (54.3%) of patients. All studied samples

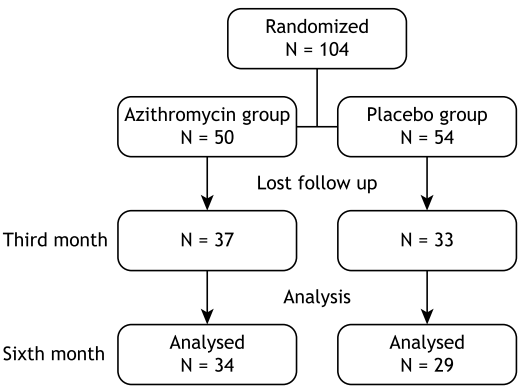


Figure 1. Flowchart with randomization and follow-up data. N: sample size.

Table 1. Demographic and clinical characteristics of analyzed patients to follow up (n=70).

	Azithromycin Group n = 37	Placebo Group n = 33	*P*
Age at enrollment, months, mean (SD)	3.26 (2.49)	3.14 (2.29)	0.843
Weight at enrollment, kg, mean (SD)	5.72 (1.76)	5.85 (1.50)	0.749
Gender, boys, n (%)	22 (59.5)	21 (63.6)	0.720
Use of ß2 agonist, n (%)	9 (24.3)	11 (33.3)	0.405
Hypoxemia at admission, n (%)	37 (100)	33 (100)	1.000
Positive for any virus	20 (54.1)	22 (66.7)	0.288
Positive for RSV, n (%)	17 (45.9)	21 (63.6)	0.182
Duration of hospitalization, days, mean (SD)	5.32 (2.63)	5.85 (3.30)	0.464

SD: Standard Deviation; RSV: respiratory syncicial virus; n: sample size; p-value: significance level (probability of obtaining test results as extreme as the results observed).

Table 2. Risk of recurrent wheezing and hospital readmission after acute bronchiolitis.

	Azithromycin Group - Placebo Group (%)	RR (CI)	P- value
3st month (wheezing)	**19.1-39.5**	**0.48 (0.24-0.98)**	**0.038**
3st month (readmission)	8.5-10.5	0.80 (0.21-3.02)	0.752
6st month (wheezing)	25.6-27.3	0.93 (0.44-1.99)	0.868
6st month (readmission)	9.3-3.0	3.07 (0.36-26.2)	1.274

RR: Relative Risk; CI: Confidence Interval; p-value: significance level (probability of obtaining test results as extreme as the results observed).

were evaluated by direct immunofluorescence, which does not allow the detection of rhinovirus or metapneumovirus.

Recurrent wheezing risk was significantly reduced in infants at 3 months after AB episode (RR=0.48, CI=0.24 – 0.98, p= 0.038). Hospital readmission was not significantly different between the groups.

According to our results in the third month of follow-up, the recurrence rate of wheezing in the azithromycin group was 19.1%, whereas in the placebo group it was 39.5%, showing a significant difference (p =0.038). Analyzing the data at sixth month of follow-up, there was no significant difference between the two groups (p = 0.868). In the group that used azithromycin 25.6% had recurrence of episodes of wheezing while in the placebo group the index was 27.3% (Table 2).

DISCUSSION

A relevant proportion (30-40%) of infants hospitalized for acute bronchiolitis in the first year of life present recurrent wheezing episodes after the first hospital admission.[16] In the present study, the treatment with Azithromycin at the time of an admission for acute bronchiolitis showed relevant protection for recurrence of wheezing 3 months after hospitalization for AB (RR = 0.48 (CI = 0.24-0.98)). The same effect was not observed 6 months after hospital discharge.

Data from previous studies[12,13,17,18] support the hypothesis that recurrent wheezing, or even childhood asthma, could be prevented by interventions to prevent acute severe viral bronchiolitis. This concept is supported by studies demonstrating reductions in recurrent wheezing among preterm infants who received Palivizumab.[19,20] Although Palivizumab can be an effective intervention for the prevention of severe RSV bronchiolitis and subsequent wheezing its use has some limitations. Palivizumab is recommended for a high-risk group of preterm infants, especially because it is quite expensive and requires monthly intra-muscular injections during the virus season.[19] Therefore, there is a need to identify other interventions that could be used in children with bronchiolitis to prevent the common and costly event of post-bronchiolitis wheezing. Conventional asthma controller medications have shown limited efficacy for the prevention of post-RSV recurrent wheezing.[20-23] Seeing that neutrophils are predominant inflammatory cells in the airways of AB,[8,9] a medication with anti-neutrophilic properties would have, theoretically, the mechanistic rationale to serve as a potential intervention for the prevention of post-RSV recurrent wheezing.

To the best of our knowledge, there are few previous trials using macrolides as a treatment for prevention of post-bronchiolitis wheezing.[10,13,24] The treatment with clarithromycin among children hospitalized for RSV bronchiolitis was initially reported to be associated with shorter length of stay and fewer readmissions for wheezing during the period of follow-up. Subsequent communications refuted the efficacy of macrolides at the time of acute bronchiolitis, but it did not investigate its impact on recurrent wheezing.[10] A recent clinical trial testing preschool children showed that early use of Azithromycin for 5 days, when children had signs and symptoms of lower respiratory tract illness, reduced the risk of a LRTI to progress into severe disease.[13]

A recent meta-analysis has suggested that macrolide therapy may be safe and effective in achieving better outcomes in childhood reactive airway diseases.

Treatment with Azithromycin may decrease the need for short-acting β2-agonists among preschool children with recurrent wheezing.[25]

The unique pharmacokinetic properties of Azithromycin might explain the differential effect observed in the risk of post-bronchiolitis wheezing. In general, Azithromycin accumulates in lung tissue, resulting in alveolar macrophages and bronchoalveolar lavage fluid concentrations higher than in serum concentrations.[3,26,27] Moreover, the intracellular accumulation property of Azithromycin results in a long half-life in the airway because it persists in measurable quantities in human airway macrophages for three weeks after the last dose of an 8-day course.[26] However, the correct doses and duration of macrolides needed to provide long-term anti-inflammatory effects are not yet clear.

Co-detection of upper airway virus and bacteria in children was associated with an increased risk of experiencing asthma exacerbations.[28] Therefore, the beneficial effects of Azithromycin detected in our study could, instead of being purely anti-neutrophilic, it is also mediated by antimicrobial properties. Interestingly, results from experimental studies using human respiratory cells showed that Azithromycin treatment inhibited rhinovirus replication,[12,29] and that Clarithromycin reduced RSV and influenza titers.[24]

In the present study, we included otherwise healthy infants admitted by AB, which is the first cause of hospitalization in infants. However, the findings at 6 months follow-up limits our conclusions to more long-term efficacy. Future trials with longer treatment and follow-up should be designed to determine the long-term effects of macrolides on wheezing and asthma. Our research question was investigated among a group of patients experiencing the most severe disease since all infants required hospitalization and these children generally experience the greatest morbidity in terms of subsequent wheezing and asthma. Relative high levels of response of participants during follow-up further strengthen our findings. Finally, we evaluated the potential effects of Azithromycin for an important and highly prevalent clinical endpoint (recurrent wheezing).

The relatively small sample size during the follow-up may be considered a limitation to our findings. Although the overall trend toward improved clinical outcomes is encouraging that we cannot firmly conclude that Azithromycin intervention during AB definitely reduces the occurrence of recurrent wheezing. Another recent publication showed similar results to our study. In this clinical trial, 40 infants with the first episode of RSV wheezing received either Azithromycin or placebo for 14 days, with Azithromycin reducing IL-8 levels in nasal lavage, and significantly reducing the time for the third episode of wheezing.[12]

In summary, the results of our trial showed that treatment with Azithromycin during AB hospitalization resulted in reduction of recurrent wheezing episodes, but this effect is not sustained at six months after AB hospitalization. Considering the important clinical impact of our findings and the risk of increased widely use of macrolides in this group of patients, further studies should try to better define which infants could be better responders to macrolides and whether severity is also a factor associated with efficacy of treatment.

REFERENCES

1. Zorc JJ, Hall CB. Bronchiolitis: recent evidence on diagnosis and management. Pediatrics 2010;125(2):342-9. http://dx.doi.org/10.1542/peds.2009-2092. PMid:20100768.
2. Lakoš AK, Pangercic A, Gasparic M, Kukuruzovic MM, Kovacic D, Barsic B. Safety and effectiveness of azithromycin in the treatment of respiratory infections in children. Curr Med Res Opin. 2012;28(1):155-62. http://dx.doi.org/10.1185/03007995.2011.639355. PMid:22070514.
3. Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. Clin Microbiol Rev. 2010;23(3):590-615. http://dx.doi.org/10.1128/CMR.00078-09. PMid:20610825.
4. Friedlander AL, Albert RK. Chronic macrolide therapy in inflammatory airways diseases. Chest. 2010;138(5):1202-12. http://dx.doi.org/10.1378/chest.10-0196. PMid:21051396.
5. Pinto LA, Camozzato C, Avozani M, Machado DC, Jones MH, Stein RT, et al. Effect of clarithromycin on the cell profile of bronchoalveolar lavage fluid in mice with neutrophil-predominant lung disease. Rev Hosp Clin Fac Med Sao Paulo. 2004;59(3):99-103. http://dx.doi.org/10.1590/S0041-87812004000300002. PMid:15286828.
6. Johnston SL. Macrolide antibiotics and asthma treatment. J Allergy Clin Immunol. 2006;117(6):1233-6. http://dx.doi.org/10.1016/j.jaci.2006.03.035. PMid:16750980.
7. Desaki M, Takizawa H, Ohtoshi T, Kasama T, Kobayashi K, Sunazuka T, et al. Erythromycin suppresses nuclear factor-kappaB and activator protein-1 activation in human bronchial epithelial cells. Biochem Biophys Res Commun. 2000;267(1):124-8. http://dx.doi.org/10.1006/bbrc.1999.1917. PMid:10623585.
8. Everard ML, Swarbrick A, Wrightham M, McIntyre J, Dunkley C, James PD, et al. Analysis of cells obtained by bronchial lavage of infants with respiratory syncytial virus infection. Arch Dis Child. 1994;71(5):428-32. http://dx.doi.org/10.1136/adc.71.5.428. PMid:7826113.
9. Pitrez PM, Pinto LA, Machado DC, Tsukazan MT, Jones MH, Stein RT. Upper airway cellular pattern in infants with acute bronchiolitis: neutrophils or eosinophils? J Pediatr. 2003;79(5):443-8. http://dx.doi.org/10.2223/JPED.1078. PMid:14557845.
10. Pinto LA, Pitrez PM, Luisi F, de Mello PP, Gerhardt M, Ferlini R, et al. Azithromycin therapy in hospitalized infants with acute bronchiolitis is not associated with better clinical outcomes: a randomized, double-blinded, and placebo-controlled clinical trial. J Pediatr. 2012;161(6):1104-8. http://dx.doi.org/10.1016/j.jpeds.2012.05.053. PMid:22748516.
11. McCallum GB, Morris PS, Grimwood K, Maclennan C, White AV, Chatfield MD, et al. Three-weekly doses of azithromycin for indigenous infants hospitalized with bronchiolitis: a multicentre, randomized, placebo-controlled trial. Front Pediatr. 2015;3:32. http://dx.doi.org/10.3389/fped.2015.00032. PMid:25954737.
12. Beigelman A, Isaacson-Schmid M, Sajol G, Baty J, Rodriguez OM, Leege E, et al. Randomized trial to evaluate azithromycin's effects on serum and upper airway IL-8 levels and recurrent wheezing in infants with respiratory syncytial virus bronchiolitis. J Allergy Clin Immunol. 2015;135(5):1171-8.e1. http://dx.doi.org/10.1016/j.jaci.2014.10.001. PMid:25458910.
13. Bacharier LB, Guilbert TW, Mauger DT, Boehmer S, Beigelman A, Fitzpatrick AM, et al. Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses a randomized clinical trial. JAMA. 2015;314(19):2034-44. http://dx.doi.org/10.1001/jama.2015.13896. PMid:26575060.
14. UBC: University of British Columbia [homepage on the Internet]. Vancouver: University of British Columbia; 2019 [cited 2019 Jan 1]. Available from: https://www.stat.ubc.ca/~rollin/stats/ssize/

15. ReBEC: Registro Brasileiro de Ensaios Clínicos [homepage on the Internet]. local: editora; 2019 [cited 2019 Jan 1]. Available from: http://www.ensaiosclinicos.gov.br/
16. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009;360(6):588-98. http://dx.doi.org/10.1056/NEJMoa0804877. PMid:19196675.
17. Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Pedersen TM, Vinding RK, et al. Azithromycin for episodes with asthma-like symptoms in young children aged 1-3 years: a randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2016;4(1):19-26. http://dx.doi.org/10.1016/S2213-2600(15)00500-7. PMid:26704020.
18. Mandhane PJ, Paredes Zambrano de Silbernagel P, Aung YN, Williamson J, Lee BE, Spier S, et al. Treatment of preschool children presenting to the emergency department with wheeze with azithromycin: a placebo-controlled randomized trial. PLoS One. 2017;12(8):e0182411. http://dx.doi.org/10.1371/journal.pone.0182411. PMid:28771627.
19. Yoshihara S, Kusuda S, Mochizuki H, Okada K, Nishima S, Simões EA. Effect of palivizumab prophylaxis on subsequent recurrent wheezing in preterm infants. Pediatrics 2013;132(5):811-8. http://dx.doi.org/10.1542/peds.2013-0982. PMid:24127479.
20. Simões EA, Groothuis JR, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick LM, et al. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. J Pediatr. 2007;151(1):34-42. http://dx.doi.org/10.1016/j.jpeds.2007.02.032. PMid:17586188.
21. Fox GF, Everard ML, Marsh MJ, Milner AD. Randomised controlled trial of budesonide for the prevention of post-bronchiolitis wheezing. Arch Dis Child. 1999;80(4):343-7. http://dx.doi.org/10.1136/adc.80.4.343. PMid:10086941.
22. Clavenna A, Sequi M, Cartabia M, Fortinguerra F, Borghi M, Bonati M. Effectiveness of nebulized beclomethasone in preventing viral wheezing: an RCT. Pediatrics 2014;133(3):e505-12. http://dx.doi.org/10.1542/peds.2013-2404. PMid:24534400.
23. Brodlie M, Gupta A, Rodriguez-Martinez CE, Castro-Rodriguez JA, Ducharme FM, McKean MC. Leukotriene receptor antagonists as maintenance and intermittent therapy for episodic viral wheeze in children. Cochrane Database Syst Rev. 2015;(10):CD008202. http://dx.doi.org/10.1002/14651858.CD008202.pub2. PMid:26482324.
24. Tahan F, Ozcan A, Koc N. Clarithromycin in the treatment of RSV bronchiolitis: a double-blind, randomised, placebo-controlled trial. Eur Respir J. 2007;29(1):91-7. http://dx.doi.org/10.1183/09031936.00029206. PMid:17050564.
25. Lei W-T, Lin HH, Tsai M-C, Hung H-H, Cheng Y-J, Liu S-J, et al. The effects of macrolides in children with reactive airway disease: a systematic review and metaanalysis of randomized controlled trials. Drug Des Devel Ther. 2018;12:3825-45. http://dx.doi.org/10.2147/DDDT.S183527. PMid:30510399.
26. Matzneller P, Krasniqi S, Kinzig M, Sörgel F, Hüttner S, Lackner E, et al. Blood, Tissue, and Intracellular Concentrations of Azithromycin during and after End of Therapy. Antimicrob Agents Chemother. 2013;57(4):1736-42. http://dx.doi.org/10.1128/AAC.02011-12. PMid:23357769.
27. Beigelman A, Mikols CL, Gunsten SP, Cannon CL, Brody SL, Walter MJ. Azithromycin attenuates airway inflammation in a mouse model of viral bronchiolitis. Respir Res. 2010;11(1):90. http://dx.doi.org/10.1186/1465-9921-11-90. PMid:20591166.
28. Kloepfer KM, Lee WM, Pappas TE, Kang TG, Vrtis RF, Evans MD, et al. Detection of Pathogenic Bacteria During Rhinovirus Infection is Associated with Increased Respiratory Symptoms and asthma Exacerbations. J Allergy Clin Immunol. 2014;133(5):1301-7. http://dx.doi.org/10.1016/j.jaci.2014.02.030. PMid:24698319.
29. Gielen V, Johnston LS, Edwards MR. Azithromycin induces anti-viral responses in bronchial epithelial cells. Eur Respir J. 2010;36(3):646-54. http://dx.doi.org/10.1183/09031936.00095809. PMid:20150207.

J Bras Pneumol. 2020;46(3):e20190021
https://dx.doi.org/10.36416/1806-3756/e20190021

ORIGINAL ARTICLE

Do impulse oscillometry parameters differ between children and adolescents with symptoms of rhinitis and those without?

Juliana Cardoso[1], Bianca Kons dos Santos[1], Luana Vincensi Dorigo[1], Renata Maba Gonçalves Wamosy[1], Bianca Dana Horongozo Itaborahy[1], Camila Isabel Santos Schivinski[1]

1. Departamento de Fisioterapia, Universidade do Estado de Santa Catarina –UDESC – Florianópolis (SC) Brasil.

Submitted: 24 January 2019.
Accepted: 20 July 2019.

Study carried out at the Universidade do Estado de Santa Catarina – UDESC – Florianópolis (SC) Brasil.

ABSTRACT

Objective: To compare impulse oscillometry parameters between healthy children and adolescents with symptoms of rhinitis and those without. **Methods:** This was a cross-sectional analytical study of healthy individuals 7-14 years of age. Health status was determined through the use of questionnaires. We performed anthropometric measurements, impulse oscillometry, and spirometry. **Results:** The sample comprised 62 students, with a mean age of 9.58 ± 2.08 years and a mean body mass index (BMI) of 17.96 ± 3.10 kg/m^2. The students were divided into two **groups:** those with symptoms of rhinitis (n = 29) and those without such symptoms (n = 33). The oscillometry results and anthropometric parameters were normal in both groups and did not differ significantly between the two. The variables age, height, and body mass, respectively, correlated negatively and moderately with most of the following **parameters:** total airway resistance (r = −0.529, r = −0.548, and r = −0.433); central airway resistance (r = −0.441, r = −0.468, and r = −0.439); respiratory impedance (r = −0.549, r = −0.567, and r = −0.455); reactance at 5 Hz (r = 0.506, r = −0.525, and r = −0.414); reactance area (r = −0.459, r = −0.471, and r = −0.358); and resonance frequency (r = −0.353, r = −0.371, and r = −0.293). We found that BMI did not correlate significantly with any of the parameters evaluated. The same was true when we analyzed each group in isolation. **Conclusions:** In our sample, impulse oscillometry parameters did not differ between the students who had symptoms of rhinitis and those who did not.

Keywords: Oscillometry; Anthropometry; Rhinitis; Child; Adolescent.

INTRODUCTION

There have been numerous studies aimed at developing instruments, methods, and techniques that are specific and effective for the assessment of pulmonary function and respiratory mechanics in children and adolescents with respiratory diseases,[1-3] as well as in healthy individuals. Considered complementary to spirometry, impulse oscillometry (IOS) has been applied in research and in clinical practice because it is a simple, rapid technique that requires little patient collaboration and allows investigation of the involvement of specific lung areas.[4]

Although IOS has increasingly been recommended for the clinical follow-up of some diseases,[1-3,5] studies of IOS in healthy populations are scarce, which complicates comparisons and the establishment of normal ranges.[1] Such an investigation under normal health conditions makes it possible to understand the changes resulting from the presence of respiratory disease, as well as its progression.

Studies have shown the relationship of anthropometric variables with spirometric and IOS parameters,[6,7] reporting that, with increasing age and height, healthy individuals tend to have decreased airway resistance due to the increasing size of the chest and airways In obese individuals, as well as in children with cystic fibrosis[2] and individuals with asthma,[3] there is an increase in IOS parameter values, which are representative of airway obstruction.[1,5]

In common situations, often associated with respiratory symptoms, such as those of rhinitis, investigations are still scarce. Rhinitis is a condition that is commonly related to asthma, which is explained by the one-airway theory, according to which there are similarities in the inflammatory processes in the nasal and bronchial mucosas.[8,9]

Rhinitis is induced by exposure to allergens and is mediated by IgE, being clinically characterized by chronic and recurrent symptoms, including inflammation of the mucous membranes of the nose, nasal congestion and obstruction, coryza with colorless, transparent discharge, pruritus, sneezing, decreased olfactory function, and mouth breathing.[10] The presentation of rhinitis is known to depend on the interaction between genetics and the environment Therefore, the diagnosis is based on history taking, physical examination, and the results of ancillary tests. Although epidemiological data on rhinitis in Brazil are limited, rhinitis is believed to affect approximately 25-35% of individuals, mainly children and adolescents.[9] Despite being considered a less severe condition compared with other respiratory

Correspondence to:
Camila Isabel Santos Schivinski. Rua Pascoal Simone, 358, Coqueiros, CEP 88080-350, Florianópolis, SC, Brasil.
Tel.: 55 48 99123-2420. E-mail: cacaiss@yahoo.com.br
Financial support: This study received financial support from Fundação de Amparo à Pesquisa do Estado de Santa Catarina (FAPESC, Foundation for the Support of Research in the State of Santa Catarina no. 522/2017, term of agreement no. 2017TR645).

ISSN 1806-3713

disorders, rhinitis can have negative effects in the lungs, such as increased lung resistance and decreased lung compliance, which affects chest expansion and leads to inadequate alveolar ventilation.[11] Thus, it becomes relevant to investigate the effects of rhinitis on respiratory mechanics However, to date, most studies have not investigated rhinitis symptoms.

The primary objective of this study was to compare IOS parameters between healthy children and adolescents with symptoms of rhinitis and those without, and a secondary objective was to investigate the relationships that age and anthropometric variables have with IOS parameters in this population.

METHODS

This was a cross-sectional analytical study involving healthy children and adolescents 7 to 14 years of age who attended schools in the greater metropolitan area of the city of Florianópolis, Brazil. We included students who, at the time of data collection, had no chronic or acute respiratory disease and whose health status was determined through the use of parent/guardian-completed questionnaires. We excluded students who were unable to perform any of the steps of the evaluation and whose FEV_1 was less than 80% predicted,[12] as well as whose FEV_1/FVC ratio was less than 70% predicted.[13] The study was approved by the Research Ethics Committee of the *Universidade do Estado de Santa Catarina* (CAAE no 52891215.7.0000.0118), and the parents or legal guardians of the participants gave written informed consent.

Health status was assessed through the use of two questionnaires: a health diary created by the researchers, assessing aspects such as the presence of concomitant diseases, passive smoking, history of prematurity, level of physical activity, socioeconomic factors, and environmental factors; and the International Study of Asthma and Allergies in Childhood, modules 1 and 2.[14] Module 1 was used in order to screen for asthma (an exclusion criterion), and module 2 was used in order to divide the sample into two groups: participants with symptoms of rhinitis (rhinitis group) and participants without symptoms of rhinitis (non-rhinitis group).

The following measures were recorded: body mass (in kg); height (in cm); and body mass index (BMI), which was calculated with the online calculator of the Brazilian National Ministry of Health.[15] Subsequently, participants underwent IOS, in accordance with the American Thoracic Society standards,[16] with the use of a MasterScreen IOS device (Jaeger, Würtzburg, Germany), which was calibrated before each trial Participants were instructed to remain in a seated position with a nose clip in place and seal their lips around the mouthpiece while their cheeks were pressed by the examiner. Participants were instructed not to obstruct the mouthpiece with their tongue, as well as not to swallow, cough, or vocalize during the maneuver. Maneuvers lasting at least 20 s were accepted, and at least three should be acceptable and reproducible.[5] The minimum acceptable coherence value was 0.8 at 10 Hz.[17] After a rest period of approximately 20 s, spirometry was performed, in accordance with the American Thoracic Society standards.[18]

The following IOS parameters were analyzed: respiratory impedance (Z); respiratory resistance (R), measured at 5 Hz (R5), which represents total airway resistance, or at 20 Hz (R20), which represents central airway resistance; reactance (X), measured at 5 Hz (X5), which characterizes airway obstruction and restriction; and resonance frequency (Fres), which is the point at which capacitive reactance (related to thoracopulmonary elasticity and change in volume) equals inertial reactance (a reflection of the movement of the air column in the airways)[19] and which, together with R, is a parameter that has high specificity and sensitivity for detecting airway obstruction.[20] The reactance area (AX), which is related to lung compliance and to the degree of obstruction of the peripheral airways,[5] was also analyzed. We then recorded absolute and predicted values of R5, R20, X5, Fres, and AX, in accordance with de Assumpção et al.[21] The parameters measured by spirometry included FVC, FEV_1, and PEF.[12,13]

Descriptive statistical analysis was performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA), and the significance level adopted was 5% for all tests. Initially, we used descriptive and frequency statistics, and data were expressed as means and standard deviations. Data distribution was tested by using the Shapiro-Wilk test, and we used Pearson's or Spearman's test to assess correlations between study variables, the correlations being classified, in accordance with Dancey & Reidy,[22] as weak (0.10 to 0.30), moderate (0.40 to 0.60), or strong (0.70 to 1.0). The Student's t-test for independent samples and the Mann Whitney U test were used for between-group comparisons. To calculate the sample size, we analyzed data obtained in a pilot study, which included 12 children (6 in each group). The IOS parameter R5 was selected for the analysis, with a between-group difference to be detected of 0.11 kPa and a standard deviation of 0.12 kPa. Our calculation indicated that, to achieve a power of 80% and a significance level of 5% (two-tailed test),[23] a sample size of 21 students in each group would be sufficient for our study. Considering a potential loss to follow-up, we estimated the final sample size to be 58 children, 29 in each group.

RESULTS

We evaluated 69 participants. However, 7 were excluded because their performance of spirometry did not meet acceptability and reproducibility criteria. Therefore, a total of 62 healthy children and adolescents, 33 (53%) of whom were girls, participated in this study, with a mean age of 9.58 ± 2.08 years and a BMI of 17.96 ± 3.10 kg/m^2. Of those, 33 children and adolescents (20 girls) comprised the non-rhinitis group, whereas 29 children and adolescents (16 boys) comprised the rhinitis group. Data on the characteristics and health

status assessment of participants, which are shown in Tables 1 and 2, reveal that the two groups did not differ in terms of the anthropometric or spirometric variables analyzed.

In the sample as a whole, age correlated negatively with the IOS parameters Z5 (r = −0.549), R5 (r = −0.529), R20 (r = −0.441), AX (r = −0.459), and Fres (r = −0.353), whereas it correlated positively with the IOS parameter X5 (r = 0.506), and all of the correlations were significant ($p < 0.05$). The variables height and body mass, respectively, showed significant negative correlations with Z5 (r = −0.567 and −0.455), R5 (r = −0.548 and −0.433), R20 (r = −0.468 and −0.439), X5 (r = −0.525 and −0.414), AX (r = −0.471 and −0.358), and Fres (r = −0.371 and −0.293). We found that BMI did not correlate significantly with any of the parameters evaluated.

In the rhinitis group, similar to what was seen in the sample as a whole, there were significant correlations between anthropometric/demographic variables and IOS parameters. Age showed negative correlations with Z5, R5, R20, Fres (r = −0.425), and AX (r = −0.522) and showed a positive correlation with X5 (Figure 1). Height showed negative correlations with Z5, R5, R20, Fres (r = −0.479), and AX (r = −0.501) and showed a positive correlation with X5 (Figure 2). Body mass correlated positively with X5 (r = 0.415) and negatively with Z5 (r = −0.425), R5 (r = −0.414), and R20 (r = −0.513). The BMI showed positive correlations with Fres (r = 0.497) and AX (r = 0.394).

The results in the non-rhinitis group were similar to those obtained in the rhinitis group, with significant correlations between variables. Age showed negative correlations with Z5, R5, R20, and AX (r = −0.407) and showed a positive correlation with X5 (Figure 1). Height correlated negatively with Z5, R5, R20, Fres (r = −0.356), and AX (r = −0.414) and positively with X5 (Figure 2). Body mass showed a positive correlation with X5 (r = 0.450), whereas it showed negative correlations with Z5 (r = −0.469), R5 (r = −0.517), R20 (r = −0.374), Fres (r = −0.413), and AX (r = −0.445).

There were no significant differences between the rhinitis and non-rhinitis groups in any of the IOS parameters evaluated (Table 2).

DISCUSSION

The behavior of IOS parameters in children and adolescents, in relation to the presence of rhinitis

Table 1. Anthropometric and demographic characteristics in the sample as a whole and by group.[a]

Variable	Sample as a whole	Non-rhinitis group (n = 33)	Rhinitis group (n = 29)	p*
Age, years	9.58 (9.05-10.1)	9.61 (8.85-10.3)	9.55 (8.77-10.3)	0.989
Body mass, kg	36.9 (34.4-39.5)	38.1 (34.6-41.7)	35.6 (31.7-39.4)	0.321
Height, cm	140.7 (137.7-143.7)	142.5 (138.4-146.6)	138.7 (134.3-143.1)	0.207
BMI, kg/m^2	17.9 (17.1-18.7)	17.9 (16.8-19.0)	17.9 (16.7-19.1)	0.982

Non-rhinitis group: participants without symptoms of rhinitis; rhinitis group: participants with symptoms of rhinitis; and BMI: body mass index. [a]Values are expressed as mean (95% CI). *Between-group comparisons with the Student's t-test for independent samples.

Table 2. Spirometric and impulse oscillometry parameters in the sample as a whole and by group.[a]

Parameter[b]	Sample as a whole	Non-rhinitis group (n = 33)	Rhinitis group (n = 29)	p*
%FVC	98.2 (95.1-101.2)	99.9 (95.3-104.5)	96.2 (92.3-100.2)	0.232
%FEV_1	101.6 (100.0-103.2)	101.3 (99.1-103.5)	102.0 (99.6-104.3)	0.623
%PEF	82.8 (78.3-87.3)	83.1 (76.7-89.5)	82.5 (75.8-89.2)	0.989
%$FEF_{25-75\%}$	88.7 (83.5-93.9)	86.6 (79.9-93.3)	91.2 (82.7-99.7)	0.388
R5 (kPa/L/s)	0.64 (0.60-0.68)	0.68 (0.57-0.68)	0.66 (0.59-0.72)	0.521
%R5	107.4 (102.1-112.7)	107.0 (100.3-113.7)	107.9 (99.1-116.6)	0.864
R20 (kPa/L/s)	0.50 (0.47-0.52)	0.50 (0.46-0.53)	0.50 (0.46-0.54)	0.981
%R20	101.1 (96.2-106.1)	104.0 (96.8-111.2)	97.8 (90.9-104.7)	0.213
Z5 (kPa/L/s)	0.67 (0.62-0.71)	0.65 (0.59-0.70)	0.69 (0.62-0.75)	0.370
%Z5	156.7 (146.9-166.5)	157.4 (143.2-171.7)	155.9 (141.7-170.1)	0.876
X5 (kPa/L/s)	−0.17 (−0.19 to −0.16)	−0.17 (−0.19 to −0.14)	−0.18 (−0.21 to −0.15)	0.511
%X5	124.7 (113.9-135.6)	123.2 (108.3-138.1)	126.5 (109.8-143.2)	0.767
Fres (Hz)	18.8 (17.4-20.1)	18.1 (16.3-20.0)	19.4 (17.4-21.5)	0.339
%Fres	113.6 (106.3-121.0)	111.9 (101.3-122.4)	115.6 (104.9-126.4)	0.610
AX (kPa/L)	1.39 (1.13-1.66)	1.26 (0.90-1.62)	1.55 (1.15-1.95)	0.233
%AX	133.8 (107.9-159.7)	120.7 (86.2-155.2)	148.63(107.9-189.2)	0.290

Non-rhinitis group: participants without symptoms of rhinitis; rhinitis group: participants with symptoms of rhinitis; R5: total airway resistance; R20: central airway resistance; Z5: respiratory impedance; X5: reactance at 5 Hz; Fres: resonance frequency; and AX: reactance area. [a]Values are expressed as mean (95% CI). [b]%variable: percent predicted variable. *Between-group comparisons were made with the Student's t-test for independent samples.

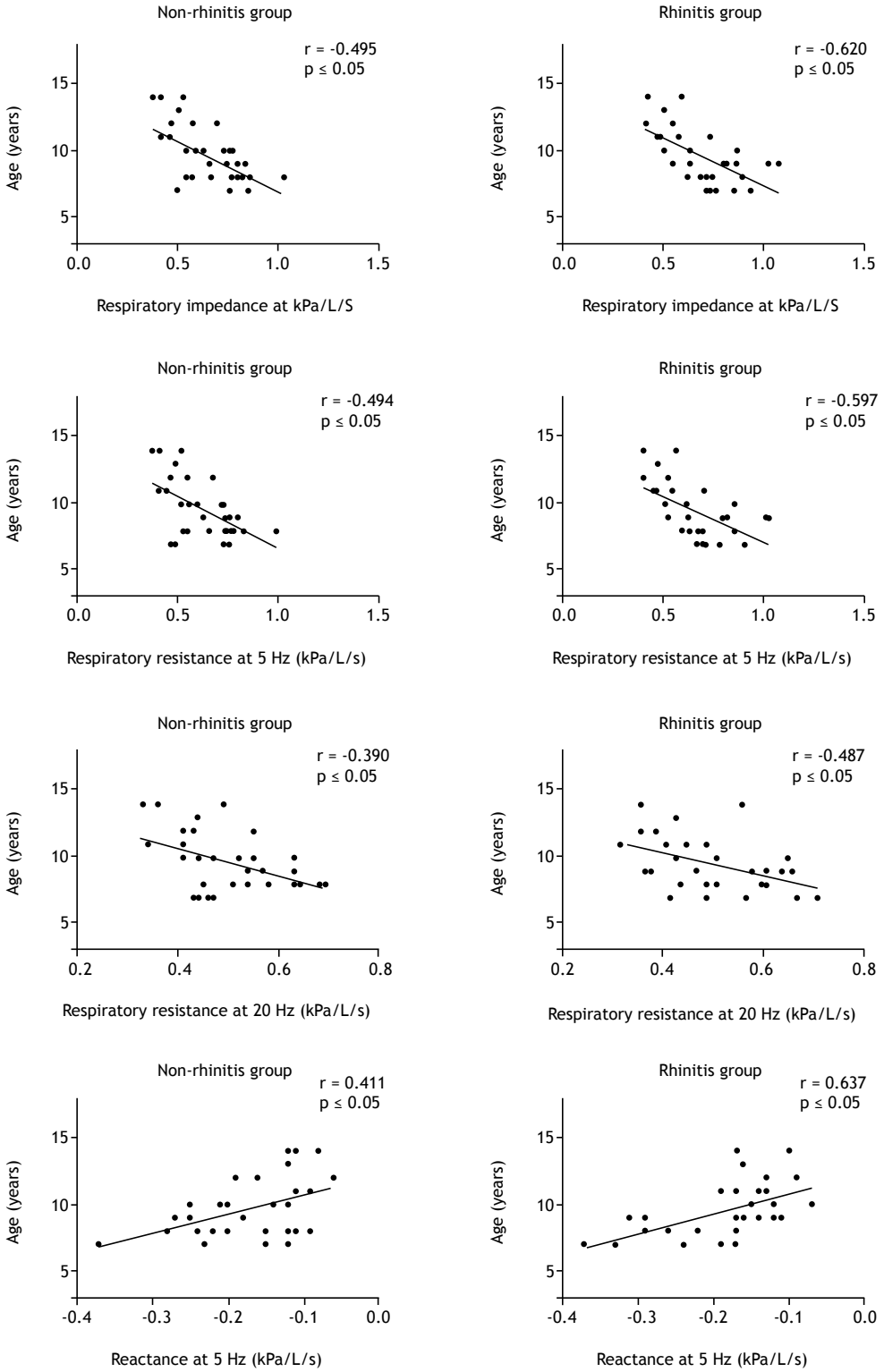


Figure 1. Correlations between age and impulse oscillometry parameters in the rhinitis and non-rhinitis groups. Non-rhinitis group: participants without symptoms of rhinitis; and rhinitis group: participants with symptoms of rhinitis.

symptoms, has not been extensively investigated. Most studies on IOS have reported its relationship with anthropometric variables in studies on reference values,[9] as well as in specific respiratory diseases, such as asthma and cystic fibrosis,[24] and in hyperresponsiveness.[25]

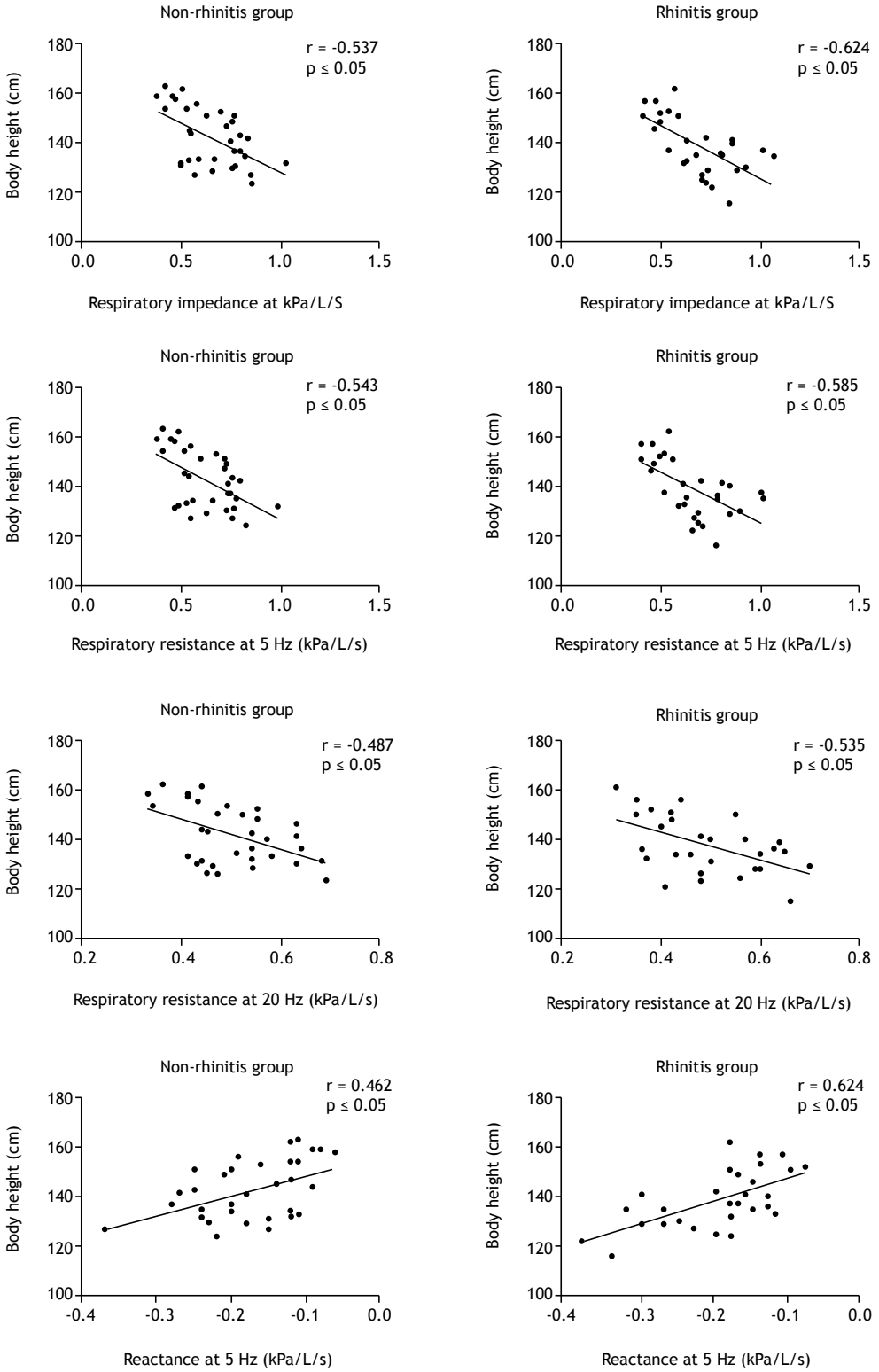


Figure 2. Correlations between height and impulse oscillometry parameters in the rhinitis and non-rhinitis groups. Non-rhinitis group: participants without symptoms of rhinitis; and rhinitis group: participants with symptoms of rhinitis.

In the present study, our hypothesis was that there would be differences between the rhinitis and non-rhinitis groups, given the one-airway theory.[8,9] However, that hypothesis was not confirmed. Symptoms of rhinitis can lead to inflammation and edema of the upper airway mucosa, which generate a turbulent flow to

the airways and, consequently, an increase in airway resistance.[10,11] In addition, the presence of such symptoms favors mouth breathing, and, consequently, cold, dry, unfiltered air is allowed to enter, which also has negative effects on the airways,[26] among which is hyperresponsiveness.[25]

According to Galant et al.,[27] IOS, which assesses airway caliber, and spirometry, which reflects airflow characteristics, could detect potential changes resulting from the presence of rhinitis symptoms. The fact that such changes were not detected in the present study can be attributed to the transitory nature of rhinitis symptoms, which thus had no effect on the lower airways. In addition, IOS and spirometry both involve the use of a mouthpiece, with closed nares, and the nares are the primary areas of inflammatory involvement in respiratory tract conditions. Arshi et al.[25] also used IOS and spirometry to compare airway responses in similar patients (i.e., patients with symptoms of rhinitis) before and after treadmill exercise testing. However, their sample consisted of children and adults (12-44 years). Those authors found no relationship between IOS and spirometry measures and considered treadmill exercise testing inappropriate for determining the presence of airway hyperresponsiveness in symptomatic individuals.

It is essential to note that our study sample was homogeneous, consisting of children and adolescents who attended the same school, had a similar socioeconomic status, had no history of passive smoking or prematurity, were physically active but were not athletes registered in sports federations, and were not obese. Participants were differentiated, and consequently grouped, on the basis of the presence or absence of rhinitis symptoms, which is hypothesized to be a determinant of potential differences in IOS parameters, a hypothesis that was not confirmed. Along the same line, Costa[11] also found no differences when comparing IOS parameters between a group with allergic rhinitis and a control group. Therefore, these findings are of great relevance for clinical practice, given that many children who have been included in studies investigating lower airway diseases routinely exhibit symptoms of rhinitis, which do not appear to compromise the results of tests that assess the respiratory system.

In the present study, the normal Fres and R5 values found in the sample as a whole, consistent with lower airway integrity, as well as in the rhinitis and non-rhinitis groups separately, appear to refute the one-airway theory,[8,9] which gave rise to this research. Fres tends to be higher in children, to decrease with increasing age, and to be elevated in restrictive or obstructive disease states. Airway resistance decreases with increasing age, and, in patients with small airway disease, changes in resistance at low frequencies (R5) become apparent[28]; such changes were not detected here. This topic has been investigated. Song et al.[29] conducted a study involving 226 children with allergic and non-allergic rhinitis and examined the relationship between the anatomy of the nasal cavity and increased lower airway resistance, as measured by IOS. As in the present study, participants were selected by means of the International Study of Asthma and Allergies in Childhood questionnaire. The authors found that children with a smaller nasal cavity had higher values for the parameters related to resistance in the lower airways.

Kim et al.[30] evaluated 340 children, among whom were healthy children, children with asthma, and children with allergic rhinitis. The authors concluded, on the basis of the one-airway theory, that children with rhinitis have greater inflammation and mild reversible obstruction of the airways, detectable by IOS, when compared with healthy children. These findings differ from those obtained in the present study, in which there were no significant differences in IOS parameters or anthropometric variables between students with symptoms of rhinitis and those without. One potential limitation of the present study is the lack of a clinical diagnosis of rhinitis, made on the basis of ear, nose, and throat assessment and objective tests, similar to that observed in studies mentioned here,[25,29,30] which leads to a potential selection bias.

When we analyzed the groups separately, we found that the presence of rhinitis symptoms was associated with higher correlation coefficients between the IOS parameters Z5, R5, R20, and X5 and the variables age and height, a finding that was not true for the sample as a whole. Also in the rhinitis group, the correlation between height and the IOS parameters Fres and AX was of greater magnitude, whereas in the non-rhinitis group, no relationship was found between age and Fres. In the rhinitis group, similar to what was seen in the sample as a whole, the variables body mass and BMI correlated significantly with the IOS parameters Z5, R5, R20, X5, AX, and Fres. Assumpção et al.,[31] when comparing obese and normal-weight children and finding that the values of the IOS parameters Z5, R5, Fres, and AX were higher in those with increased body mass, argued that greater attention should be paid to this anthropometric variable in order for us to understand its influence on respiratory system mechanics. This is because enlarged tissue structures, such as adipose tissue, lead to a reduction in lung volumes and, consequently, a decrease in small airway caliber, directly resulting in an increase in respiratory system resistance.[11,32]

The present study primarily found that, although the correlations observed between IOS parameters and anthropometric variables were of greater magnitude in the rhinitis group, there were no statistically significant differences in IOS parameters between the non-rhinitis group and the sample as a whole. These findings raise the need for further studies to investigate the impact that rhinitis symptoms have on respiratory mechanics parameters in children and adolescents, as well as on their anthropometric status. Secondarily, we found correlations between most IOS parameters and the anthropometric/demographic variables analyzed in this sample of students. However, the presence of rhinitis symptoms merits further investigation in this population.

REFERENCES

1. De Assumpção MS. Avaliação da função pulmonar em crianças e adolescentes pelo sistema de oscilometria de impulso em três situações distintas: obesidade, exposição ao tabagismo passivo e teste de caminhada de seis minutos [thesis]. Campinas: Universidade Estadual de Campinas; 2017.
2. Sakarya A, Uyan ZS, Baydemir C, Anık Y, Erdem E, Gokdemir Y, et al. Evaluation of children with cystic fibrosis by impulse oscillometry when stable and at exacerbation. Pediatr Pulmonol. 2016;51(11):1151-1158. https://doi.org/10.1002/ppul.23449
3. Sharshar RS, Mohamed AS. The utility of impulse oscillometry in asthma: A comparison of spirometry versus impulse oscillometry system. Egypt J Chest Dis Tuberc 2017;66(2):207-9. https://doi.org/10.1016/j.ejcdt.2017.03.002
4. Gonçalves RM, Ferreira LG, Assumpção MS, Schivinski CIS. Impact of sports activities on respiratory function and mechanics in children. Fisioter Mov. 2017;30(3):485-92. https://doi.org/10.1590/1980-5918.030.003.ao06
5. De Assumpção MS, Gonçalves RM, Ferreira LG, Schivinski CIS. Sistema de oscilometria de impulso em pediatria: Revisão de literatura. Medicina (Ribeirao Preto). 2014; 47(2): 131-142. https://doi.org/10.11606/issn.2176-7262.v47i2p131-142
6. Tenorio LHS, Santos AC, Oliveira AS, Lima AMJ, Brasileiro-Santos MS. Obesidade e testes de função pulmonar em crianças e adolescentes: uma revisão sistemática. Rev Paul Pediatr. 2012;30(3):423-430. https://doi.org/10.1590/S0103-05822012000300018
7. De Assumpcao MS, da Silva Goncalves E, Oliveira MS, Ribeiro JD, Toro AADC, Barros-Filho AA, et al. Impulse Oscillometry System and Anthropometric Variables of Preschoolers, Children and Adolescents Systematic Review. Curr Pediatr Rev. 2017;13(2):126-135. https://doi.org/10.2174/1573396313666170622075940
8. Sakano E, Sarinho ESC, Cruz AA, Pastorino AC, Tamashiro E, Kushnir F, et al. IV Brazilian Consensus on Rhinitis - an update on allergic rhinitis. Braz J Otorhinolaryngol. 2017;S1808-8694(17)30187-8.
9. Mion O, Di Francesco RC, Amato FS, Sakai AP. Rinite Alérgica. Rev Bras Med (Rio J). 2014;17:84-94.
10. Saranz RJ, Lozano A, Valero A, Lozano NA, Martijena MDPB, Agresta F et al. Impact of rhinitis on lung function in children and adolescents without asthma. Allergol Immunopathol (Madr). 2016;44(6):556-562. https://doi.org/10.1016/j.aller.2016.04.006
11. Costa RCS. Avaliação da função pulmonar em crianças portadoras de rinite alérgica por meio do sistema de oscilometria de impulso [dissertation]. Recife: Universidade Federal de Pernambuco; 2015.
12. Polgar G, Weng TR. The functional development of the respiratory system from the period of gestation to adulthood. Am Rev Respir Dis. 1979;120(3):625-695.
13. Knudson RJ, Slatin RC, Lebowitz MD, Burrows B. The maximal expiratory flow-volume curve. Normal standards, variability, and effects of age. Am Rev Respir Dis. 1976;113(5):587-600.
14. Macaira EF, Algranti E, Stelmach R, Ribeiro M, Nunes MP, Mendonça EC, et al. Determining the score and cut-off point that would identify asthmatic adults in epidemiological studies using the asthma module of the International Study of Asthma and Allergies in Childhood questionnaire. J Bras Pneumol 2005;31(6):477-485. https://doi.org/10.1590/S1806-37132005000600004
15. Brasil. Ministério da Saúde. Biblioteca Virtual em Saúde [homepage on the Internet]. Brasília: o Ministério; c2012 [cited 2019 Jan 1]. Rede Telessaúde Brasil–Calculadoras. Available from: http://www.telessaudebrasil.org.br/apps/calculadoras
16. Rodrigues JC, Jocelina M, Cardieri A, Bussamra MH, Nakaie CM, Almeida MB, et al. Provas de função pulmonar em crianças e adolescentes. J Pneumol. 2002;28(Suppl 3):S207-S221.
17. Komarow HD, Myles IA, Uzzaman A, Metcalfe DD. Impulse oscillometry in the evaluation of diseases of the airways in children. Ann Allergy Asthma Immunol. 2011;106(3):191-199. https://doi.org/10.1016/j.anai.2010.11.011
18. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-338. https://doi.org/10.1183/09031936.05.00034805
19. Goldman MD. Clinical application of forced oscillation. Pulm Pharmacol Ther. 2001;14(5):341-350. https://doi.org/10.1006/pupt.2001.0310
20. Janssens JP, Nguyen MC, Herrmann FR, Michel JP. Diagnostic value of respiratory impedance measurements in elderly subjects. Respir Med. 2001;95(5):415-422. https://doi.org/10.1053/rmed.2001.1062
21. de Assumpção MS, Gonçalves RM, Martins R, Bobbio TG, Schivinski CI. Reference Equations for Impulse Oscillometry System Parameters in Healthy Brazilian Children and Adolescents. Respir Care. 2016;61(8):1090-1099. https://doi.org/10.4187/respcare.04226
22. Dancey CP, Reidy J. Estatística sem matemática para psicologia: usando SPSS para Windows. 3rd ed. Porto Alegre: Artmed; 2006.
23. Armitage P, Berry G. Statistical methods in medical research. 2nd ed. Oxford: Blackwell; 1987.
24. Ducharme FM, Jroundi I, Jean G, Lavoie Boutin G, Lawson C, Vinet B. Interdevice agreement in respiratory resistance values by oscillometry in asthmatic children. ERJ Open Res. 2019;5(1):00138-2018. https://doi.org/10.1183/23120541.00138-2018
25. Arshi S, Nabavi M, Babaie D, Bahrami A, Ghalehbaghi B. Exercise induced changes in spirometry and impulse oscillometry measurements in persistent allergic rhinitis. Iran J Allergy Asthma Immunol. 2012;11(3):259-266.
26. Turkalj M, Živković J, Lipej M, Lokas SB, Erceg D, Anzić SA, et al. The effect of mouth breathing on exercise induced fall in lung function in children with allergic asthma and rhinitis. Int J Pediatr Otorhinolaryngol. 2016;86:53-56. https://doi.org/10.1016/j.ijporl.2016.04.020
27. Galant SP, Komarow HD, Shin HW, Siddiqui S, Lipworth BJ. The case for impulse oscillometry in the management of asthma in children and adults. Ann Allergy Asthma Immunol. 2017;118(6):664-671. https://doi.org/10.1016/j.anai.2017.04.009
28. Bickel S, Popler J, Lesnick B, Eid N. Impulse oscillometry: interpretation and practical applications. Chest. 2014;146(3):841-847. https://doi.org/10.1378/chest.13-1875
29. Song JY, Ha EK, Sheen YH, Kim MA, Lee SW, Yoon JW et al. The association of nasal patency with small airway resistance in children with allergic and nonallergic rhinitis. Clin Respir J. 2018;12(7):2264-2270. https://doi.org/10.1111/crj.12902
30. Kim YH, Park HB, Kim MJ, Kim HS, Lee HS, Han YK, et al. Fractional exhaled nitric oxide and impulse oscillometry in children with allergic rhinitis. Allergy Asthma Immunol Res. 2014;6(1):27-32. https://doi.org/10.4168/aair.2014.6.1.27
31. Assumpção MS, Ribeiro JD, Wamosy RMG, Figueiredo FCXS, Parazzi PLF, Schivinski CIS. Impulse oscillometry and obesity in children. J Pediatr (Rio J). 2018;94(4):419-424. https://doi.org/10.1016/j.jped.2017.06.007
32. Albuquerque CG, Andrade FM, Rocha MA, Oliveira AF, Ladosky W, Victor EG, et al. Determining respiratory system resistance and reactance by impulse oscillometry in obese individuals. J Bras Pneumol. 2015;41(5):422-426. https://doi.org/10.1590/S1806-37132015000004517

J Bras Pneumol. 2020;46(3):e20180261
https://dx.doi.org/10.36416/1806-3756/e20180261

ORIGINAL ARTICLE

Impact of a multidisciplinary checklist on the duration of invasive mechanical ventilation and length of ICU stay

Ruy de Almeida Barcellos[1], José Miguel Chatkin[1]

1. Programa de Pós-Graduação em Medicina e Ciências da Saúde, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.

Submitted: 17 August 2018.
Accepted: 30 September 2019.

Study carried out under the auspices of the Programa de Pós-Graduação em Medicina e Ciências da Saúde, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.

ABSTRACT

Objective: To assess the impact that implementing a checklist during daily multidisciplinary rounds has on the duration of invasive mechanical ventilation (IMV) and length of ICU stay. **Methods:** This was a non-randomized clinical trial in which the pre-intervention and post-intervention duration of IMV and length of ICU stay were evaluated in a total of 466 patients, including historical controls, treated in three ICUs of a hospital in the city of Caxias do Sul, Brazil. We evaluated 235 and 231 patients in the pre-intervention and post-intervention periods, respectively. The following variables were **studied:** age; gender; cause of hospitalization; diagnosis on admission; comorbidities; the Simplified Acute Physiology Score 3; the Sequential Organ Failure Assessment score; days in the ICU; days on IMV; reintubation; readmission; in-hospital mortality; and ICU mortality. **Results:** After the implementation of the checklist, the median (interquartile range) for days in the ICU and for days on IMV decreased from 8 (4-17) to 5 (3-11) and from 5 (1-12) to 2 (< 1-7), respectively, and the differences were significant ($p \leq 0.001$ for both). **Conclusions:** The implementation of the checklist during daily multidisciplinary rounds was associated with a reduction in the duration of IMV and length of ICU stay among the patients in our sample.

Keywords: Checklist; Respiration, artificial; Length of stay; Intensive care units.

INTRODUCTION

The duration of invasive mechanical ventilation (IMV) and length of ICU stay can be considered at least partial indicators of quality of care. It has been reported that 5-20% of ICU patients require mechanical ventilation, which is required for more than 7 days in 25%.[1-4]

Longer duration of IMV is associated with increased mortality, longer ICU/hospital stays, and substantially increased health care costs. Therefore, protective mechanical ventilation strategies are essential for early ventilator weaning, i.e., as soon as patients are stable and show signs of recovery.[5-9]

Among critically ill patients, the average ICU length of stay ranges from 2 days to 13 days depending on patient profile and case severity.[10] This wide variation can be explained by the proportion of postoperative patients admitted for shorter stays. Among adult patients on IMV, the average ICU length of stay ranges from 7.2 days to 13.7 days.[4]

In a multicenter study conducted in Brazil, Azevedo et al.[11] showed that patients receiving IMV had an average ICU length of stay of 10 days, with high in-hospital mortality (42%). Nassar Junior et al.[3] showed similar results, reporting an in-hospital mortality of 43.3% among patients on IMV.

In intensive care settings, the complexity of the environment, as well as ineffective communication among health care professionals, together with the fact that professionals are under enormous pressure, can lead to errors of omission during daily rounds and, consequently, negative outcomes.[12-14]

Several studies have examined the use of checklists during daily multidisciplinary rounds, showing that the implementation of checklists improves clinical outcomes, as well as reducing the duration of IMV and length of ICU stay.[12] In addition, checklists improve the quality of multidisciplinary care processes by increasing error detection, improving patient care, enforcing safety standards, and promoting patient-centered care.[13-16] Although populations and outcomes have varied across studies, the implementation of a checklist during daily multidisciplinary rounds appears to be highly beneficial to patients. However, in a study conducted in Brazil,[16] checklists were found to have no impact on the mortality of critically ill patients, having no effect in reducing the duration of IMV or the length of ICU stay.

Given the conflicting results found in the literature, the objective of the present study was to assess the impact that implementing a checklist during daily multidisciplinary rounds has on the duration of IMV and length of ICU stay.

METHODS

This was a non-randomized clinical trial involving 466 patients, including historical controls, treated between

Correspondence to:
Ruy de Almeida Barcellos. Pontifícia Universidade Católica do Rio Grande do Sul, Avenida Ipiranga, 6681, Partenon, CEP 90619-900, Porto Alegre, RS, Brasil.
Tel.: 55 51 3320-3500. E-mail: rbarcellos@hcpa.edu.br
Financial support: None.

February of 2015 and July of 2016 in three ICUs in a hospital located in the city of Caxias do Sul, Brazil.

The inclusion criteria were as follows: being ≥ 18 years of age, having been on IMV, and having stayed in the ICU for at least 48 h. The exclusion criteria were as follows: patient medical records missing data on initial diagnosis or primary outcome; patients receiving exclusive palliative care; and patients with a diagnosis of brain death.

The content of the intervention (the checklist) was developed on the basis of the needs expressed by the multidisciplinary ICU team and is shown in Chart 1. The checklist was tailored to the local context and consisted of five items (analgesia and sedation; IMV; prophylaxis; invasive devices; and nutritional status) addressing safety, clinical management, and treatment goals for the next 24 h.

In July of 2015, a 30-day pilot study of 90 patients was conducted to evaluate the applicability of the checklist at the bedside. The study examined the following: team adaptation to the checklist; checklist completion time; clarity of checklist items; and checklist appropriateness to the local context (item review and revision). At the end of the study period, the final version of the checklist was approved for use during daily multidisciplinary rounds.

No data were collected in the first 6 months of checklist use (from August of 2015 to January of 2016), in order to allow checklist use to become routine in the ICUs and avoid outcome bias.

Data collection was conducted in two phases, electronic medical records being used for both phases. For patients admitted to the ICU prior to the intervention, data were retrospectively collected between February and June of 2015. For patients admitted to the ICU after the intervention, data were collected between February and July of 2016.

The checklist was performed daily during early morning multidisciplinary rounds, the multidisciplinary team consisting of an intensivist, a nurse, a physical therapist, a pharmacist, and a nutritionist, as well as of students and health professionals in training in the ICUs. Rounds lasted 10 min on average per patient, being performed at the bedside with the use of a laptop computer. The intensivist read the checklist

Chart 1. Checklist used in the present study.

CHECKLIST ROUND MULTIPROFISSIONAL		
Adequate analgesia and sedation?		
( ) Yes	( ) No	( ) Not applicable
Reduction/interruption?		
( ) Yes	( ) No	( ) Not applicable
Appropriate/lung-protective ventilation?		
( ) Yes	( ) No	( ) Not applicable
SBT?		
( ) Yes	( ) No	( ) Not applicable
Mobilization?		
( ) Yes	( ) No	( ) Not applicable
Appropriate prophylaxis (DVT, pressure sores, gastric ulcer, VAP) ?		
( ) Yes	( ) No	( ) Not applicable
Discontinuation of invasive devices?		
( ) Yes. Which?_____	( ) No	( ) Not applicable
Discontinuation of antibiotics?		
( ) Yes. Which?_____	( ) No	( ) Not applicable
Adequate caloric intake?		
( ) Yes	( ) No	( ) Not applicable
Continue with current diet?		
( ) Yes. How long for?_____	( ) No	( ) Not applicable
GOALS OF THE DAY		
_____		
_____		
_____		
_____		

SBT: spontaneous breathing trial; DVT: deep vein thrombosis; and VAP: ventilator-associated pneumonia.

aloud and the remaining team members responded, making suggestions regarding interventions.

Neither investigator was directly involved in patient care. The health care team was the same in both phases of the study. None of the health care professionals were aware of the study; the checklist was simply introduced into daily ICU practice as a new protocol, thus minimizing information bias.

The sample size was calculated with WINPEPI, version 11.43 (http://www.brixtonhealth.com/pepi4windows.html), on the basis of a pilot study of 40 patients (20 patients in each study period). A sample size of at least 438 was estimated to be required for a level of significance of 5%, a power of 90%, and a minimum effect size of 0.31 standard deviations for the two outcomes (duration of IMV and length of ICU stay), which was defined as the smallest difference between the means for the pre- and post-intervention groups in the pilot study divided by the standard deviation.

With regard to the duration of IMV, the pilot study showed a mean duration of 7 days prior to the intervention and a mean duration of 3.9 days after the intervention, a post-intervention reduction of 3.1 ± 10 days being assumed. With regard to the length of ICU stay, the pilot study showed a mean length of stay of 16 days prior to the intervention and a mean length of stay of 7 days after the intervention, a post-intervention reduction of 9 ± 17 days being assumed.

For descriptive statistics, categorical variables were expressed as absolute and relative frequencies. Continuous variables were expressed as means and standard deviations or as medians and interquartile ranges, depending on the distribution of the variables.

For group comparisons, the following tests were used: the Student's t-test, for continuous variables with normal distribution; Pearson's chi-square test or Fisher's exact test, for nominal categorical variables; and the Mann-Whitney test, for continuous variables with non-normal distribution.

Backward stepwise multiple linear regression was used in order to identify factors independently associated with the duration of IMV and length of ICU stay. All of the variables showing $p < 0.20$ in the univariate analysis were included in the multivariate model, although only those showing $p < 0.10$ remained in the final model. Outcomes were log-transformed for parametric analysis. Differences were considered significant at $p < 0.05$.

The research project was approved by the Scientific Committee and Research Ethics Committee of the Pontifical Catholic University of Rio Grande do Sul (Ruling no. 1,355,805), located in the city of Porto Alegre, Brazil. Because the study used secondary data, the requirement for informed consent was waived.

RESULTS

During the study periods, 489 patients received IMV in the ICUs. Of those, 466 met the inclusion criteria (235 in the pre-intervention group and 231 in the post-intervention group). As can be seen in Figure 1, 23 patients were excluded, the reasons being as follows: brain death, in 12, exclusive palliative care, in 8, and missing data (no initial diagnosis or primary outcome), in 3.

The general characteristics of the patients are shown in Table 1. Male patients predominated in both groups. There was no significant difference between the pre- and post-intervention groups regarding disease severity as assessed by the Simplified Acute Physiology Score 3 (SAPS 3). The patients in the post-intervention group were significantly older than those in the pre-intervention group.

Although neurological disease was the most common reason for ICU admission in the pre- and post-intervention groups, the number of patients admitted to the ICU for neurological care was significantly lower in the latter group. Hypertension and smoking were the most prevalent comorbidities in both groups.

Patient outcomes are shown in Table 2. The implementation of the checklist resulted in significant reductions in the duration of IMV and length of ICU stay.

Factors independently associated with the duration of IMV and length of ICU stay are shown in Table 3. After linear regression adjustment, the intervention itself was the only variable that remained significantly associated with a reduction in the length of ICU stay. Age, admission for trauma, a diagnosis of respiratory disease on admission, SAPS 3, and reintubation within 48 h were significantly associated with longer ICU stays.

The intervention itself and a diagnosis of renal/urological disease were associated with a shorter duration of IMV ($p \leq 0.001$). Admission for trauma, a diagnosis of respiratory disease on admission, the Sequential Organ Failure Assessment score on admission, and reintubation within 48 h were significantly associated with a longer duration of IMV ($p \leq 0.001$, $p = 0.014$, $p \leq 0.001$, and $p \leq 0.002$, respectively).

DISCUSSION

In the present study, the implementation of a checklist during daily multidisciplinary rounds was found to be associated with a reduction in the duration of IMV and length of ICU stay.

Although studies examining the use of checklists have shown conflicting results, the findings indicate that checklists improve adherence to care processes, communication among health care professionals, and clinical outcomes.[16-22]

In a prospective multicenter study conducted in Brazil and examining the impact of checklists on mortality,[16] the duration of IMV and length of ICU stay were found to be shorter in the intervention group than in the control group; however, the difference was not significant. The population in that study was similar to the current population in terms of mean age, male predominance,

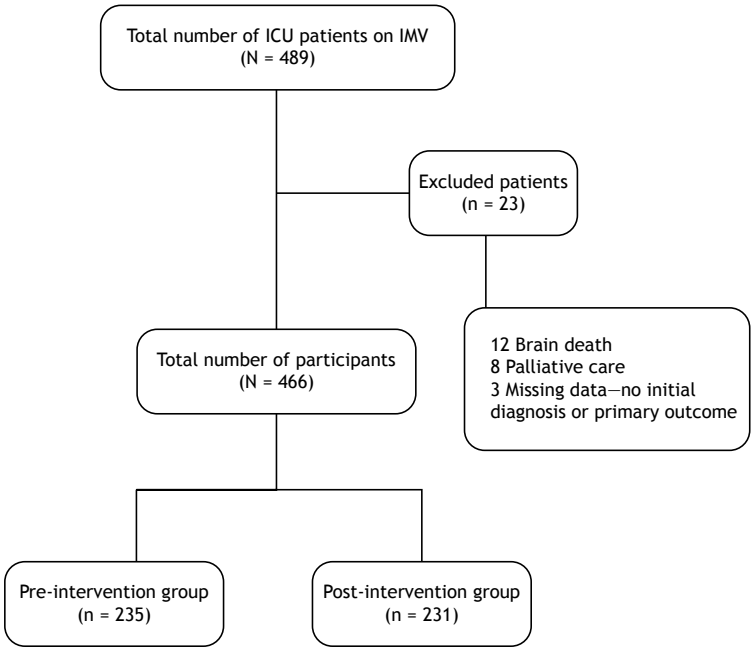


Figure 1. Flow chart of patient recruitment. IMV: invasive mechanical ventilation.

and disease severity as assessed by the SAPS 3; however, the results were different.[16] This might be due to the following: differences in study objective and design between the two studies; differences in intervention duration between the two studies; differences in the profiles of the institutions participating in the studies; the fact that the health care team was blinded to the outcomes of our study; the fact that the checklist used in the present study was tailored to the local context; and the fact that the present study included only patients receiving IMV. The conclusions should be interpreted with caution because of the many methodological differences.[22] However, despite the differences, both studies reinforce the importance of a multidisciplinary team and a daily checklist in the ICU.

Differences in results might be due to other differences. In studies including mostly postoperative patients, most of whom require a shorter duration of IMV and are extubated at the end of the procedure or shortly after arrival in the ICU,[8] the results obtained with the use of a checklist might not be significant, because postoperative care is the primary reason for ICU admission.

There was a predominance of male patients in the present study, and the disease profiles and general characteristics of the participants are similar to those of those in previous studies conducted in Brazil and describing the profile of critically ill ICU patients.[23,24]

The median duration of IMV and the median length of ICU stay were lower in the present study than in a study conducted by Azevedo et al.[11] This is expected to a certain extent because of the differences in profile and disease severity between the two populations, as well as because the present study included only patients receiving IMV.

The participation of a multidisciplinary team in the development and implementation of a checklist can lead to better results than those obtained with the introduction of a new tool in an established routine, as recommended elsewhere.[16] Future studies should examine the specific role that a multidisciplinary team plays in the yield of a checklist.

In the present study, data were collected after 6 months of checklist use, so as to allow health care team members to become familiar with the new protocol. Implementation of a new tool or protocol ideally requires strategies to overcome organizational and behavioral barriers to change, meaning that it takes time to implement a new tool/protocol and demonstrate its clinical impact, as reported in previous studies.[12,25,26]

Multidisciplinary team involvement in the implementation of local quality management strategies is important because team members are aware of the strengths and weaknesses of the facility, identifying opportunities for improvement.[27,28] Joint management appears to play a fundamental role in establishing effective organizational processes and protocols.[29,30]

In a single-center study conducted in Sweden over the course of 6 years and including 5,950 patients, the authors evaluated the effects of a quality improvement program on the quality of ICU care.[31] Restructuring the ICU workforce into multidisciplinary teams was found to contribute to the improvement of clinical performance. There were reductions of 24%, 43%, and 52% in long-term mortality, length of ICU stay, and duration of IMV, respectively.

Table 1. General characteristics of the study sample (N = 466).[a]

Variable	Group		p
	Pre-intervention (n = 235)	Post-intervention (n = 231)	
Age, years	50.6 ± 19.5	55.6 ± 18.4	0.004
Age group, years			0.011
< 30	44 (18.7)*	25 (10.8)	
30-49	62 (26.4)	56 (24.2)	
50-59	49 (20.9)	40 (17.3)	
≥ 60	80 (34.0)	110 (47.6)*	
Sex			0.139
Female	83 (35.3)	98 (42.4)	
Male	152 (64.7)	133 (57.6)	
Reason for ICU admission			0.202
Medical condition	112 (47.6)	117 (50.6)	
Surgical condition	69 (29.4)	76 (32.9)	
Trauma	54 (23.0)	38 (16.5)	
Diagnosis on admission			0.001
Neurological disease	101 (43.0)*	92 (39.8)	
Cardiovascular disease	39 (16.6)	27 (11.7)	
Hemodynamic instability	26 (11.1)	36 (15.6)	
Respiratory disease	23 (9.8)	16 (6.9)	
External causes	17 (7.2)*	7 (3.0)	
Gastric/abdominal disease	8 (3.4)	32 (13.9)*	
Cancer	8 (3.3)	5 (2.2)	
Renal/urological disease	7 (3.0)	12 (5.2)	
Other	6 (2.6)	4 (1.7)	
Comorbidities			
Hypertension	87 (37.0)	95 (41.1)	0.416
Smoking	59 (25.1)	63 (27.3)	0.670
Alcoholism	44 (18.7)	36 (15.6)	0.438
Diabetes	35 (14.9)	42 (18.2)	0.406
Heart disease	21 (8.9)	31 (13.4)	0.165
COPD/asthma	18 (7.7)	15 (6.5)	0.757
Neurological disease	18 (7.7)	5 (2.2)	0.012
Drug addiction	12 (5.1)	5 (2.2)	0.148
Dyslipidemia	6 (2.6)	8 (3.5)	0.761
Cancer	3 (1.3)	2 (0.9)	1.000
Kidney disease	7 (3.0)	1 (0.4)	0.068
SAPS 3	50.8 ± 15.7	52.8 ± 15.1	0.163
SOFA score on admission	6 [3-9]	4 [1-7]	0.036
SOFA score 48 h after admission	4 [1-8]	4 [1-7]	0.494

SAPS 3: Simplified Acute Physiology Score 3; and SOFA: Sequential Organ Failure Assessment. [a]Values expressed as n (%), mean ± SD, or median [interquartile range]. *Statistically significant association as assessed by analysis of adjusted residuals at a significance level of 5%.

One of the contributions of the present study was the examination of the possible impact that a checklist tailored to the local context has on the duration of IMV and length of ICU stay. The results suggest that multidisciplinary team involvement in the development and implementation of checklists leads to better results. However, further studies are needed in order to confirm that.

The risk of information bias was minimized by the fact that data were collected from electronic medical records by individuals who were not involved in patient care, as well as by the fact that none of the health care professionals using the checklist were aware of the study.

The present study confirms the findings of previous studies[16-22] and provides the impetus for future studies in different contexts, as well as for future validation studies.

Limitations of the present study include the use of historical data, the lack of validation of the checklist, the lack of randomization, and the issue

Table 2. Patient outcomes, by group.[a]

Variable	Group		p
	Pre-intervention (n = 235)	Post-intervention (n = 231)	
Length of hospital stay, days			
Prior to ICU admission	2 [< 1-6]	1 [< 1-6]	0.371
ICU stay	8 [4-17]	5 [3-11]	< 0.001
After ICU discharge	5 [< 1-12]	2 [< 1-7]	0.095
Duration of invasive mechanical ventilation, days	5 [1-12]	2 [< 1-7]	< 0.001
Reintubation within 48 h	11 (4.7)	6 (2.6)	0.341
Readmission within 48 h	4 (1.7)	3 (1.3)	1.000
ICU mortality	57 (24.3)	59 (25.5)	0.831
In-hospital mortality	73 (31.1)	76 (32.9)	0.745

[a]Values expressed as n (%) or median [interquartile range].

Table 3. Backward stepwise multiple linear regression for factors associated with the duration of invasive mechanical ventilation and length of ICU stay.

Variable	β	p
Length of ICU stay*		
Post-intervention	−0.182	< 0.001
Age	0.114	0.023
Admission for trauma	0.187	< 0.001
Diagnosis of respiratory disease on admission	0.099	0.023
SAPS 3	0.164	< 0.001
Reintubation within 48 h	0.176	< 0.001
Duration of mechanical ventilation**		
Post-intervention	−0.111	0.002
Admission for trauma	0.164	< 0.001
Diagnosis of respiratory disease on admission	0.094	0.014
Diagnosis of renal/urological disease on admission	−0.144	< 0.001
SOFA score on admission	0.561	< 0.001
Reintubation within 48 h	0.110	0.002

SAPS 3: Simplified Acute Physiology Score 3; and SOFA: Sequential Organ Failure Assessment. *Variables in the multivariate model: pre-intervention, post-intervention, age, reason for ICU admission, diagnosis on admission (external causes, neurological disease, heart disease, respiratory disease, cancer, renal/urological disease, hemodynamic instability, or metabolic disease), infections (community-acquired or nosocomial infections), foci of infection (nervous system, lung, urinary tract, bloodstream), SAPS 3, sepsis, septic shock, SOFA score, and reintubation. **Variables in the multivariate model: post-intervention, evaluation period, age, reason for ICU admission, diagnosis on admission (external causes, neurological disease, heart disease, respiratory disease, cancer, renal/urological disease, hemodynamic instability or metabolic disease), SAPS 3, SOFA score, and reintubation within 48 h.

of external validity (i.e., the generalizability of the study findings). However, our study has high internal validity because the participating ICUs are referral ICUs for 48 municipalities in the Brazilian state of Rio Grande do Sul.

In summary, the implementation of a checklist during daily multidisciplinary rounds was associated with a reduction in the duration of IMV and length of ICU stay in the study population. Multicenter randomized controlled studies are needed in order to confirm these findings.

REFERENCES

1. Combes A, Costa MA, Trouillet JL, Baudot J, Mokhtari M, Gibert C, et al. Morbidity, mortality, and quality-of-life outcomes of patients requiring >or=14 days of mechanical ventilation. Crit Care Med. 2003;31(5):1373-1381. https://doi.org/10.1097/01.CCM.0000065188.87029.C3
2. Esteban A, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA. 2002;287(3):345-355. https://doi.org/10.1001/jama.287.3.345
3. Nassar Junior AP, Park M. Daily sedative interruption versus intermittent sedation in mechanically ventilated critically ill patients: a randomized trial. Ann Intensive Care. 2014;4:14. https://doi.org/10.1186/2110-5820-4-14
4. Mehta S, Burry L, Cook D, Fergusson D, Steinberg M, Granton J, Herridge M, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial [published correction appears in JAMA. 2013 Jan 16;309(3):237]. JAMA. 2012;308(19):1985-1992. https://doi.org/10.1001/jama.2012.13872
5. Hooper MH, Girard TD. Sedation and weaning from mechanical

ventilation: linking spontaneous awakening trials and spontaneous breathing trials to improve patient outcomes. Crit Care Clin. 2009;25(3):515-viii. https://doi.org/10.1016/j.ccc.2009.04.002

6. Nery P, Pastore L, Carvalho CR, Schettino G. Shortening ventilatory support with a protocol based on daily extubation screening and noninvasive ventilation in selected patients. Clinics (Sao Paulo). 2011;66(5):759-766. https://doi.org/10.1590/S1807-59322011000500009
7. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372(8):747-755. https://doi.org/10.1056/NEJMsa1410639
8. Mechanical Ventilation Committee of the Brazilian Intensive Care Medicine Association; Commission of Intensive Therapy of the Brazilian Thoracic Society. Brazilian recommendations of mechanical ventilation 2013. Part I. J Bras Pneumol. 2014;40(4):327–363. https://doi.org/10.1590/S1806-37132014000400002
9. Brazilian recommendations of mechanical ventilation 2013. Part 2. J Bras Pneumol. 2014;40(5):458–486. https://doi.org/10.1590/S1806-37132014000500003
10. Elliott D. Measuring the health outcomes of general ICU patients: a systematic review of methods and findings. Aust Crit Care. 1999;12(4):132-140. https://doi.org/10.1016/S1036-7314(99)70598-9
11. Azevedo LC, Park M, Salluh JI, Rea-Neto A, Souza-Dantas VC, Varaschin P, et al. Clinical outcomes of patients requiring ventilatory support in Brazilian intensive care units: a multicenter, prospective, cohort study. Crit Care. 2013;17(2):R63. https://doi.org/10.1186/cc12594
12. Weiss CH, Moazed F, McEvoy CA, Singer BD, Szleifer I, Amaral LA, et al. Prompting physicians to address a daily checklist and process of care and clinical outcomes: a single-site study. Am J Respir Crit Care Med. 2011;184(6):680-686. https://doi.org/10.1164/rccm.201101-0037OC
13. Lane D, Ferri M, Lemaire J, McLaughlin K, Stelfox HT. A systematic review of evidence-informed practices for patient care rounds in the ICU*. Crit Care Med. 2013;41(8):2015-2029. https://doi.org/10.1097/CCM.0b013e31828a435f
14. Khorfan F. Daily goals checklist–a goal-directed method to eliminate nosocomial infection in the intensive care unit. J Healthc Qual. 2008;30(6):13-17. https://doi.org/10.1111/j.1945-1474.2008.tb01165.x
15. Conroy KM, Elliott D, Burrell AR. Validating a process-of-care checklist for intensive care units. Anaesth Intensive Care. 2013;41(3):342-348. https://doi.org/10.1177/0310057X1304100311
16. Writing Group for the CHECKLIST-ICU Investigators and the Brazilian Research in Intensive Care Network (BRICNet), Cavalcanti AB, Bozza FA, Machado FR, Salluh JI, Campagnucci VP, et al. Effect of a Quality Improvement Intervention With Daily Round Checklists, Goal Setting, and Clinician Prompting on Mortality of Critically Ill Patients: A Randomized Clinical Trial. JAMA. 2016;315(14):1480-1490. https://doi.org/10.1001/jama.2016.3463
17. Silva CS, Timenetsky KT, Taniguchi C, Calegaro S, Azevedo CS, Stus R, et al. Low mechanical ventilation times and reintubation rates associated with a specific weaning protocol in an intensive care unit setting: a retrospective study. Clinics (Sao Paulo). 2012;67(9):995-1000. https://doi.org/10.6061/clinics/2012(09)02
18. Roquilly A, Cinotti R, Jaber S, Vourc'h M, Pengam F, Mahe PJ, et al. Implementation of an evidence-based extubation readiness bundle in 499 brain-injured patients. a before-after evaluation of a quality improvement project. Am J Respir Crit Care Med. 2013;188(8):958-966. https://doi.org/10.1164/rccm.201301-0116OC
19. Rose L, Blackwood B, Egerod I, Haugdahl HS, Hofhuis J, Isfort M, et al. Decisional responsibility for mechanical ventilation and weaning: an international survey. Crit Care. 2011;15(6):R295. https://doi.org/10.1186/cc10588
20. Yoo EJ, Edwards JD, Dean ML, Dudley RA. Multidisciplinary Critical Care and Intensivist Staffing: Results of a Statewide Survey and Association With Mortality. J Intensive Care Med. 2016;31(5):325-332. https://doi.org/10.1177/0885066614534605
21. Eulmesekian P, Pérez A, Díaz S, Ferrero M. Implementation of a checklist to increase adherence to evidence-based practices in a single pediatric intensive care unit. Arch Argent Pediatr. 2017;115(5):446-452. https://doi.org/10.5546/aap.2017.eng.446
22. Nunez RM, Perdomo HA, Chavez IC. Quality Improvement Intervention and Mortality of Critically Ill Patients. JAMA. 2016;316(8):879. https://doi.org/10.1001/jama.2016.9269
23. Fialkow L, Farenzena M, Wawrzeniak IC, Brauner JS, Vieira SR, Vigo A, et al. Mechanical ventilation in patients in the intensive care unit of a general university hospital in southern Brazil: an epidemiological study. Clinics (Sao Paulo). 2016;71(3):144-151. https://doi.org/10.6061/clinics/2016(03)05
24. Loss SH, de Oliveira RP, Maccari JG, Savi A, Boniatti MM, Hetzel MP, et al. The reality of patients requiring prolonged mechanical ventilation: a multicenter study. Rev Bras Ter Intensiva. 2015;27(1):26-35. https://doi.org/10.5935/0103-507X.20150006
25. Walsh TS, Dodds S, McArdle F. Evaluation of simple criteria to predict successful weaning from mechanical ventilation in intensive care patients. Br J Anaesth. 2004;92(6):793-799. https://doi.org/10.1093/bja/aeh139
26. Russ S, Rout S, Sevdalis N, Moorthy K, Darzi A, Vincent C. Do safety checklists improve teamwork and communication in the operating room? A systematic review. Ann Surg. 2013;258(6):856-871. https://doi.org/10.1097/SLA.0000000000000206
27. Yoo EJ, Edwards JD, Dean ML, Dudley RA. Multidisciplinary Critical Care and Intensivist Staffing: Results of a Statewide Survey and Association With Mortality. J Intensive Care Med. 2016;31(5):325-332. https://doi.org/10.1177/0885066614534605
28. Brilli RJ, Spevetz A, Branson RD, Campbell GM, Cohen H, Dasta JF, et al. Critical care delivery in the intensive care unit: defining clinical roles and the best practice model. Crit Care Med. 2001;29(10):2007-2019. https://doi.org/10.1097/00003246-200110000-00026
29. Nassar AP Jr, Zampieri FG, Salluh JI, Bozza FA, Machado FR, Guimarães HP, et al. Organizational factors associated with target sedation on the first 48 h of mechanical ventilation: an analysis of checklist-ICU database. Crit Care. 2019;23(1):34. https://doi.org/10.1186/s13054-019-2323-y
30. Soares M, Bozza FA, Angus DC, Japiassú AM, Viana WN, Costa R, et al. Organizational characteristics, outcomes, and resource use in 78 Brazilian intensive care units: the ORCHESTRA study. Intensive Care Med. 2015;41(12):2149-2160. https://doi.org/10.1007/s00134-015-4076-7
31. Ersson A, Beckman A, Jarl J, Borell J. Effects of a multifaceted intervention QI program to improve ICU performance. BMC Health Serv Res. 2018;18(1):838. https://doi.org/10.1186/s12913-018-3648-y

J Bras Pneumol. 2020;46(3):e20190095
https://dx.doi.org/10.36416/1806-3756/e20190095

Comparison between the health-related quality of life of children/adolescents with asthma and that of their caregivers: a systematic review and meta-analysis

Cristian Roncada[1], Tássia Machado Medeiros[2,3], Márcio Júnior Strassburger[4], Simone Zeni Strassburger[4], Paulo Márcio Pitrez[2]

1. Centro Universitário da Serra Gaúcha – FSG – Porto Alegre (RS) Brasil.
2. Programa de Pós-Graduação em Medicina e Ciências da Saúde, Pontifícia Universidade Católica do Rio Grande do Sul – PUCRS – Porto Alegre (RS) Brasil.
3. Serviço de Radiologia, Hospital Unimed Noroeste Ijuí, Ijuí (RS) Brasil.
4. Departamento de Ciências da Vida, Universidade Regional do Noroeste do Estado do Rio Grande do Sul – UNIJUI – Ijuí (RS) Brasil.

Submitted: 19 March 2019.
Accepted: 18 July 2019.

Study carried out at the Universidade Regional do Noroeste do Estado do Rio Grande do Sul – UNIJUI – Ijuí (RS) Brasil.

ABSTRACT

Objective: To evaluate the health-related quality of life (HRQoL) of children/adolescents with asthma and that of their caregivers, comparing the two. **Methods:** This was a systematic review and meta-analysis based on the criteria of Preferred Reporting Items for Systematic Reviews and Meta-Analyses, with a strategy of searching five health-related databases (MEDLINE/PubMed, EMBASE, ScienceDirect, SciELO, and LILACS). We included studies that evaluated the HRQoL of children/adolescents with asthma and that of their caregivers with the Pediatric Asthma Quality of Life Questionnaire and the Pediatric Asthma Caregiver's Quality of Life Questionnaire, respectively, using the total scores and the scores on the domains activity limitation, symptoms (children/adolescents only), and emotional function. **Results:** We identified 291 articles, and we evaluated 133 of those. A total of 33 articles, collectively including 4,101 subjects, were included in the meta-analysis. An analysis stratified by study design showed no differences between the HRQoL of the caregivers and that of the children/adolescents in the activity limitation domain and in the total score. However, the mean emotional function domain scores were significantly higher (better) among children/adolescents with asthma than among their caregivers in longitudinal studies—$\Delta = 0.82$ (0.21-1.44)—and randomized clinical trials—$\Delta = 0.52$ (0.29-0.79)—although not in cross-sectional studies—$\Delta = -0.20$ (−0.03 to 0.43). **Conclusions:** The total HRQoL scores proved to be similar between children/adolescents with asthma and their caregivers. However, the two groups differed in their perception of their emotional function, the caregivers scoring significantly lower than the children/adolescents in that domain.

Keywords: Asthma; Quality of life; Surveys and questionnaires.

INTRODUCTION

Asthma is a chronic inflammatory disease that affects individuals of all ages, especially children. Asthma is considered a global health problem, affecting 300 million people worldwide,[1] and it is estimated that there are approximately 20 million individuals with asthma in Brazil. In pediatric patients, the prevalence of asthma is 20%.[2,3]

Asthma affects not only the patient but also their family. Over time, asthma can negatively affect the quality of life (QoL) of children and adolescents, as well as that of their parents and family members.[4]

The World Health Organization Quality of Life Group defines QoL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns".[5] Therefore, for a complete picture of patient health status, conventional clinical indices and health-related QoL (HRQoL) must be assessed.[6]

Parents and family members play an important role in the QoL of children and adolescents with asthma. Parental perception of asthma severity is an important determinant of asthma management and control.[7,8] In the process of caring for a child or adolescent with asthma, parents and family members should have a correct perception of the disease.[9]

Pediatric chronic disease negatively affects family function and HRQoL. Parents and family members of children and adolescents with chronic disease have concerns and responsibilities related to the health needs of their children, educational/medical services, disease costs, missed social opportunities, and work absenteeism, as well as having to cope with physical and emotional problems.[10]

In this context, the objective of the present study was to evaluate the HRQoL of children and adolescents with asthma and that of their caregivers, comparing the two.

Correspondence to:
Márcio Junior Strassburger. Rua do Comércio, 3000, Bairro Universitário, CEP 98700-000, Ijuí, RS, Brasil.
Tel.: 55 55 3332-0461. E-mail: marcio.s@unijui.edu.br
Financial support: None.

ISSN 1806-3713

METHODS

This was a meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria,[11] with a strategy of searching five health-related databases for studies assessing disease control in children and adolescents with asthma, as well as the HRQoL of the patients and their parents and family members.

We included studies that evaluated the HRQoL of children/adolescents with asthma and that of their caregivers with the Pediatric Asthma Quality of Life Questionnaire (PAQLQ)[12] and the Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ),[13] respectively, using the total scores and the scores on the domains activity limitation, symptoms (children/adolescents only), and emotional function. The primary outcome measure was a comparison of the total scores and the scores on the domains activity limitation and emotional function between the two groups (i.e., children/adolescents with asthma and their parents/caregivers).

Search strategy

The search strategy included the following terms and Boolean operators: (Asthma AND (PAQLQ OR "Pediatric Asthma Quality of Life Questionnaire") AND (PACQLQ OR "Pediatric Asthma Caregiver's Quality of Life Questionnaire"). We searched the following databases: MEDLINE (PubMed); EMBASE and ScienceDirect (Elsevier); and SciELO and LILACS (BIREME). All searches were performed in October of 2018, and no date limits were applied to the searches.

Searches were limited to title, keyword, and abstract fields. In the MEDLINE (PubMed) database, for example, we employed the following search strategy: (Asthma[Title/Abstract] OR Asthma[MeshTerms]) AND (PAQLQ[Title/Abstract] OR PAQLQ[MeshTerms] OR "Pediatric Asthma Quality of Life Questionnaire"[Title/Abstract] OR "Pediatric Asthma Quality of Life Questionnaire"[MeshTerms]) AND (PACQLQ[Title/Abstract] OR PACQLQ[MeshTerms] OR "Pediatric Asthma Caregiver's Quality of Life Questionnaire"[Title/Abstract] OR "Pediatric Asthma Caregiver's Quality of Life Questionnaire"[MeshTerms]). Searches were not limited by language of publication or target audience. Potentially eligible articles were exported from the aforementioned health-related databases as .txt (MEDLINE), .bib (BibiTeX), or .ris (RIS) files including the following data: author names, article title, keywords, journal of publication, year of publication, type of article, and abstract.

Identification, selection bias, inclusion criteria, and study characteristics

The StArt (State of the Art through Systematic Review) software, developed by the Federal University of São Carlos Software Engineering Research Laboratory (located in the city of São Carlos, Brazil) and designed specifically for systematic reviews,[14] was used in order to design a flow chart of the article selection process, including the following steps: a) Identification: identification of potentially eligible studies; b) Selection: exclusion of duplicates and screening by reading titles and abstracts; c) Eligibility: screening by reading the full text; and d) Inclusion: eligible studies meeting the inclusion criteria. Each step of the process was performed by two researchers and reviewed by a third, the criteria for article selection being as follows: inclusion of all articles selected by both researchers; exclusion of all articles selected by neither researcher; inclusion of all articles selected by only one researcher but meeting the inclusion criteria according to the reviewer. To identify additional studies (gray literature) for inclusion, we carried out a hand search of the references cited in the studies selected during the Eligibility step of the article selection process (i.e., screening by reading the full text).

The studies included in the systematic review were cross-sectional studies or early-phase longitudinal studies, case-control studies, or randomized clinical trials that used primary or secondary data on total and domain scores on the PAQLQ (children/adolescents with asthma) and PACQLQ (parents/caregivers).[12,13] We excluded studies in which the HRQoL of children/adolescents with asthma and that of their parents/caregivers was assessed by instruments other than the PAQLQ and PACQLQ.

Data extraction and presentation

We extracted and tabulated data on the characteristics of each eligible study, including the name of the first author, year of publication, study site, study design, patient age, and study participants. The eligibility criteria for data extraction were the same as the criteria used in order to classify the sample and included patient age, sex, race, asthma severity/level of asthma control, physician-diagnosed rhinitis/atopy, lung function, and fractional exhaled nitric oxide. For comparative analysis, we extracted data on total and domain scores on the PAQLQ and PACQLQ.[12,13]

Data are presented so as to demonstrate values for each study design, general study characteristics (author(s) and year of publication), and participant characteristics, as well as weighted means of total scores, activity limitation domain scores, and emotional function domain scores on the HRQoL questionnaires.

Statistical analysis

For the meta-analysis of the outcome measures, we used the Review Manager software, version 5.3 (RevMan 5; Cochrane Collaboration, Oxford, UK),[15] using random-effects models and inverse variance weighting to calculate the (bivariate) mean difference rate, with 95% CIs, heterogeneity (I^2), and total overall effect size (Z). The level of significance was set at $p < 0.05$ for mean total and domain HRQoL scores for within-group and between-group comparisons by study design: cross-sectional studies, longitudinal (cohort) studies, and randomized clinical trials.

Systematic review registration

The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) prior to research activities (Registration no. CRD42017081293).

RESULTS

A total of 129 articles were retrieved from the health-related databases: MEDLINE/PubMed (n = 22), EMBASE (n = 55), ScienceDirect (n = 43), SciELO (n = 4), and LILACS (n = 5). Another 5 were added from the gray literature. Therefore, a total of 134 articles were initially selected for inclusion. Of those 133 articles, 100 were excluded. Of those, 9 were duplicates (appearing in more than one database), 78 were screened out following a review of titles and abstracts, and 13 were screened out following full-text assessment. Therefore, as can be seen in Figure 1, a total of 33 studies were included in the meta-analysis.[16-48]

Of the 33 included studies,[16-48] 28 (85%) were published in the last decade, evaluating children and adolescents in the 2- to 18-year age bracket. With regard to study design, 15 (45.4%) were randomized clinical trials, 11 (33%) were cross-sectional studies, and 7 (21.2%) were longitudinal (cohort) studies. With regard to study site, 17 (48%) were conducted in Europe, 12 (36%) were conducted in North or South America, 4 (12%) were conducted in Asia, and 1 (3%) was conducted in Africa (Table 1).

Table 2 shows the weighted values for the 33 studies included in the systematic review. The studies collectively included a total of 4,101 participants (children/adolescents with asthma and their parents/caregivers) assessed for QoL by total PAQLQ and PACQLQ scores, respectively.[12,13]

Figure 2 shows a comparison of activity limitation domain scores between children/adolescents with asthma and their caregivers, by study design. A total of 8 cross-sectional studies collectively assessed 1,295 participants (caregivers/children), showing high heterogeneity (I^2 = 97%) and a total effect size with no significant difference in mean scores between the two groups (Z = 1.06; p = 0.290). A total of 6 longitudinal studies collectively assessed 661 participants, showing high heterogeneity (I^2 = 98%) and Z = 0.07 (p = 0.940). A total of 8 randomized clinical trials collectively assessed 840 participants, showing high heterogeneity (I^2 = 98%) and Z = 0.96 (p = 0.340).

These results were reflected in the total weighted mean, with no between-group differences in activity limitation domain scores among 2,796 participants and with high within-group heterogeneity (I^2 = 98%; p < 0.001), high but not significant between-group

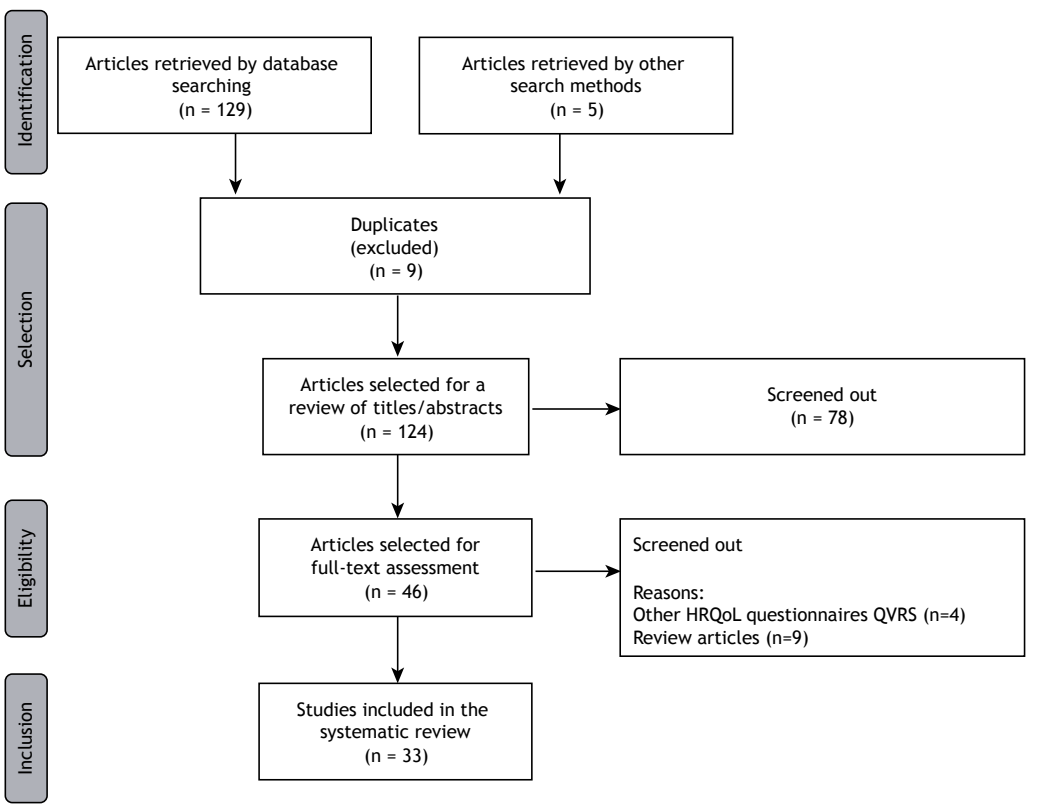


Figure 1. Flow chart of the article selection process, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria.[11] HRQoL: health-related quality of life.

Table 1. General characteristics of the included studies (N = 33), including the total number of participants (N = 4,101).

Author	Year	Country	Study design	Age of asthma patients, years	Study participants, n
Ahmed et al.[16]	2016	Nigeria	Longitudinal	7-17	43
Almomani et al.[17]	2017	Jordan	RCT	7-18	206
Ammari et al.[18]	2017	UK	RCT	7-17	76
Berger et al.[19]	2010	USA	RCT	6-11	186
Burks et al.[20]	2013	USA	Cross-sectional	5-17	79
Bushnell et al.[21]	2003	USA	Cross-sectional	7-17	104
Cano-Garcinuño et al.[22]	2007	Spain	RCT	9-13	245
Ducret et al.[23]	2013	Switzerland	Longitudinal	4-12	54
Erickson et al.[24]	2002	USA	Cross-sectional	9-17	99
Fleming et al.[25]	2015	UK	Longitudinal	6-17	271
Halterman et al.[26]	2011	USA	Longitudinal	12-15	30
Juniper et al.[27]	2010	Canada	Cross-sectional	6-16	35
Kamps et al.[28]	2003	The Netherlands	RCT	2-16	74
Lang et al.[29]	2015	USA	Longitudinal	10-17	56
Lenney et al.[30]	2013	UK	RCT	6-14	63
Liu et al.[31]	2016	China	RCT	9-13	72
Meza et al.[32]	2012	Colombia	Longitudinal	2-15	168
Minard et al.[33]	2011	Canada	Cross-sectional	7-17	63
Minard et al.[34]	2016	Canada	Cross-sectional	7-17	126
Moreira et al.[35]	2008	Portugal	RCT	8-17	34
Murray et al.[36]	2017	UK	RCT	3-17	284
Mussaffi et al.[37]	2007	Israel	RCT	7-17	115
Nair et al.[38]	2014	India	Longitudinal	7-17	69
Ovšonková et al.[39]	2012	Slovakia	Cross-sectional	7-17	72
Strunk et al.[40]	2008	USA	RCT	6-17	55
Szabó et al.[41]	2010	Hungary	Cross-sectional	7-17	102
Tibosch et al.[42]	2010	The Netherlands	Cross-sectional	6-16	339
van Bragt et al.[43]	2015	The Netherlands	RCT	6-11	29
van Gent et al.[44]	2007	The Netherlands	Cross-sectional	7-10	413
Voorend-van Bergen et al.[45]	2014	The Netherlands	RCT	4-18	197
Voorend-van Bergen et al.[46]	2015	The Netherlands	RCT	4-18	270
Williams et al.[47]	2003	UK	Cross-sectional	7-17	42
Yun et al.[48]	2012	USA	RCT	7-17	30

RCT: randomized controlled trial.

homogeneity (I^2 = 0%; p = 0.789), and a low total overall effect size (Z = 1.81; p = 0.070).

Figure 3 shows a comparison of emotional function domain scores between children/adolescents with asthma and their caregivers, by study design. A total of 8 cross-sectional studies collectively assessed 1,295 participants, showing high heterogeneity (I^2 = 82%; p < 0.001) and a low overall effect size (Z = 1.73; p = 0.080). A total of 5 longitudinal studies collectively assessed 390 subjects, showing high heterogeneity (I^2 = 93%; p < 0.001). However, there was a significant difference between children/adolescents with asthma and their caregivers regarding the weighted means (Δ = 0.82; 95% CI: 0.213-1.44), with a high overall effect size (Z = 2.61; p = 0.009). A total of 7 randomized clinical trials collectively assessed 806 participants, showing high heterogeneity (I^2 = 82%; p < 0.001), the significant difference between children/adolescents with asthma and their caregivers regarding the weighted means (Δ = 0.63; 95% CI: 0.36-0.90) being reflected in the overall effect size (Z = 4.49; p < 0.001).

The total weighted mean of emotional function domain scores showed that they were higher (better) among children/adolescents with asthma than among their caregivers. A total of 2,491 participants were assessed. Although heterogeneity was high (I^2 = 93%; p < 0.001), the total overall effect size was moderate (Z = 4.52; p < 0.001), with a statistically significant difference between the two groups (Δ = 0.52; 95% CI: 0.29-0.75). In addition, there was moderate between-group heterogeneity among study designs (I^2 = 73.4%; p < 0.05), with longitudinal studies showing the highest mean (Δ = 0.82; 95% CI: 0.21-1.44) and cross-sectional studies showing the lowest mean (Δ = −0.20; 95% CI: −0.03 to 0.43).

A comparison of the weighted means of total HRQoL scores between children/adolescents with asthma

Table 2. Weighted characteristics of the analyzed sample (N = 4,101).[a]

Characteristic	Result
Total sample[b]	4,101 (100.0)
Children/adolescents with asthma	
Male sex (n = 4,101)	2,495 (60.8)
Age, years (n = 3,660)	10.3 ± 4.0
White (n = 1,018)	699 (68.7)
Mild/moderate asthma (n = 1,149)	896 (78.0)
Pharmacological treatment (n = 2,549)	
MDI	1,240 (48.7)
SABA	814 (31.9)
LABA	495 (19.4)
Controlled asthma (n = 1,063)	576 (54.2)
ACQ (n = 585)	1.0 ± 0.8
C-ACT (n = 553)	21.4 ± 2.6
ACT (n = 1,000)	20.2 ± 2.8
Rhinitis (n = 422)	157 (37.2)
Atopia (n = 441)	307 (69.5)
Lung function	
FEV_1, % predicted (n = 2,303)	92.0 ± 14.6
FVC, % predicted (n = 1,427)	97.3 ± 13.8
FEV_1/FVC (n = 495)	0.8 ± 0.1
FeNO (n = 858)	31.4 ± 16.9
PAQLQ (children/adolescents)	
Activity limitation (n = 2,796)	5.1 ± 1.1
Symptoms (n = 2,618)	5.2 ± 1.1
Emotional function (n = 2,796)	5.6 ± 1.0
Total score (n = 4,101)	5.5 ± 1.0
PACQLQ (caregivers)	
Activity limitation (n = 2,491)	5.3 ± 1.2
Emotional function (n = 2,607)	5.1 ± 1.1
Total score (n = 4,101)	5.4 ± 1.0

MDI: metered dose inhaler; SABA: short-acting β_2 agonist; LABA: long-acting β_2 agonist; ACQ: Asthma Control Questionnaire; C-ACT: Childhood Asthma Control Test; ACT: Asthma Control Test; FeNO: fractional exhaled nitric oxide; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; and PACQLQ: Pediatric Asthma Caregiver's Quality of Life Questionnaire. [a]Values expressed as n (%) or mean ± SD. [b]Total number of individuals assessed (children/adolescents + parents/caregivers).

and their caregivers (N = 4,101; Figure 4) showed high within-group heterogeneity by study design and a statistically insignificant total effect size, being reflected in the overall between-group heterogeneity (I^2 = 96%; Δ = 0.03 [95% CI: −0.10 to −0.17]), with a total overall effect size of Z = 0.49 (p = 0.620).

DISCUSSION

Asthma is a chronic noncommunicable disease with a high global burden, resulting in high rates of work/school absenteeism, as well as in increased emergency room visits and hospitalizations, primarily due to a lack of medical diagnosis and to government neglect of asthma management.[1]

In the last two decades, the assessment of HRQoL in children/adolescents with asthma and their families has gained a prominent role in the management (treatment and control) of asthma. Pharmacological treatment adherence and symptom control, as well as self-perceived physical, emotional, and social well-being among patients and their families, play a crucial role in effective disease management.[49]

In the present study, we conducted a meta-analysis of studies assessing total and individual domain scores on previously validated and widely used HRQoL questionnaires, performing an analysis stratified by study design. Longitudinal studies and randomized clinical trials showed that mean emotional function domain scores were significantly higher (better) among children/adolescents with asthma than among their caregivers, the difference between mean scores being greatest in longitudinal studies. Although there was no significant difference in mean emotional function domain scores across cross-sectional studies, the magnitude of the difference between the two groups remained the same in the overall analysis. These results corroborate the hypothesis that parents/caregivers are more emotionally affected by asthma than are their children, because parents/caregivers have concerns and responsibilities related to the health needs of their children. Self-perceived emotional functioning among parents/caregivers can vary depending on the age of the children, the negative impact of asthma on emotional function being greater on parents/caregivers of younger children.[41,50,51] With regard to activity limitation domain scores, no significant differences were found between children/adolescents with asthma and their caregivers. Previous studies[47,51] have shown that activity limitation assessment is affected by the fact that caregivers tend to assign lower activity limitation domain scores to asthma patients than do the patients themselves. With regard to total HRQoL scores, no significant differences were found between children/adolescents with asthma and their caregivers.

HRQoL questionnaires play an important role in assessing the health status of children and adolescents with asthma. However, the level of agreement between children/adolescents with asthma and their caregivers regarding HRQoL was found to range from low to moderate. Of the 33 studies included in the present review, 6 were aimed at correlating the QoL of children with that of their caregivers.[16,33,38,39,47,52] Nair et al.[38] correlated the QoL of children with asthma and that of their parents with asthma treatment. In 69 children in the 7- to 17-year age bracket, asthma treatment had no impact on the scores on the emotional function domain of the PAQLQ, and caregivers failed to understand the psychological effects of asthma on their children. In addition, asthma treatment had no impact on PACQLQ scores.

Minard et al.[33] studied 63 children in the 7- to 17-year age bracket, comparing the original versions of the PAQLQ and PACQLQ with their electronic

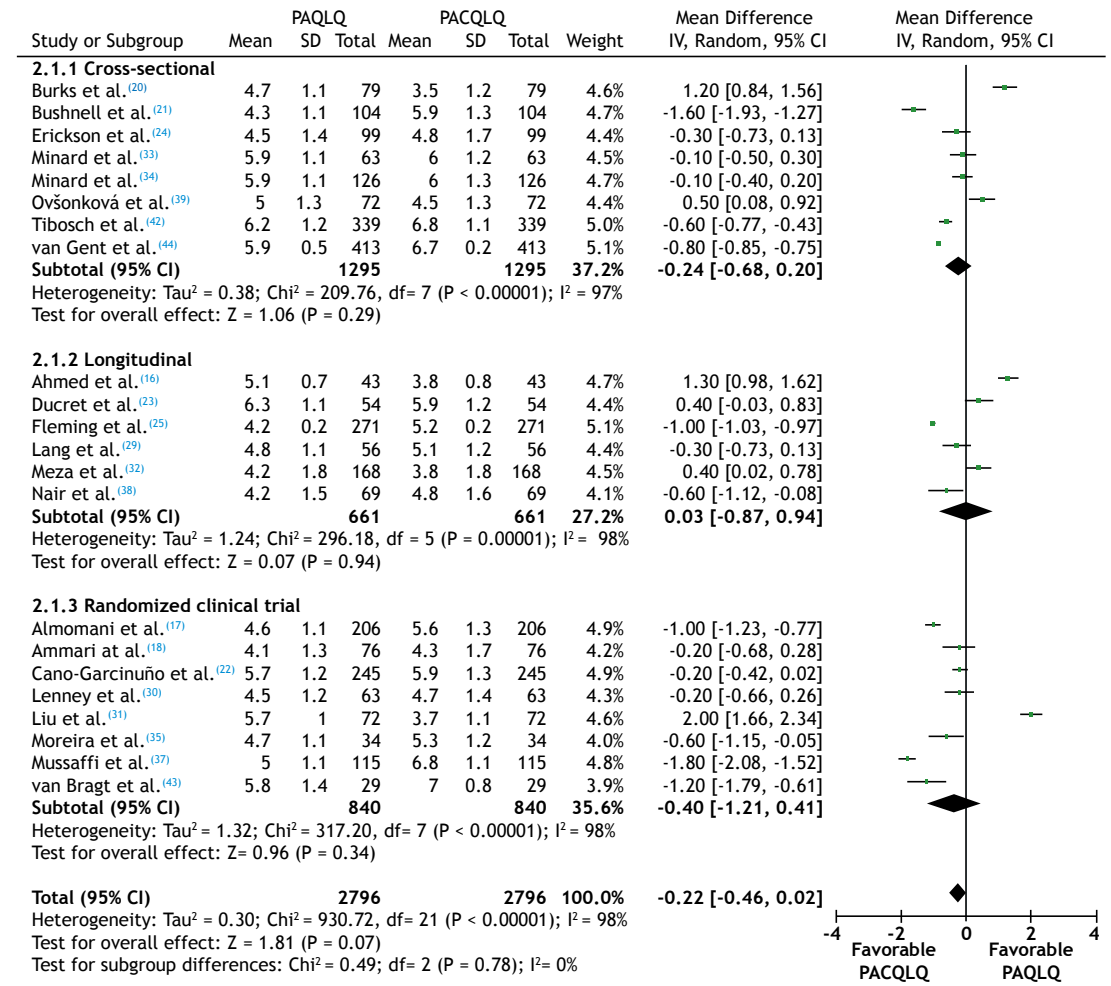


Figure 2. Comparison between mean Pediatric Asthma Quality of Life Questionnaire (PAQLQ) and Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) activity limitation domain scores.

versions and correlating PAQLQ scores with PACQLQ scores; the authors demonstrated the validity of the electronic versions of the questionnaires and the relationship between children/adolescents and their caregivers. In addition, they found no changes in activity limitations or symptoms.

Burks et al.[20] studied 79 patients in the 5- to 17-year age bracket and their caregivers, assessing the level of agreement between PAQLQ and PACQLQ scores. The scores were similar, with a moderate correlation between emotional function and overall QoL; however, children/adolescents had higher (better) activity limitation domain scores than those assigned by their caregivers (4.62 vs. 3.49; $p < 0.001$), a finding that suggests that QoL parameters should be assessed in both pediatric patients and their caregivers.

In a study involving 43 children/adolescents in the 7- to 16-year age bracket with varying levels of asthma severity,[16] activity limitation domain scores were found to be more severely affected in girls than in boys and in children/adolescents with severe/uncontrolled asthma than in those with less severe asthma. In addition, a significant positive correlation was found between total QoL scores and emotional function domain scores (4.98 vs. 4.86; $p = 0.015$). Williams & Williams[47] found a low correlation between the overall scores of children/adolescents and those of their caregivers ($r = 0.19$; $p = 0.18$), as well as no correlation between the QoL scores of the children/adolescents and the judgment of the clinician in charge regarding asthma control ($r = 0.02$; $p = 0.98$). The authors also found a low correlation between the activity limitation domain scores achieved by the children/adolescents and those assigned by their caregivers ($r = 0.01$; $p = 0.45$); the children/adolescents reported less limitation in activities than did their caregivers (4.8 vs. 4.1). Szabó et al.[41] reported that caregivers of children/adolescents with asthma have at least mild depressive symptoms and tend to have increased symptoms of anxiety.

The present meta-analysis showed high heterogeneity across studies in an analysis stratified by study design (within-group comparisons). Considerable variability was found across studies, as is often the case in

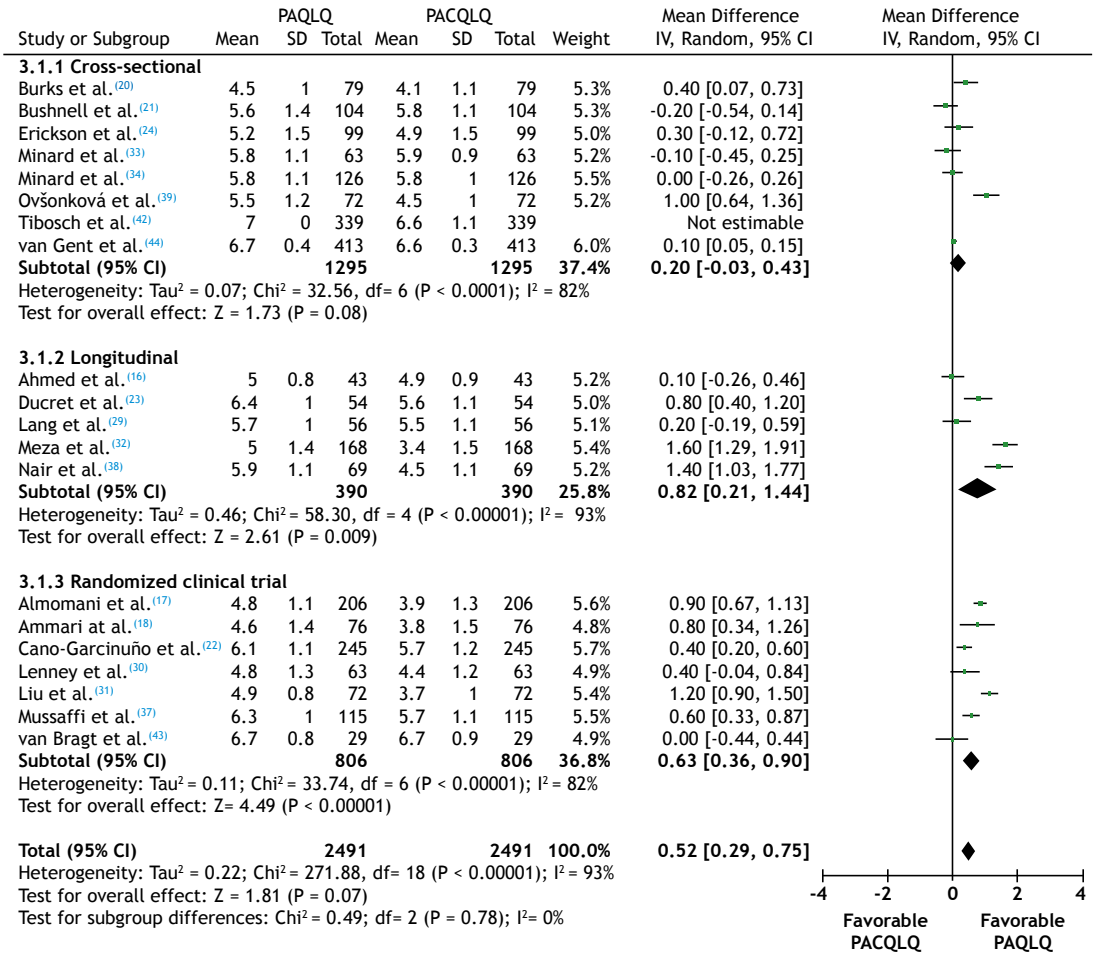


Figure 3. Comparison between mean Pediatric Asthma Quality of Life Questionnaire (PAQLQ) and Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) emotional function domain scores.

systematic reviews. Because asthma is multifactorial and the prevalence of asthma varies widely (2-33%), high heterogeneity is expected. In addition, factors such as study design, disease severity, geographic location, and socioeconomic status can increase heterogeneity.

Ovšonková et al.[39] showed that the level of asthma control has a statistically significant impact on the QoL of children/adolescents with asthma and on that of their caregivers, a better QoL in asthma patients translating to a better QoL in their caregivers. Voorend-van Bergen et al.[45] examined the validity of a Web-based diary in assessing asthma control in children/adolescents in the 4- to 18-year age bracket; for those under 12 years of age, the diary was completed by the caregivers. In that age group, the median PACQLQ score was 6.5, whereas, among adolescents, the mean PAQLQ score was slightly lower (6.2), PACQLQ and PAQLQ scores being significantly higher in children/adolescents with well-controlled asthma than in those with partly controlled or uncontrolled asthma ($p < 0.001$).[53]

Although every effort was made to minimize bias, the present study has some limitations. Because the results of the studies included in our meta-analysis were obtained by using subjective tools (HRQoL questionnaires), there is a possibility of recall bias. In addition, there is a possibility that patient age and level of education affected their understanding of the questions. Furthermore, there were differences across studies regarding the time elapsed between questionnaire administration and intervention implementation. Moreover, none of the included studies assessed the time spent by caregivers in the caregiving role; for example, children in whom symptoms are more severe tend to receive more attention and care from their caregivers.[37]

Our meta-analysis clearly showed that asthma can affect emotional function domain scores in patients and caregivers, the two groups differing in their perception of their emotional function. However, there were no differences between the two groups regarding activity limitation domain scores and total scores. Therefore, pediatric asthma patients and their families should be closely monitored, with special attention being given to the impact of asthma on their psychological and emotional functioning.

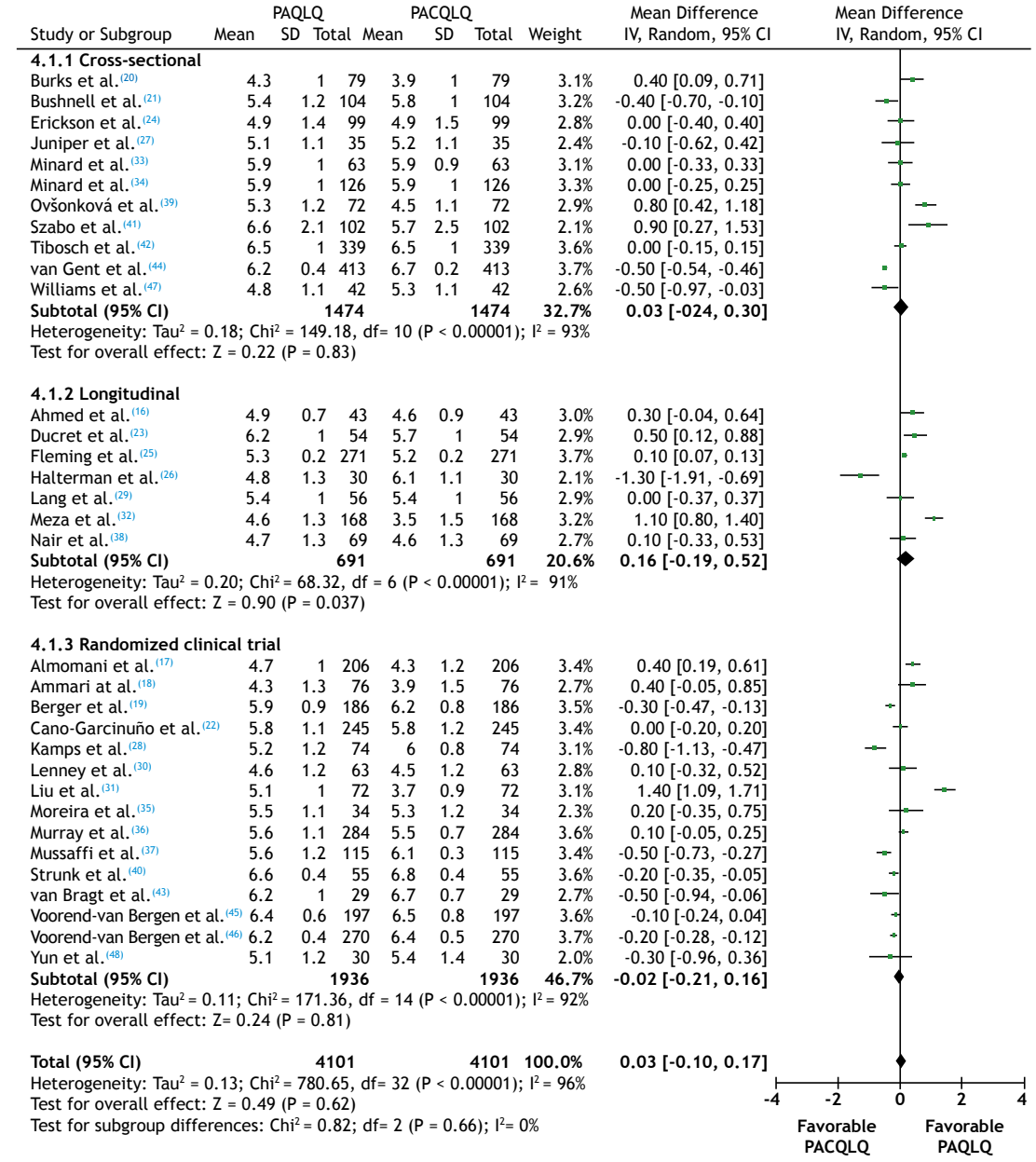


Figure 4. Comparison between mean total Pediatric Asthma Quality of Life Questionnaire (PAQLQ) and Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) scores.

REFERENCES

1. Global Initiative for Asthma (GINA) [homepage on the Internet]. Bethesda: GINA; c2017 [cited 2018 Mar 6]. 2017 GINA Report Global Strategy for Asthma Management and Prevention. Available from: http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/
2. Solé D, Camelo-Nunes IC, Wandalsen GF, Pastorino AC, Jacob CM, Gonzalez C, et al. Prevalence of symptoms of asthma, rhinitis, and atopic eczema in Brazilian adolescents related to exposure to gaseous air pollutants and socioeconomic status. J Investig Allergol Clin Immunol. 2007;17(1):6-13.
3. Roncada C, de Oliveira SG, Cidade SF, Sarria EE, Mattiello R, Ojeda BS, et al. Burden of asthma among inner-city children from Southern Brazil. J Asthma. 2016;53(5):498-504. https://doi.org/10.3109/02770903.2015.1108438
4. Nogueira KT. Avaliação da qualidade de vida entre adolescentes asmáticos [thesis]. Rio de Janeiro: Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro; 2007.
5. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med. 1995;41(10):1403-1409. https://doi.org/10.1016/0277-9536(95)00112-K
6. Juniper EF. How important is quality of life in pediatric asthma? Pediatr Pulmonol Suppl. 1997;15:17-21. https://doi.org/10.1002/(SICI)1099-0496(199709)15+<17::AID-PPUL5>3.0.CO;2-O
7. Mandhane PJ, McGhan SL, Sharpe HM, Wong E, Hessel PA, Befus AD, et al. A child's asthma quality of life rating does not significantly influence management of their asthma. Pediatr Pulmonol. 2010;45(2):141-148. https://doi.org/10.1002/ppul.21157
8. Park M, Chesla CK. Understanding complexity of Asian American

family care practices. Arch Psychiatr Nurs. 2010;24(3):189-201. https://doi.org/10.1016/j.apnu.2009.06.005

9. Payrovee Z, Kashaninia Z, Alireza Mahdaviani S, Rezasoltani P. Effect of Family Empowerment on the Quality of life of School-Aged Children with Asthma. Tanaffos. 2014;13(1):35-42.
10. Hockenberry MJ, Wilson D. Wong's nursing care of infants and children-E-book. Philadelphia: Elsevier Health Sciences; 2014.
11. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement [published correction appears in Int J Surg. 2010;8(8):658]. Int J Surg. 2010;8(5):336-341. https://doi.org/10.1016/j.ijsu.2010.02.007
12. Elizabeth C, Suzanna S, Tim CF, Shek LP, Mital R, Bee Wah L. Pediatric asthma quality of life questionnaire: validation in children from Singapore [published correction appears in Asian Pac J Allergy Immunol. 2014;32(2):144. Chi, S L [corrected to Shek, L P] Bee-Wah, L [corrected to Bee Wah, L]]. Asian Pac J Allergy Immunol. 1999;17(3):155-161.
13. Stelmach I, Podlecka D, Smejda K, Majak P, Jerzyńska J, Stelmach R, et al. Pediatric asthma caregiver's quality of life questionnaire is a useful tool for monitoring asthma in children. Qual Life Res. 2012;21(9):1639-1642. https://doi.org/10.1007/s11136-011-0070-x
14. Srivastava SK. Green supply chain management: a state-of-the-art literature review. Int J Management Rev. 2007;9(1):53-80. https://doi.org/10.1111/j.1468-2370.2007.00202.x
15. Deeks JJ, Higgins JP. Statistical algorithms in review manager 5. Statistical Methods Group of The Cochrane Collaboration. 2010;1-11.
16. Ahmed PA, Ulonnam CC, Mohammed-Nafi'u R. Assessment of quality of life among children with bronchial asthma and their caregivers at the National Hospital Abuja, Nigeria. Niger J Paediatr. 2016;43(2):88-94. https://doi.org/10.4314/njp.v43i2.5
17. Almomani BA, Mayyas RK, Ekteish FA, Ayoub AM, Ababneh MA, Alzoubi SA. The effectiveness of clinical pharmacist's intervention in improving asthma care in children and adolescents: Randomized controlled study in Jordan. Patient Educ Couns. 2017;100(4):728-735. https://doi.org/10.1016/j.pec.2016.11.002
18. Ammari WG, Al-Hyari N, Obeidat N, Khater M, Sabouba A, Sanders M. Mastery of pMDI technique, asthma control and quality-of-life of children with asthma: A randomized controlled study comparing two inhaler technique training approaches. Pulm Pharmacol Ther. 2017;43:46-54. https://doi.org/10.1016/j.pupt.2017.02.002
19. Berger WE, Leflein JG, Geller DE, Parasuraman B, Miller CJ, O'Brien CD, et al. The safety and clinical benefit of budesonide/formoterol pressurized metered-dose inhaler versus budesonide alone in children. Allergy Asthma Proc. 2010;31(1):26-39.
20. Burks ML, Brooks EG, Hill VL, Peters JI, Wood PR. Assessing proxy reports: agreement between children with asthma and their caregivers on quality of life [published correction appears in Ann Allergy Asthma Immunol. 2013;111(4):309]. Ann Allergy Asthma Immunol. 2013;111(1):14-19. https://doi.org/10.1016/j.anai.2013.05.008
21. Bushnell DM, Martin ML, Parasuraman B. Electronic versus paper questionnaires: a further comparison in persons with asthma. J Asthma. 2003;40(7):751-762. https://doi.org/10.1081/JAS-120023501
22. Cano-Garcinuño A, Díaz-Vázquez C, Carvajal-Urueña I, Praena-Crespo M, Gatti-Viñoly A, García-Guerra I. Group education on asthma for children and caregivers: a randomized, controlled trial addressing effects on morbidity and quality of life. J Investig Allergol Clin Immunol. 2007;17(4):216-226.
23. Ducret CB, Verga M, Stoky-Hess A, Verga J, Gehri M. Impact d'une école de l'asthme sur la consommation en soins et la qualité de vie des enfants âgés de 4 à 12 ans et de leurs parents. Arch Pediatr. 2013;20(11):1201-1205. https://doi.org/10.1016/j.arcped.2013.08.021
24. Erickson SR, Munzenberger PJ, Plante MJ, Kirking DM, Hurwitz ME, Vanuya RZ. Influence of sociodemographics on the health-related quality of life of pediatric patients with asthma and their caregivers. J Asthma. 2002;39(2):107-117. https://doi.org/10.1081/JAS-120002192
25. Fleming L, Murray C, Bansal AT, Hashimoto S, Bisgaard H, Bush A, et al. The burden of severe asthma in childhood and adolescence: results from the paediatric U-BIOPRED cohorts [published correction appears in Eur Respir J. 2017;49(6):]. Eur Respir J. 2015;46(5):1322-1333. https://doi.org/10.1183/13993003.00780-2015
26. Halterman JS, Riekert K, Bayer A, Fagnano M, Tremblay P, Blaakman S, et al. A pilot study to enhance preventive asthma care among urban adolescents with asthma. J Asthma. 2011;48(5):523-530. https://doi.org/10.3109/02770903.2011.576741
27. Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. Eur Respir J. 2010;36(6):1410-1416. https://doi.org/10.1183/09031936.00117509
28. Kamps AW, Brand PL, Kimpen JL, Maillé AR, Overgoor-van de Groes AW, van Helsdingen-Peek LC, et al. Outpatient management of childhood asthma by paediatrician or asthma nurse: randomised controlled study with one year follow up. Thorax. 2003;58(11):968-973. https://doi.org/10.1136/thorax.58.11.968
29. Lang JE, Hossain MJ, Lima JJ. Overweight children report qualitatively distinct asthma symptoms: analysis of validated symptom measures. J Allergy Clin Immunol. 2015;135(4):886-93.e3. https://doi.org/10.1016/j.jaci.2014.08.029
30. Lenney W, McKay AJ, Tudur Smith C, Williamson PR, James M, Price D, et al. Management of Asthma in School age Children On Therapy (MASCOT): a randomised, double-blind, placebo-controlled, parallel study of efficacy and safety. Health Technol Assess. 2013;17(4):1-218. https://doi.org/10.3310/hta17040
31. Liu Z, Qureshi K. Efficacy of an Asthma Self-management Education Intervention for Children (9-13 Years) with Asthma and Their Caregiver in Wuhan, China. J US-China Med Sci. 2016;13:117-128. https://doi.org/10.17265/1548-6648/2016.03.001
32. Meza ÉD, Puentes ÓUB, Blanc JPG, García MG, Halley PD, Duque CAT. Evaluación del control del asma y la calidad de vida de los niños y sus padres o cuidadores en un programa de atención integral del asma (Programa Asmaire Infantil). Rev Medica Sanitas. 2012;15(4):36-42.
33. Minard JP, Thomas N, Olajos-Clos J, Juniper EF, Jiang X, Jenkins B, et al. Burden Of Childhood Asthma: Relationship Between Pediatric And Caregiver Electronic Quality Of Life Questionnaires. ATS. 2011:A1435. https://doi.org/10.1164/ajrccm-conference.2011.183.1_MeetingAbstracts.A1435
34. Minard JP, Thomas NJ, Olajos-Clow JG, Wasilewski NV, Jenkins B, Taite AK, et al. Assessing the burden of childhood asthma: validation of electronic versions of the Mini Pediatric and Pediatric Asthma Caregiver's Quality of Life Questionnaires. Qual Life Res. 2016;25(1):63-69. https://doi.org/10.1007/s11136-015-1055-y
35. Moreira A, Delgado L, Haahtela T, Fonseca J, Moreira P, Lopes C, et al. Physical training does not increase allergic inflammation in asthmatic children. Eur Respir J. 2008;32(6):1570-1575. https://doi.org/10.1183/09031936.00171707
36. Murray CS, Foden P, Sumner H, Shepley E, Custovic A, Simpson A. Preventing Severe Asthma Exacerbations in Children. A Randomized Trial of Mite-Impermeable Bedcovers. Am J Respir Crit Care Med. 2017;196(2):150-158. https://doi.org/10.1164/rccm.201609-1966OC
37. Mussaffi H, Omer R, Prais D, Mei-Zahav M, Weiss-Kasirer T, Botzer Z, et al. Computerised paediatric asthma quality of life questionnaires in routine care. Arch Dis Child. 2007;92(8):678-682. https://doi.org/10.1136/adc.2006.111971
38. Nair S, Nair S, Sundaram KR. A prospective study to assess the quality of life in children with asthma using the pediatric asthma quality of life questionnaire. Indian J Allergy Asthma Immunol. 2014;28(1):13-18. https://doi.org/10.4103/0972-6691.134210
39. Ovšonková A, Plavnická I, Jeseňák M. The quality of life of parents and children with asthma bronchial. Ošetřovatelství a porodní asistence. 2012;3(3):424-432.
40. Strunk RC, Bacharier LB, Phillips BR, Szefler SJ, Zeiger RS, Chinchilli VM, et al. Azithromycin or montelukast as inhaled corticosteroid-sparing agents in moderate-to-severe childhood asthma study. J Allergy Clin Immunol. 2008;122(6):1138-1144.e4. https://doi.org/10.1016/j.jaci.2008.09.028
41. Szabó A, Mezei G, Kovári E, Cserháti E. Depressive symptoms amongst asthmatic children's caregivers. Pediatr Allergy Immunol. 2010;21(4 Pt 2):e667-e673. https://doi.org/10.1111/j.1399-3038.2009.00896.x
42. Tibosch M, Reidsma C, Landstra A, Hugen C, Gerrits P, Brouwer M, et al. An asthma-related quality of life instrument is unable to identify asthmatic children with major psychosocial problems. Eur J Pediatr. 2010;169(12):1495-1501. https://doi.org/10.1007/s00431-010-1250-3
43. van Bragt S, van den Bemt L, Kievits R, Merkus P, van Weel C, Schermer T. PELICAN: a cluster-randomized controlled trial in Dutch general practices to assess a self-management support intervention based on individual goals for children with asthma. J Asthma.

2015;52(2):211-219. https://doi.org/10.3109/02770903.2014.952439

44. van Gent R, van Essen LE, Rovers MM, Kimpen JL, van der Ent CK, de Meer G. Quality of life in children with undiagnosed and diagnosed asthma. Eur J Pediatr. 2007;166(8):843-848. https://doi.org/10.1007/s00431-006-0358-y
45. Voorend-van Bergen S, Vaessen-Verberne AA, Landstra AM, Brackel HJ, van den Berg NJ, Caudri D, et al. Monitoring childhood asthma: web-based diaries and the asthma control test. J Allergy Clin Immunol. 2014;133(6):1599-605.e2. https://doi.org/10.1016/j.jaci.2013.10.005
46. Voorend-van Bergen S, Vaessen-Verberne AA, Brackel HJ, Landstra AM, van den Berg NJ, Hop WC, et al. Monitoring strategies in children with asthma: a randomised controlled trial. Thorax. 2015;70(6):543-550. https://doi.org/10.1136/thoraxjnl-2014-206161
47. Williams J, Williams K. Asthma-specific quality of life questionnaires in children: are they useful and feasible in routine clinical practice?. Pediatr Pulmonol. 2003;35(2):114-118. https://doi.org/10.1002/ppul.10206
48. Yun TJ, Jeong HY, Hill TD, Lesnick B, Brown R, Abowd GD, et al. Using SMS to provide continuous assessment and improve health outcomes for children with asthma. Proceedings of the 2nd ACM SIGHIT International Health Informatics Symposium; 2012 Jan; Miami FL, USA. ACM; 2012. p. 621-630. https://doi.org/10.1145/2110363.2110432
49. Schmier JK, Chan KS, Leidy NK. The impact of asthma on health-related quality of life. J Asthma. 1998;35(7):585-597. https://doi.org/10.3109/02770909809048961
50. Costa DD, Pitrez PM, Barroso NF, Roncada C. Asthma control in the quality of life levels of asthmatic patients' caregivers: a systematic review with meta-analysis and meta-regression. J Pediatr (Rio J). 2019;95(4):401-409. https://doi.org/10.1016/j.jped.2018.10.010
51. Guyatt GH, Juniper EF, Griffith LE, Feeny DH, Ferrie PJ. Children and adult perceptions of childhood asthma. Pediatrics. 1997;99(2):165-168. https://doi.org/10.1542/peds.99.2.165
52. Burks ML, Brooks EG, Hill VL, Peters JI, Wood PR. Assessing proxy reports: agreement between children with asthma and their caregivers on quality of life [published correction appears in Ann Allergy Asthma Immunol. 2013;111(4):309]. Ann Allergy Asthma Immunol. 2013;111(1):14-19. https://doi.org/10.1016/j.anai.2013.05.008
53. Kew KM, Carr R, Crossingham I. Lay-led and peer support interventions for adolescents with asthma. Cochrane Database Syst Rev. 2017;4(4):CD012331. https://doi.org/10.1002/14651858.CD012331.pub2

J Bras Pneumol. 2020;46(3):e20190280
https://dx.doi.org/10.36416/1806-3756/e20190280

REVIEW ARTICLE

Palliative care in pulmonary medicine

Ellen Pierre de Oliveira[1], Pedro Medeiros Junior[2]

1. Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. A.C. Camargo Cancer Center, São Paulo (SP) Brasil.

Submitted: 14 August 2019.
Accepted: 8 March 2020.

Study carried out at A.C. Camargo Cancer Center and at the Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Palliative care was initially developed for patients with advanced cancer. The concept has evolved and now encompasses any life-threatening chronic disease. Studies carried out to compare end-of-life symptoms have shown that although symptoms such as pain and dyspnea are as prevalent in patients with lung disease as in patients with cancer, the former receive less palliative treatment than do the latter. There is a need to refute the idea that palliative care should be adopted only when curative treatment is no longer possible. Palliative care should be provided in conjunction with curative treatment at the time of diagnosis, by means of a joint decision-making process; that is, the patient and the physician should work together to plan the therapy, seeking to improve quality of life while reducing physical, psychological, and spiritual suffering.

Keywords: Palliative care; Pulmonary medicine; Quality of life.

INTRODUCTION

According to the World Health Organization, palliative care is "an approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."[1]

The word "palliative" comes from the verb "to palliate" (from the Latin *palliatus*—covered in a cloak; to alleviate without curing). Therefore, palliative care means to relieve human suffering at any stage of their illness. The early introduction of palliative care can improve the functioning and quality of life of patients dealing with limitations imposed by various conditions, such as respiratory diseases. The inability to manage symptoms such as pain and dyspnea in patients with serious conditions, together with difficulties in communication during treatment, leads to a deterioration of the relationship between patients, families, and caregivers.[2]

In light of the concept of early introduction, we understand that the palliative and the curative approaches complement each other throughout the course of the disease. In the early stages, priority should be given to curative treatment. As the disease progresses and the condition of the patient deteriorates, symptom control becomes the main focus. Even at more advanced stages, treatments to slow disease progression can be provided, as long as they do not cause any further suffering. Bereavement is also part of the palliative care sphere; in bereavement care, family members facing the loss of a loved one are provided with support and comfort (Figure 1).[3]

In pulmonary medicine, the main focus of palliative care is the early detection of respiratory decompensation and the promotion of interventions to prevent and relieve symptoms. In addition to alleviating the symptoms caused by disease progression, such interventions are aimed at reducing the numbers of emergency department visits and hospitalizations, as well as providing end-of-life support. An effective implementation of palliative care in pulmonary medicine would ideally rely on a multidisciplinary team (of physicians, physical therapists, nurses, psychologists, and social workers) with proper knowledge and training. Nevertheless, a good understanding by the attending physician alone is enough to define how the disease should be managed, with an emphasis on symptom control.[4] For example, one study showed that the prevalence of untreated symptoms (dyspnea, asthenia, and anxiety) is higher in patients with COPD than in those with cancer or heart failure.[5]

A BRIEF HISTORY OF PALLIATIVE CARE

Palliative care became a formal area of expertise in medicine in the 20th century. However, practices focusing on the management of critical patients and end-of-life care are as old as medicine itself.

The term "hospice", which is currently used to refer to the place where patients in palliative care are hospitalized, originated in medieval times, when it meant shelter for pilgrims. In 17th-century Europe, charitable institutions with entire wards reserved for patients with tuberculosis and cancer appeared. That is when the concept of what we currently call "hospice" originated.[6]

England played a prominent role in the development of palliative medicine. As early as the late 19th century, the English have shown their concern with caring for dying patients, as evidenced by the use of the Brompton cocktail (an elixir made of opioid, cocaine, and chlorpromazine) for controlling severe pain and the regular use of oral

Correspondence to:
Ellen Pierre de Oliveira. Avenida Dr. Enéas de Carvalho Aguiar, 44, CEP 05403-900, São Paulo, SP, Brasil.
Tel.: 55 11 2661-5034. E-mail: lenna7772003@yahoo.com
Financial support: None.

ISSN 1806-3713

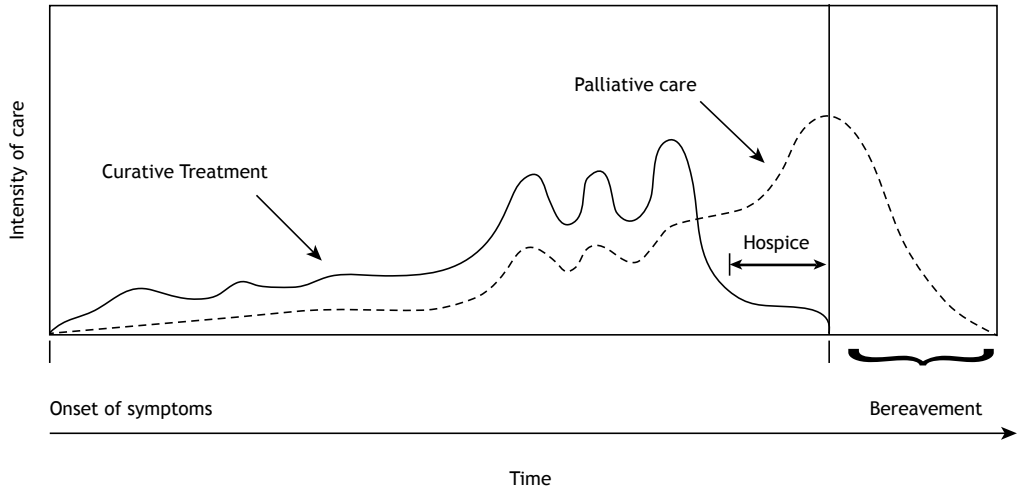


Figure 1. Evolution of palliative care in chronic diseases.

morphine in patients nearing the end of life at St. Luke's Home. It was at St. Luke's Home that nurse Cicely Saunders worked in the mid 20th century. In 1967, she founded St. Christopher's Hospice in London, giving rise to what is currently known as the modern hospice movement.[7]

In 1982, the WHO Coordinating Committee on Cancer set up a working group to establish policies aimed at relieving the pain of and providing hospice care to cancer patients. In 1986, the WHO published its first definition of palliative care, which was revised in 2002 to broaden the concept and make it applicable to all diseases. In 1987, England became the first country to acknowledge palliative medicine as a medical specialty, paving the way for other countries to do the same.[8]

PALLIATIVE CARE GOALS AND DOMAINS

Several guidelines have already been proposed in an attempt to standardize palliative care practices. One of the most successful of these frameworks is the fourth edition of the Clinical Practice Guidelines for Quality Palliative Care. That document sets forth the following goals for palliative care planning[2]:

- To provide relief from pain and from other distressing symptoms
- To affirm life and to see dying as a natural process
- Not to hasten or postpone death
- To integrate the psychological and spiritual aspects into patient care
- To offer support to help patients live as actively as possible until death
- To offer support to help the family cope with the illness and their own bereavement
- To apply a multidisciplinary approach to address the needs of patients and their families, including bereavement counseling
- To enhance quality of life and positively influence the course of illness
- To enable better understanding of the illness and its clinical complications

In addition to defining the aforementioned goals, the document divides palliative care into eight domains, all of them centered on patient and family care (Chart 1).[2] Communication is yet another extremely important part of palliative care. Therefore, we decided to add it to the list as the ninth domain.

COMMUNICATION

Clear and straightforward communication is crucial in the treatment of a life-limiting illness. Proper communication can relieve suffering and facilitate end-of-life care.[9] A study conducted at the University of Texas MD Anderson Cancer Center and the Toronto-Sunnybrook Regional Cancer Center established an effective protocol for breaking bad news in the field of oncology.[10] Their protocol is named SPIKES, an acronym for the six steps it comprises (Figure 2): S for setting, P for perception, I for invitation, K for knowledge, E for emotions with empathy, and S for strategy or summary. The SPIKES protocol consists of studying the case thoroughly, assessing the degree of perception of patients and families, giving the prognosis in simple and clear language, showing empathy during the conversation, and assessing what has been assimilated and devising care strategies.[10]

A study involving 115 patients diagnosed with lung cancer, breast cancer, prostate cancer, lymphoma, or melanoma showed that the use of the SPIKES protocol created communication that was more empathic, facilitating care planning and the delivery of bad news.[11]

PALLIATIVE CARE IN VARIOUS LUNG PATHOLOGIES

COPD

According to the WHO, there were 251 million cases of COPD in 2016. It is expected to be the third leading cause of death in the world in 2020.[12]

Chart 1. Domains of palliative care.

Domain	Brief description
Structure of care	Based on patient/family goals of care and diagnosis/prognosis, as well as the incorporation of quality and safety
Physical aspects	Assessment and multidimensional treatment of physical symptoms such as pain, dyspnea, nausea/vomiting, fatigue, constipation, and definition of functionality in order to adjust medication
Psychological aspects	Assessment of psychological concerns and psychiatric diagnoses that include anxiety, depression, and grief, together with their respective treatments
Social aspects	Identification and resolution of social issues that afflict the patient/family
Spiritual, religious, and existential aspects	Assessment of spirituality to address spiritual concerns throughout the disease trajectory, promoting the exploration of hope, fear, and forgiveness
Cultural aspects	Cultural assessment as a source of resilience, linguistic competence emphasizing plain language and linguistically appropriate service delivery
End-of-life care	Control and documentation of the signs and symptoms of the death process. Focus on planning end-of-life care in advance, with ongoing discussion of goals of care
Ethical and legal aspects	Acknowledgment of the complexity of ethical issues and the importance of seeking support from ethical and legal counseling
Communication	Empathic communication that uses clear and straightforward language, respecting patient autonomy

Adapted from Narsavage et al.[2]

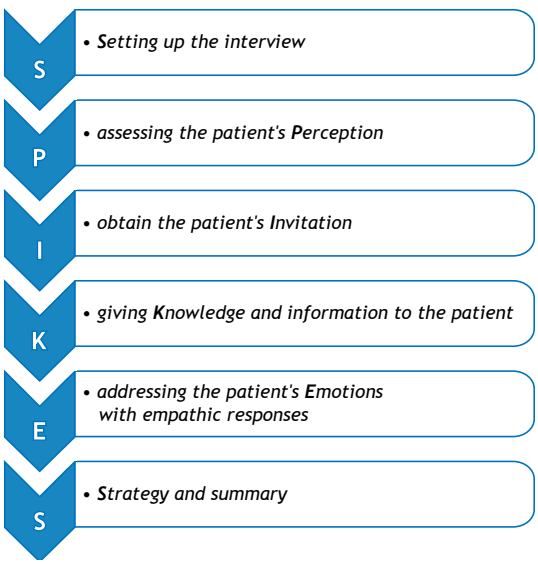


Figure 2. The SPIKES protocol. Adapted from Baile et al.[10]

The progression of COPD is marked by a gradual, clinical decline in respiratory capacity, progressive dyspnea, and exacerbations associated with an increased risk of death and worsening of the quality of life. Although the probability of dying during hospitalization for COPD exacerbation has decreased in recent years, it is still high, ranging from 23% to 80%.[13]

The American Thoracic Society/European Respiratory Society guidelines, published in 2015,[14] established the importance and benefits of including palliative care in the management of COPD. Although the guidelines underscore the importance of palliative care, a study carried out from 2004 to 2015 showed that only one in five patients with COPD in the United Kingdom received that type of care at the end of life.[15] The difficulty in establishing an accurate prognosis is certainly one of the challenges to implementing palliative care. Indices that attempt to predict mortality for COPD patients can be found in the literature.[14] Among them are: the **B**ody mass index, airway **O**bstruction, **D**yspnea, and **E**xercise capacity (BODE) index and the **A**ge, **D**yspnea, and airflow **O**bstruction (ADO) index. However, those indices have low accuracy, mainly because they do not take into account other aggravating factors, such as cardiovascular disease.[16] Therefore, integrating palliative care into the treatment of COPD patients earlier has proven to be one of the best options for symptom control and improving quality of life, striking a balance between socioeconomic costs and psychological/emotional costs.[17]

Interstitial lung diseases

Interstitial lung diseases (ILDs) are a group of heterogeneous disorders, classified according to their clinical, radiological, and functional findings. Examples of ILDs include idiopathic pulmonary fibrosis (IPF), hypersensitivity pneumonitis, sarcoidosis, nonspecific interstitial pneumonia, occupational diseases, organizing pneumonia, and the various forms of bronchiolitis.[18] All ILDs are associated with an intensification of symptoms such as cough, dyspnea, and fatigue, which leads to a deterioration of patient quality of life. As the disease progresses, the symptoms exacerbate and resemble those of patients with terminal lung cancer.[4,19,20]

In an assessment of the quality of life of patients with IPF,[21] the following three questionnaires were applied: The World Health Organization Quality of Life assessment instrument 100, the Beck Depression Inventory, and the Bath Breathlessness Scale. The assessment revealed that pain, fatigue, low self-esteem, and impaired mobility are more common among such patients, who are also more dependent on others for their activities of daily living and for the treatment of the disease, including the administration of medication.[21]

The most common symptoms in patients with ILD are dyspnea, fatigue, cough, anxiety, and depression. A systematic review showed that 68-98% of patients with ILD have dyspnea, 59-94% have cough, 25-65% have heartburn, and 10-49% have depression.[22] This review also showed a higher prevalence of symptoms such as sleep disorders, weight loss, fatigue, and anorexia among such patients.[22]

Despite the severity of ILD, patients still seem to have a limited understanding of the disease and its prognosis. In a survey of patients with IPF and their caregivers,[23] one of the participants reported "I was so relieved that the diagnosis wasn't lung cancer. I wasn't sure what idiopathic pulmonary fibrosis was, but I figured it couldn't be as bad as lung cancer."

Although the prognosis of IPF can be as poor as that of some lung cancers, palliative care is not widely indicated in patients with the disease. A study involving 277 patients with IPF carried out at the University of Pittsburgh[24] revealed that 57.0% of patients died in a hospital setting and only 13.7% received end-of-life support from a team specializing in palliative care. Of the patients who died in the hospital, 34.2% were in the ICU. Therefore, patients with ILD have a guarded prognosis, especially in cases of acute decompensation, which can have various causes, such as exposure to aeroallergens, infection, and disease progression. These patients usually have severe hypoxemia and often require ventilatory support. The use of invasive mechanical ventilation is questionable because of the high mortality rate associated with it, ranging from 87.4% to 94.1% in patients with this condition.[25] However, the same study showed that the use of noninvasive ventilation (NIV) within the first 24 h after admission was able to reduce 30-day mortality. The early use of NIV is associated with a lower rate of endotracheal intubation, reduced complications, better survival rates, and increased numbers of hospital discharges.[25]

Cystic fibrosis

Cystic fibrosis (CF) or mucoviscidosis is a serious hereditary condition that is passed on through an autosomal recessive inheritance pattern. In CF, an increase in mucus viscosity leads to an obstructive process that most commonly affects the lungs and the pancreas. That increase in viscosity blocks the airways in the lungs, facilitating bacterial growth (especially *Pseudomonas* sp. and staphylococci), which leads to chronic infection, lung injury, respiratory dysfunction, and death.[26]

Advances in the treatment of CF have led to a significant increase in the mean survival of patients, which increased from 14 years in 1969 to 40 years in 2013, making it a chronic illness of young adults. As a result, there has been a greater impact on family relationships and on the way patients make choices for the future (occupation, love life, parenthood, and infertility).[27]

The slow, prolonged deterioration of lung function, combined with pancreatic (endocrine and exocrine) and gastrointestinal tract dysfunction, leads to the appearance of the most common symptoms: headache, chest pain, chronic cough, dyspnea, and bronchorrhea. These patients spend, on average, 108 min a day on the administration of oral, inhaled, and injected medications.[28] The time spent dealing with unpleasant symptoms and administering medications to control them greatly affects their quality of life.[29]

In an attempt to assess patients with CF, 16 severity scores have been developed at different historical moments in the scientific understanding of the disease, such as the Taussig Score and the Simplified Cystic Fibrosis Scale.[30] Despite the evident severity of the condition, not many patients receive palliative care in the final stages of the disease.

In 2009, a study carried out in the United Kingdom[31] evaluated 40 patients with CF who died of respiratory failure. Of those 40 patients, 5 died after lung transplantation. Of the nontransplanted patients, 16 (45.71%) were in a palliative care program, 6 (17.14%) received no palliative care, and 13 (37.14%) experienced an abrupt transition from curative treatment to palliative care alone in the last two days of life.[31] Another study showed that patients with CF on a waiting list for lung transplantation were likely to die in the ICU under invasive ventilation, having had no discussion about end-of-life care.[29]

Because this patient population is young, there is great difficulty in indicating palliative care for symptom control. Although some centers already offer this service, it remains underutilized because the patient and the care team both have trouble accepting it.[29]

Pulmonary hypertension

Pulmonary hypertension (PH) is a hemodynamic result common to various processes and mechanisms that lead to an increase in blood pressure in the pulmonary vascular territory, together with right ventricular overload and failure, culminating in heart failure.

The symptoms of PH are nonspecific and are mainly related to progressive dysfunction of the right ventricle. The symptoms are usually effort-induced and include shortness of breath, fatigue, weakness, angina, and syncope. As the disease progresses, the symptoms intensify and patients become more dependent on the aid of family members to perform their basic activities of daily living, which has a major impact on their quality of life. If the PH is secondary to systemic sclerosis, liver disease, or congenital heart diseases, the impact on patient quality of life is even greater.[32]

Patients with worse (New York Heart Association) functional classes and reduced cardiac exercise capacity have a higher risk of depression. In addition, the diagnosis of PH in and of itself causes great psychological and emotional frustration, manifesting as feelings of low self-esteem and helplessness.[33]

There is as yet no consensus on a definitive score that can predict mortality from PH. Nevertheless, some attempts have been made in that direction. The Registry to Evaluate Early and Long-term [Pulmonary Arterial Hypertension] Disease[34] calculated a score combining clinical and demographic data, functional class, vital signs, six-minute walk test results, brain natriuretic peptide (BNP) levels, echocardiogram results, lung function test results, and data on right heart catheterization. It revealed that, 7 years after diagnosis, 50% of the patients had died. It also showed that the high morbidity associated with PH has a dramatic effect on the quality of life of these patients.[34] Patients who have syncope, cardiac indices < 2 L/min/m^2, BNP > 300 ng/L, and mixed venous oxygen saturation < 60% have a > 10% risk of death at one year, even with optimized care.[32]

The treatment of PH can be divided into invasive and noninvasive. The invasive modalities include atrial septostomy, right ventricular assist device implantation, and pulmonary artery denervation. Preeminent among the noninvasive modalities are specific drug therapies. Although not curative, they can improve quality of life and slow disease progression. Other important noninvasive measures include educating patients about the disease and psychological and spiritual support groups.[35-37]

SYMPTOM MANAGEMENT IN PATIENTS WITH RESPIRATORY DISEASES

The most common symptoms presented by patients with lung diseases are dyspnea, cough, fatigue, cachexia, hemoptysis, physical pain, and psychological symptoms such as depression and anxiety.[3] Below, we briefly discuss the therapy for each symptom.

Dyspnea

In addition to being directly correlated to respiratory failure progression, dyspnea also arises from the interaction of other physical factors (cachexia and asthenia), psychological factors (anxiety and depression), social factors, and environmental factors.[38]

The approach to dyspnea should include an objective assessment using scales, such as the Medical Research Council dyspnea scale (Chart 2), which establishes levels of exercise intensity that will trigger breathlessness, the Baseline Dyspnea Index, and the Chronic Respiratory Questionnaire.[39-42]

The initial management of dyspnea should focus on controlling the underlying cause. Optimizing the use of bronchodilators, controlling pleural effusion, achieving volume optimization, and using oxygen therapy should be prioritized, when indicated. Other important measures to reduce the perception of dyspnea are rehabilitation and NIV. Behavioral measures, such as keeping utensils and tools at waist level and avoiding carrying objects, serve as energy savers and reduce the dyspnea sensation.[43]

Chart 2. The Medical Research Council dyspnea scale.

Grade	Description
0	No dyspnea, except during strenuous exercise
1	Breathless when hurrying on level ground or walking up a slight grade
2	Walks slower or has to stop to catch their breath
3	Stops after walking 100 yards
4	Breathless after undemanding activities like dressing or undressing

Adapted from Papiris et al.[41]

If dyspnea persists at rest in spite of the implementation of these measures, making it impossible for patients to perform minimal effort activities such as brushing their teeth, an opioid can be added, morphine being the drug of choice. The initial dose of morphine varies, possibly starting at 5 mg p.o. every 4 h for patients without kidney failure (in the elderly, use this dose with caution and reduce it if there are side effects). Morphine reaches its peak serum concentration in less than 1 h, has a half-life of 2-3 h and action duration of 4 h. Higher doses may be needed in cases of disease progression or tolerance to the medication. If that is the case, the baseline dose can be increased by 25%, although one should always be cautious and try to prevent severe side effects, such as bradypnea and a reduced level of consciousness.[44]

Long-term opioid use is associated with clinical conditions such as the opioid use disorders included in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders.[45] These disorders manifest as difficulty in controlling the use of, tolerance to, and physical dependence on these substances. In addition, the use of opioids can lead to cardiovascular and respiratory complications, as well as overdose and death. To prevent that, the Centers for Disease Control and Prevention issued the following recommendations[45]:

- Establish pain control or dyspnea goals and discontinue the use of the medication if those goals are not achieved.
- Explain the risks and benefits of opioid use to patients.
- Start therapy with an immediate-release opioid at the minimum effective dose.
- After opioid introduction, schedule weekly appointments to assess side effects and determine the optimal dose.

The most common side effects of morphine use are pruritus, drowsiness, and constipation. For constipation, the recommendation is to start concomitant use of stimulant laxatives at night and osmotic laxatives during the day. Preeminent among the stimulant laxatives are bisacodyl, 5-10 mg p.o.; picosulfate, 5-10 mg p.o.; and senna (*Cassia angustifolia* and *C. acutifolia*) 5-10 mg p.o. The most commonly used osmotic laxatives are lactulose up to 50 mL/day and polyethylene glycol up to 14 g/day.[46]

Dyspnea management should also include the management of acute dyspnea attacks. These attacks are more common in terminal cases and educating family members to recognize them can help in their control. The acronym COMFORT can be used for controlling an attack—**C**all for help; **O**bserve and treat possible causes; **M**edicate as per medical prescription; **F**an, that is, use a fan directed to the face; **O**xygen therapy, when indicated; **R**elaxation; and **T**iming—assessing patient responses to each of these interventions.[47] A schematic diagram of the treatment of dyspnea in patients with chronic lung diseases is shown in Figure 3.

Other instances of and strategies to treat dyspnea

Psychological symptoms

Anxiety can aggravate shortness of breath, and some patients can experience concurrent attacks of panic and dyspnea. Therefore, symptoms of anxiety should be actively investigated and treated from the first contact with the patient, and medication and psychological support should be offered when necessary.[48]

Therapy with selective serotonin reuptake inhibitors can be offered to patients with dyspnea attacks accompanied by anxiety or panic attacks. These inhibitors have a direct effect on the brain area that controls dyspnea perception and can be used as an adjuvant medication. An example of this type of medication is sertraline (starting dose of 12.5-25.0 mg/day, which can be adjusted up to 50 mg/day). There is no consensus in the literature about the prolonged use of benzodiazepines; further studies are needed to evaluate their safety and efficacy.[48,49]

Psychosocial symptoms, which usually appear at the diagnosis of dyspnea, can intensify during exacerbations and at the end of life. Care planning is essential to control symptoms such as depression and anxiety. In addition, clear communication between the care team and patients/families is key to facilitating understanding of the therapeutic options. The care team should be able to understand the spiritual issues and suffering that patients/families are facing and offer support so as to help relieve their psychological discomfort.[50]

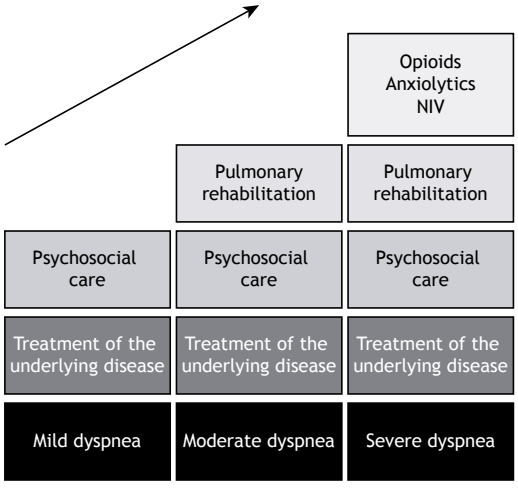


Figure 3. Dyspnea treatment. NIV: noninvasive ventilation.

Supplemental oxygen therapy

The use of supplemental oxygen is indicated for hypoxemic patients (those with an SpO_2 < 92%), aiming to relieve their symptoms and improve their quality of life. However, there is no robust evidence of its benefits for non-hypoxemic patients. Therefore, the patient response to oxygen therapy should be assessed on the basis of symptom improvement and not long-term outcomes.[51]

NIV

Physicians should be judicious in their use of NIV, the objective of which should be to relieve dyspnea and provide comfort to patients. The use of NIV can provide patients with more time to spend with their families, which often allows them to say their goodbyes. In cases in which the instructions for advanced life support have not previously been defined, NIV can buy time for patients to understand the diagnosis and for clinicians to define the prognosis, giving due consideration to proportional care and preventing invasive measures that can prove ineffective or even lead to dysthanasia.[52] There are specific situations in which NIV should not be used, such as in cases of facial deformities or skin lesions that can prevent a comfortable fit of the face mask and reduce the level of consciousness.[53]

Cachexia

Cachexia can be caused by changes in intestinal habits, endocrine disorders, metabolic disorders, malabsorption, sleep disorders, and psychological disorders. These factors must be actively investigated and addressed. After the risk factors have been corrected, nutritional counseling, diet adaptation, nutritional supplementation, and appropriate hydration should be provided.[54]

Palliative nutrition should be implemented according to the palliative care phase. In the early stages, calories, proteins, and nutrients should be offered orally, the objective being to prioritize quality of life. Food and nutrient restrictions should be avoided. In the final stages of life, the psychosocial support provided to patients and families should be intensified in order to reduce their discomfort.

Although enteral feeding or parenteral nutrition should be considered in order to minimize family conflicts caused by patients reduced oral intake, it can lead to complications such as infections and changes in bowel habits. Feeding tubes can be used in the early stages when disease-modifying treatment predominates over palliative care. When that relationship is reversed, enteral feeding is no

longer advisable. To minimize the discomfort of patients and families, nutritional status and weight should not be monitored in the final stages of life.[55]

Hemoptysis

Hemoptysis is quite common in patients with lung cancer, bronchiectasis, or pulmonary cavitations. The treatment primarily targets the underlying cause: antibiotic therapy in cases of infectious exacerbation; and palliative chemotherapy and radiation therapy in cases of lung cancer.

In emergent cases of hemoptysis, the following therapeutic options should be considered:

- nebulized tranexamic acid, 500 mg diluted in 5 mL of saline solution 0.9% administered 3 times a day for 5 days[56,57]
- bronchoscopic instillation of cold saline and adrenaline[58]
- bronchial arterial embolization, which has a success rate of 70-100% and is mainly indicated when conventional surgery is precluded by the advanced stage of the disease[59]

In irreversible cases, the use of dark-colored sheets and clothes can alleviate patient embarrassment.[59]

Cough

Cough is highly prevalent in patients with lung diseases, especially at the end of life. It can affect more than 65% of patients with lung cancer and 70% of patients with COPD.[60] Although it is a natural reflex, it can have a significant impact on quality of life and lead to complications such as muscle pain, rib fracture, urinary incontinence, asthenia, and sleep disorders.

Before a cough is alleviated, a patient clinical history should be taken in order to find its main causes. A cough can be an adverse effect of medication or can be caused by conditions such as rhinosinusitis, respiratory infection, lung disease, asthma, COPD, and gastroesophageal reflux.[61] If the cough persists after treating its underlying cause, the following medication can be used: low doses of weak opioids such as codeine (30 mg p.o., every 6 h); antitussives, such as levodropropizine (60 mg p.o., 3 times a day); and anticholinergics, such as inhaled ipratropium bromide.[62] If the patient is already on morphine, the baseline dose may be increased by 25% to achieve cough control. Patients with IPF can show a reduction in cough with the use of thalidomide (100 mg p.o., once a day), although that drug is not approved for use in Brazil.[63]

The GABA analogs gabapentin and pregabalin can also be used to control chronic cough. Although neither has been usually prescribed for that purpose, there are studies that show benefits of their use in the management of cough. The initial dose of gabapentin is 300 mg/day p.o. (up to 900 mg/day in 2-3 doses) whereas that of pregabalin is 75 mg/day p.o. (up to 300 mg/day in two doses).[64]

Bronchorrhea

Bronchorrhea is defined as the production of more than 100 mL of pulmonary secretion per day. Mucus is responsible for keeping the respiratory system hydrated and contains defensive factors against various pathogens. However, the excessive accumulation of mucus leads to airway obstruction and increases the risk of infection.

The main pharmacological approaches to bronchorrhea include inhaled ipratropium bromide, anticholinergics, atropine 1% (1-2 drops sublingual, 3-4 times a day), corticosteroids, and antibiotic therapy in extreme cases.[65]

Pain

The International Association for the Study of Pain[66] defines pain as an unpleasant sensory or emotional experience associated with actual or potential tissue damage. More than 50% of patients with an advanced-stage disease experience pain. Nevertheless, the concept of "overall pain" goes beyond physical suffering to encompass the psychosocial, spiritual, and family factors that can contribute to the persistence of the symptom.[66]

Differentiating between neuropathic pain and nociceptive pain is crucial when treating pain. Neuropathic pain can be defined as a tingling or itching sensation and altered skin tone or tenderness, caused by injury to the nervous system. Patients with lung cancer can experience pain due to the tumor infiltrating the bone after radiation therapy, chemotherapy toxicity, or damage to the nerve during surgery.[67] The treatment of neuropathic pain begins by establishing a diagnosis and eliminating the causal factors, such as relieving root compression and withdrawing triggering medications. Pharmacological options include the use of antidepressants, calcium channel ligands (gabapentin and pregabalin), and topical lidocaine.

Nociceptive pain is more localized and can be experienced as a throbbing or cramping sensation. The treatment should follow the recommendations of the WHO pain ladder.[68] It starts with simple analgesics, which can then be replaced with weak opioids and, finally, potent opioids such as morphine and methadone (Figure 4).[68] Chart 3 presents a summary of the management options for all the symptoms described in this article.

ETHICAL ISSUES

When planning the care of patients with a limited life expectancy, we are faced with certain ethical issues. Those issues are often accompanied by conflicts between the care team and patients/families about what type of care is most appropriate.

In recent decades, medicine has been transitioning from medical paternalism, a practice that was almost exclusively centered on the wills of physicians, to an approach in which patient autonomy is gaining ever

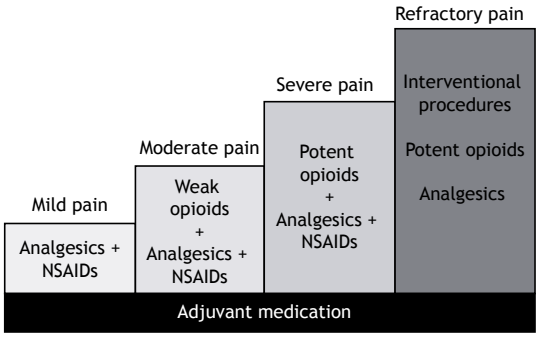


Figure 4. Pain management ladder. NSAIDs: non-steroidal anti-inflammatory drugs. Adapted from Riley et al.[68]

more ground in the planning of care.[69] This is what is called "joint decision-making"; that is, a process in which the care team, patients, and families exchange information, desires, and life values, which are then used as the foundation for defining treatment goals. Such collaboration is a determinant of the best outcomes.

One example of that evolution is the passage of the "Mário Covas" Act,[70] in the state of São Paulo, Brazil, according to which patients have autonomy and the right to reject painful or extraordinary treatments aimed at prolonging life. Resolution 1805/6 of the Brazilian Federal Council of Medicine,[71] although not

Chart 3. Management of symptoms in patients with lung diseases in palliative care.

Dyspnea
Psychological support
Disease-focused treatment
Behavioral measures
Morphine 5 mg p.o. q4h (elderly and CKD: start at ¼ of the dose)
The COMFORT strategy
Oxygen therapy for hypoxemic patients
Noninvasive ventilation
Cough
Investigate and treat gastroesophageal reflux, sinusitis, asthma, and COPD
Codeine 30 mg p.o. q6h
Levodropropizine 60 mg p.o. q8h
Inhaled ipratropium bromide
Gabapentin 300 mg/day up to 900 mg/day (in 3 doses)
Pregabalin 75 mg/day up to 300 mg/day (in 2 doses)
Bronchorrhea
Inhaled ipratropium bromide
Atropine 1% in saline, 1-2 drops q8h
Corticosteroids
Antibiotics in case of infectious exacerbation
Pain
Simple analgesics: dipyrone and paracetamol
Tramadol 50 mg p.o. q8h
Morphine 5 mg p.o. q4h (elderly and CKD: start at ¼ of the dose)
Neuropathic pain: start gabapentin or pregabalin
Hemoptysis
Bronchiectasis + altered lung structure: start antibiotic therapy
Lung cancer: evaluate the need for hemostatic radiation therapy/chemotherapy
Inhaled tranexamic acid 500 mg in saline solution 0.9%, 5 mL q8h
Bronchoscopy
Bronchial arterial embolization
Irreversible cases: use dark blue sheets and clothes
Anxiety attacks
Investigate anxiety symptoms
Sertraline 25-50 mg/day p.o.
Benzodiazepines: weak evidence
Address psychosocial suffering
Cachexia
Nutritional assessment
Investigate and treat changes in metabolism, sleep, and bowel habits
Preferably oral diet
Artificial routes of nutrition in special situations

CKD: chronic kidney disease; and COMFORT: **C**all for help; **O**bserve and treat possible causes; **M**edicate as per medical prescription; **F**an directed to the face; **O**xygen therapy, when indicated; **R**elaxation; and **T**iming, assessing patient response to each of these interventions.[47]

an act of law, states that physicians are allowed to limit or suspend treatments that prolong the life of patients in the terminal phase of a serious or incurable disease, always respecting the will of patients or their legal representatives. We believe that a joint decision-making process that gives voice to patients and families after providing them with information and understanding can optimize care and progressively distance us from the reality of dysthanasia experienced on a daily basis by patients in the ICUs and inpatient wards throughout Brazil.

BARRIERS TO PALLIATIVE CARE

The main barrier to implementing palliative care is the discomfort felt by the care teams in having open discussions about end-of-life care with their patients. This happens mainly because many patients with advanced lung diseases have uncertain short-term prognosis.[72] Other barriers identified are the limited number of healthcare professionals trained in palliative care, as well as the ethnic, cultural, and ethical issues involved.[5]

FINAL CONSIDERATIONS

Palliative care has been gaining ground in recent years. Learning how to treat patients who are experiencing pain, dyspnea, spiritual pain, and social suffering because of their lung diseases, not only at the end of their lives, can have a huge impact on how they face their disease and care. When such learning translates into proper care, there is usually less physical and emotional stress, especially in the last hours of life. As a result, the grief that unfolds is more appropriate. All of these aspects can also facilitate patient transfers when hospice care is indicated.

Given that there is still a well established tendency to perform aggressive, invasive procedures in patients in the final stages of life, the timely introduction of palliative care can improve quality of life, reducing suffering, minimize unnecessary social costs, and ultimately humanize care.

REFERENCES

1. World Health Organization [homepage on the Internet]. Geneve: World Health Organization; [cited 2019 Jul 1]. Cancer. WHO Definition of Palliative Care. [about 2 screens]. Available from: https://www.who.int/cancer/palliative/definition/en/
2. Narsavage GL, Chen YJ, Korn B, Elk R. The potential of palliative care for patients with respiratory diseases. Breathe (Sheff). 2017;13(4):278-289. https://doi.org/10.1183/20734735.014217
3. Lanken PN, Terry PB, Delisser HM, Fahy BF, Hansen-Flaschen J, Heffner JE, et al. An official American Thoracic Society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. Am J Respir Crit Care Med. 2008;177(8):912-927. https://doi.org/10.1164/rccm.200605-587ST
4. Kreuter M, Bendstrup E, Russell AM, Bajwah S, Lindell K, Adir Y, et al. Palliative care in interstitial lung disease: living well. Lancet Respir Med. 2017;5(12):968-980. https://doi.org/10.1016/S2213-2600(17)30383-1
5. Kelley AS, Morrison RS. Palliative Care for the Seriously Ill. N Engl J Med. 2015;373(8):747-755. https://doi.org/10.1056/NEJMra1404684
6. del Río MI, Palma A. Cuidados Paliativos: Historia y desarrollo. Boletín Escuela de Medicina UC, Pontificia Universidad Católica de Chile. 2007;32(1):16-22.
7. Pessini L. Cuidados paliativos: alguns aspectos conceituais, biográficos e éticos. Prat Hosp 2005;41(8)107-112.
8. Maciel MGS. A terminalidade da vida e os cuidados paliativos no Brasil: considerações e perspectivas. Prat Hosp. 2006;47(8):46-49.
9. Isaacson MJ, Minton ME. End-of-Life Communication: Nurses Cocreating the Closing Composition With Patients and Families. ANS Adv Nurs Sci. 2018;41(1):2-17. https://doi.org/10.1097/ANS.0000000000000186
10. Baile WF, Buckman R, Lenzi R, Glober G, Beale EA, Kudelka AP. SPIKES-A six-step protocol for delivering bad news: application to the patient with cancer. Oncologist. 2000;5(4):302-311. https://doi.org/10.1634/theoncologist.5-4-302
11. Back AL, Arnold RM, Baile WF, Fryer-Edwards KA, Alexander SC, Barley GE, et al. Efficacy of communication skills training for giving bad news and discussing transitions to palliative care. Arch Intern Med. 2007;167(5):453-460. https://doi.org/10.1001/archinte.167.5.453
12. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet. 1997;349(9061):1269-1276. https://doi.org/10.1016/S0140-6736(96)07493-4
13. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest. 2003;124(2):459-467. https://doi.org/10.1378/chest.124.2.459
14. Celli BR, Decramer M, Wedzicha JA, Wilson KC, Agustí A, Criner GJ, et al. An Official American Thoracic Society/European Respiratory Society Statement: Research questions in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2015;191(7):e4–e27. doi:10.1164/rccm.201501-0044ST
15. Bloom CI, Slaich B, Morales DR, Smeeth L, Stone P, Quint JK. Low uptake of palliative care for COPD patients within primary care in the UK. Eur Respir J. 2018;51(2):1701879. https://doi.org/10.1183/13993003.01879-2017
16. Maddocks M, Lovell N, Booth S, Man WD, Higginson IJ. Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease. Lancet. 2017;390(10098):988-1002. https://doi.org/10.1016/S0140-6736(17)32127-X
17. Farquhar MC, Prevost AT, McCrone P, Brafman-Price B, Bentley A, Higginson IJ, et al. The clinical and cost effectiveness of a Breathlessness Intervention Service for patients with advanced non-malignant disease and their informal carers: mixed findings of a mixed method randomised controlled trial. Trials. 2016;17:185. https://doi.org/10.1186/s13063-016-1304-6
18. Diretrizes de Doenças Pulmonares Intersticiais da Sociedade Brasileira de Pneumologia e Tisiologia. J Bras Pneumol. 2012;38(Suppl 2):S1-S133.
19. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788-824. https://doi.org/10.1164/rccm.2009-040GL
20. Matsunuma R, Takato H, Takeda Y, Watanabe S, Waseda Y, Murakami S, et al. Patients with End-stage Interstitial Lung Disease may have More Problems with Dyspnea than End-stage Lung Cancer Patients. Indian J Palliat Care. 2016;22(3):282-287. https://doi.org/10.4103/0973-1075.185035
21. De Vries J, Kessels BL, Drent M. Quality of life of idiopathic pulmonary fibrosis patients. Eur Respir J. 2001;17(5):954-961. https://doi.org/10.1183/09031936.01.17509540
22. Garibaldi BT, Danoff SK. Symptom-based management of the idiopathic interstitial pneumonia. Respirology. 2016;21(8):1357-1365. https://doi.org/10.1111/resp.12649
23. Lindell KO, Kavalieratos D, Gibson KF, Tycon L, Rosenzweig M. The palliative care needs of patients with idiopathic pulmonary fibrosis: A qualitative study of patients and family caregivers. Heart Lung. 2017;46(1):24-29. https://doi.org/10.1016/j.hrtlng.2016.10.002
24. Lindell KO, Liang Z, Hoffman LA, Rosenzweig MQ, Saul MI, Pilewski JM, et al. Palliative care and location of death in decedents with

idiopathic pulmonary fibrosis. Chest. 2015;147(2):423-429. https://doi.org/10.1378/chest.14-1127

25. Yokoyama T, Tsushima K, Yamamoto H, Koizumi T, Kubo K. Potential benefits of early continuous positive pressure ventilation in patients with rapidly progressive interstitial pneumonia. Respirology. 2012;17(2):315-321. https://doi.org/10.1111/j.1440-1843.2011.02051.x
26. Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, et al. ECFS best practice guidelines: the 2018 revision. J Cyst Fibros. 2018;17(2):153-178. https://doi.org/10.1016/j.jcf.2018.02.006
27. Chen E, Killeen KM, Peterson SJ, Saulitis AK, Balk RA. Evaluation of Pain, Dyspnea, and Goals of Care Among Adults With Cystic Fibrosis: A Comprehensive Palliative Care Survey. Am J Hosp Palliat Care. 2017;34(4):347-352. https://doi.org/10.1177/1049909116629135
28. McGuffie K, Sellers DE, Sawicki GS, Robinson WM. Self-reported involvement of family members in the care of adults with CF. J Cyst Fibros. 2008;7(2):95-101. https://doi.org/10.1016/j.jcf.2007.06.002
29. Robinson WM. Palliative and end-of-life care in cystic fibrosis: what we know and what we need to know. Curr Opin Pulm Med. 2009;15(6):621-625. https://doi.org/10.1097/MCP.0b013e3283304c29
30. Santos CI, Ribeiro JD, Ribeiro AF, Hessel G. Critical analysis of scoring systems used in the assessment of Cystic Fibrosis severity: state of the art. J Bras Pneumol. 2004;30(3):286-298. https://doi.org/10.1590/S1806-37132004000300016
31. Bourke SJ, Doe SJ, Gascoigne AD, Heslop K, Fields M, Reynolds D, et al. An integrated model of provision of palliative care to patients with cystic fibrosis. Palliat Med. 2009;23(6):512-517. https://doi.org/10.1177/0269216309106312
32. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119. https://doi.org/10.1093/eurheartj/ehv317
33. Fenstad ER, Shanafelt TD, Sloan JA, Novotny PJ, Durst LA, Frantz RP, et al. Physician attitudes toward palliative care for patients with pulmonary arterial hypertension: results of a cross-sectional survey. Pulm Circ. 2014;4(3):504-510. https://doi.org/10.1086/677365
34. Taichman DB, Shin J, Hud L, Archer-Chicko C, Kaplan S, Sager JS, et al. Health-related quality of life in patients with pulmonary arterial hypertension. Respir Res. 2005;6(1):92. https://doi.org/10.1186/1465-9921-6-92
35. Sandoval J, Gaspar J, Peña H, Santos LE, Córdova J, del Valle K, et al. Effect of atrial septostomy on the survival of patients with severe pulmonary arterial hypertension. Eur Respir J. 2011;38(6):1343-1348. https://doi.org/10.1183/09031936.00072210
36. Punnoose L, Burkhoff D, Rich S, Horn EM. Right ventricular assist device in end-stage pulmonary arterial hypertension: insights from a computational model of the cardiovascular system. Prog Cardiovasc Dis. 2012;55(2):234-243.e2. https://doi.org/10.1016/j.pcad.2012.07.008
37. Chen SL, Zhang FF, Xu J, Xie DJ, Zhou L, Nguyen T, et al. Pulmonary artery denervation to treat pulmonary arterial hypertension: the single-center, prospective, first-in-man PADN-1 study (first-in-man pulmonary artery denervation for treatment of pulmonary artery hypertension). J Am Coll Cardiol. 2013;62(12):1092-1100. https://doi.org/10.1016/j.jacc.2013.05.075
38. Cachia E, Ahmedzai SH. Breathlessness in cancer patients. Eur J Cancer. 2008;44(8):1116-1123. https://doi.org/10.1016/j.ejca.2008.03.004
39. Ambrosino N, Scano G. Dyspnoea and its measurement. Breathe. 2004;1:100-107. https://doi.org/10.1183/18106838.0102.100
40. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest. 1984;85(6):751-758. https://doi.org/10.1378/chest.85.6.751
41. Papiris SA, Daniil ZD, Malagari K, Kapotsis GE, Sotiropoulou C, Milic-Emili J, et al. The Medical Research Council dyspnea scale in the estimation of disease severity in idiopathic pulmonary fibrosis. Respir Med. 2005;99(6):755-761. https://doi.org/10.1016/j.rmed.2004.10.018
42. Wijkstra PJ, TenVergert EM, Van Altena R, Otten V, Postma DS, Kraan J, et al. Reliability and validity of the chronic respiratory questionnaire (CRQ). Thorax. 1994;49(5):465-467. https://doi.org/10.1136/thx.49.5.465
43. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med. 2012;185(4):435-452. https://doi.org/10.1164/rccm.201111-2042ST
44. Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012;13(2):e58-e68. https://doi.org/10.1016/S1470-2045(12)70040-2
45. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: 5th edition. Arlington: American Psychiatric Association; 2013.
46. Kraychete DC, Garcia JBS, Siqueira JTT. Recommendations for the use of opioids in Brazil: Part IV. Adverse opioid effects Rev Dor. 2014;15(3):215-223. https://doi.org/10.5935/1806-0013.20140047
47. Rocker GM, Simpson AC, Horton R. Palliative Care in Advanced Lung Disease: The Challenge of Integrating Palliation Into Everyday Care. Chest. 2015;148(3):801-809. https://doi.org/10.1378/chest.14-2593
48. Kamal AH, Maguire JM, Wheeler JL, Currow DC, Abernethy AP. Dyspnea review for the palliative care professional: treatment goals and therapeutic options. J Palliat Med. 2012;15(1):106-114. https://doi.org/10.1089/jpm.2011.0110
49. Bandelow B, Sher L, Bunevicius R, Hollander E, Kasper S, Zohar J, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care [published correction appears in Int J Psychiatry Clin Pract. 2012 Sep;16(3):242] [published correction appears in Int J Psychiatry Clin Pract. 2013 Feb;17(1):76]. Int J Psychiatry Clin Pract. 2012;16(2):77-84. https://doi.org/10.3109/13651501.2012.667114
50. Gomes B, Calanzani N, Curiale V, McCrone P, Higginson IJ. Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers. Cochrane Database Syst Rev. 2013;(6):CD007760. https://doi.org/10.1002/14651858.CD007760.pub2
51. Seamark DA, Seamark CJ, Halpin DM. Palliative care in chronic obstructive pulmonary disease: a review for clinicians. J R Soc Med. 2007;100(5):225-233. https://doi.org/10.1177/014107680710000512
52. Shee CD, Green M. Non-invasive ventilation and palliation: experience in a district general hospital and a review. Palliat Med. 2003;17(1):21-26. https://doi.org/10.1191/0269216303pm659oa
53. Davies JD. Noninvasive Respiratory Support at the End of Life. Respir Care. 2019;64(6):701-711. https://doi.org/10.4187/respcare.06618
54. Amano K, Baracos VE, Hopkinson JB. Integration of palliative, supportive, and nutritional care to alleviate eating-related distress among advanced cancer patients with cachexia and their family members. Crit Rev Oncol Hematol. 2019;143:117-123. https://doi.org/10.1016/j.critrevonc.2019.08.006
55. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr. 2017;36(1):49-64. https://doi.org/10.1016/j.clnu.2016.09.004
56. Jean-Baptiste E. Clinical assessment and management of massive hemoptysis. Crit Care Med. 2000;28(5):1642-1647. https://doi.org/10.1097/00003246-200005000-00066
57. Wand O, Guber E, Guber A, Epstein Shochet G, Israeli-Shani L, Shitrit D. Inhaled Tranexamic Acid for Hemoptysis Treatment: A Randomized Controlled Trial. Chest. 2018;154(6):1379-1384. https://doi.org/10.1016/j.chest.2018.09.026
58. Ittrich H, Bockhorn M, Klose H, Simon M. The Diagnosis and Treatment of Hemoptysis. Dtsch Arztebl Int. 2017;114(21):371-381. https://doi.org/10.3238/arztebl.2017.0371
59. Hanks G, Cherney NI, Christakis NA, Fallon M, Kaasa S, Portenoy RK, editors. Oxford Textbook of Palliative Medicine. 4th ed. New York: Oxford University Press; 2010. https://doi.org/10.1093/med/9780198570295.001.0001
60. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet. 2008;371(9621):1364-1374. https://doi.org/10.1016/S0140-6736(08)60595-4
61. Irwin RS, French CL, Chang AB, Altman KW; CHEST Expert Cough Panel*. Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report. Chest. 2018;153(1):196-209. https://doi.org/10.1016/j.chest.2017.10.016

62. Molassiotis A, Smith JA, Mazzone P, Blackhall F, Irwin RS; CHEST Expert Cough Panel. Symptomatic Treatment of Cough Among Adult Patients With Lung Cancer: CHEST Guideline and Expert Panel Report [published correction appears in Chest. 2017 Nov;152(5):1095]. Chest. 2017;151(4):861-874. https://doi.org/10.1016/j.chest.2016.12.028
63. Vigeland CL, Hughes AH, Horton MR. Etiology and treatment of cough in idiopathic pulmonary fibrosis. Respir Med. 2017;123:98-104. https://doi.org/10.1016/j.rmed.2016.12.016
64. Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS, et al. Treatment of Unexplained Chronic Cough: CHEST Guideline and Expert Panel Report. Chest. 2016;149(1):27-44. https://doi.org/10.1378/chest.15-1496
65. Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, Hill AT. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med. 2012;186(7):657-665. https://doi.org/10.1164/rccm.201203-0487OC
66. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain. 2019;160(1):19-27. https://doi.org/10.1097/j.pain.0000000000001384
67. Peeters-Asdourian C, Massard G, Rana PH, Van Houtte P, White AP, Grigoriu B, et al. Pain control in thoracic oncology. Eur Respir J. 2017;50(3):1700611. https://doi.org/10.1183/13993003.00611-2017
68. Riley J, Ross JR, Gretton SK, A'Hern R, du Bois R, Welsh K, et al. Proposed 5-step World Health Organization analgesic and side effect ladder. Eur J Pain Suppl. 2007;1(1):23-30. https://doi.org/10.1016/S1754-3207(08)60008-5
69. Roeland E, Cain J, Onderdonk C, Kerr K, Mitchell W, Thornberry K. When open-ended questions don't work: the role of palliative paternalism in difficult medical decisions. J Palliat Med. 2014;17(4):415-420. https://doi.org/10.1089/jpm.2013.0408
70. Brasil. Governo do Estado de São Paulo. Lei Estadual N. 10.241, Dispõe sobre os direitos dos usuários dos serviços e das ações de saúde no Estado e dá outras providências. (May 17, 1999).
71. Brasil. Conselho Federal de Medicina. Resolução N, 2217. Aprova o Código de Ética Médica. (Sep 27, 2018).
72. Fox E, Landrum-McNiff K, Zhong Z, Dawson NV, Wu AW, Lynn J. Evaluation of prognostic criteria for determining hospice eligibility in patients with advanced lung, heart, or liver disease. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. JAMA. 1999;282(17):1638-1645. https://doi.org/10.1001/jama.282.17.1638

J Bras Pneumol. 2020;46(3):e20190365
https://dx.doi.org/10.36416/1806-3756/e20190365

Angiolymphoid hyperplasia with eosinophilia in the lungs: a complex name for an innocuous disease?

Cátia Alexandra Correia Pereira[1], Filipa Mendes Ferro[1], Ana Filipa dos Santos Matos[1], Mariana Denise Lourenço Graça Antunes[2], Pierpaolo Cusati[3]

TO THE EDITOR:

Angiolymphoid hyperplasia with eosinophilia (ALHE), also known as epithelioid hemangioma, is a rare entity that was first described by Wells & Whimster in 1969.[1] It is a rare benign vascular tumor characterized by vascular proliferation, lymphoid hyperplasia, and eosinophilia.[2] The lesions are located mainly in the subcutaneous tissue of the head and neck.[1] Reported cases of pulmonary involvement are extremely rare.[3-5]

Here, we report a case of ALHE of the lung. The patient was a 59-year-old White male who was a current smoker with a smoking history of 48 pack-years and a history of illicit drug use (inhaled heroin) more than 10 years prior. He presented with a two-month history of asthenia and tiring easily. The results of the physical examination were normal. A CT scan of the chest showed a 4-cm peripheral pulmonary mass in the left lower lobe and bilateral diffuse emphysema (Figure 1A). Laboratory tests showed no anemia (hemoglobin, 14.7 g/dL), other findings of note including eosinophilia (540 × 10^9 eosinophils/L), normal total IgE (22.9 U/mL), negative serology for viral infection, normal serum protein electrophoresis results, and normal immunoglobulin levels. Positron emission tomography (PET) revealed mild uptake (maximum standardized uptake value, 1.0-1.8) in four micronodules in the left upper lobe and in three micronodules in the left lower lobe, all of which were located in the juxta-diaphragmatic region, had an undetermined nature, were solid, and measured between 3 and 6 mm. The 4-cm pulmonary mass showed no uptake. CT-guided percutaneous lung biopsy (Figure 1B) yielded histological results suggestive of ALHE, although it was not possible to completely exclude parasitic infection (Figures 1C and 1D). Concomitantly, fiberoptic bronchoscopy, with BAL, showed no endobronchial lesions. The BAL fluid tested negative for neoplastic cells, bacteria, fungus, viruses, and parasites. Although surgical resection was considered, it was contraindicated because of the severity of the obstructive disease, with low DLCO. At this writing, the patient is undergoing pulmonary rehabilitation.

ALHE is an uncommon condition of unknown etiology. It typically develops between the third and fifth decades of life and appears to occur primarily in women.[1] Lesions predominantly affect the subcutaneous cellular tissue of the neck.[1] Pulmonary involvement is rare, and, in such cases, the most commonly reported symptoms are cough and dyspnea.[2,3]

The differential diagnosis is broad and comprises malignant diseases, including low-grade lymphomas, such as mucosa-associated lymphoid tissue lymphoma; more aggressive lymphomas, such as Hodgkin lymphoma; and malignant vascular tumors, namely, primary or metastatic pulmonary angiosarcoma.[3] Benign conditions, such as nodular lymphoid hyperplasia of the lung and lymphocytic interstitial pneumonia, can also be considered; however, in these two conditions, the infiltrate is predominantly lymphoid rather than eosinophilic.[3] In addition, other benign conditions, such as parasitic infection, Langerhans cell histiocytosis, and Churg-Strauss syndrome, should be considered; in the case reported here, however, the differential diagnosis did not include Langerhans cell histiocytosis, given the absence of immunohistochemical staining for CD1a, and did not include Churg-Strauss syndrome, given the absence of other clinical criteria consistent with this disease.[3] The differential diagnosis also includes IgG4-related disease.[6,7] However, the absence of obliterating arteritis, the insignificant fibrosis, and the small number of plasma cells in the biopsy specimen allowed us to exclude that diagnosis.[8] Finally, we excluded the possibility of extramedullary erythropoiesis because there was no anemia or splenomegaly and there were no immature cells in the histological sections.[3] Therefore, biopsy is essential to establish the diagnosis; the presence of immature vessels and proliferation of epithelioid endothelial cells accompanied by marked infiltration of eosinophils and lymphocytes should suggest the diagnosis of ALHE.[1,2] With regard to the behavior of ALHE on PET, there have been scattered cases in which PET has revealed marked uptake, unlike in the case reported here; however, to date, there have been no studies describing the characteristics and usefulness of PET in patients with ALHE.[9]

Although only a few cases of ALHE of the lung have been reported, the prognosis is described as being favorable.[2] The scarcity of such cases is also the cause of the uncertainty about the appropriate therapeutic approach. Surgical resection appears to be the most option of choice,[2,3,5] although there have been reports of cases treated with nonsurgical options, including one treated with prednisolone and IFN-α2b,[4] as well as one managed by clinical and imaging monitoring.[3]

Albeit rare, ALHE of the lung should be considered in the differential diagnosis of pulmonary nodules.[5] Decisions regarding treatment should involve a multidisciplinary

1. Serviço de Pneumologia, Centro Hospitalar Lisboa Norte, Lisboa, Portugal.
2. Serviço de Cirurgia Torácica, Hospital Pulido Valente, Centro Hospitalar Lisboa Norte, Lisboa, Portugal.
3. Serviço de Anatomia Patológica, Centro Hospitalar Lisboa Norte, Lisboa, Portugal.

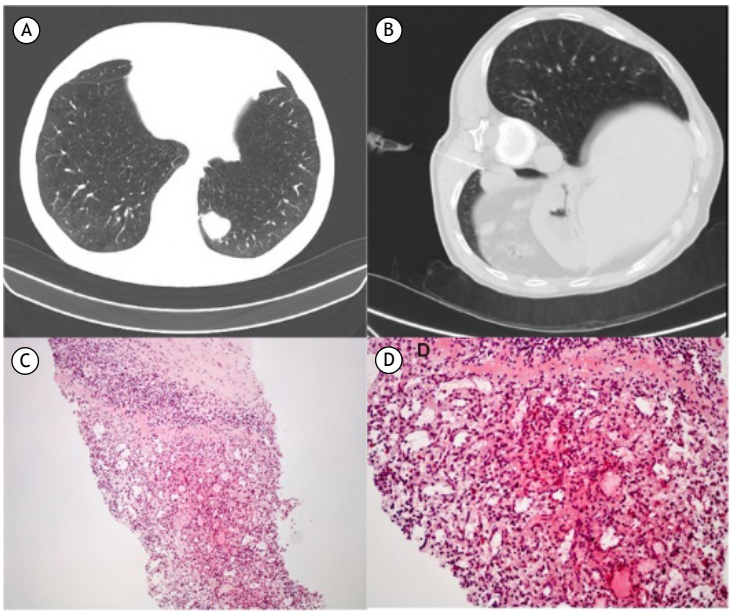


Figure 1. In A, CT scan of the chest showing a 4-cm peripheral pulmonary mass in the left lower lobe and bilateral diffuse emphysema. In B, CT-guided transthoracic biopsy. In C and D, photomicrographs of the lung parenchyma (H&E; magnification, ×100 in C and ×200 in D), showing edema, diffuse capillary proliferation, areas of fibrosis, and intense mixed inflammatory infiltrate, in which there are numerous B or T lymphocytes, together with eosinophilic granulocytes.

team and should be made in conjunction with the patient, given the many uncertainties surrounding this disease.

To our knowledge, there have been only four reported cases of ALHE of the lung. However, we believe that even a small number of ALHE cases or individual experiences with it could improve our knowledge and management of this disease.

REFERENCES

1. Wells GC, Whimster IW. Subcutaneous angiolymphoid hyperplasia with eosinophilia. Br J Dermatol. 1969;81(1):1-14. https://doi.org/10.1111/j.1365-2133.1969.tb15914.x
2. Suster S, Moran CA. Angiolymphoid hyperplasia with eosinophilia. In: Suster S, Moran CA. Diagnostic Pathology: Thoracic. 2nd ed. Philadelphia: Elsevier; 2017. p.336-339.
3. Moran CA, Suster S. Angiolymphoid hyperplasia with eosinophilia (epithelioid hemangioma) of the lung: a clinicopathologic and immunohistochemical study of two cases. Am J Clin Pathol. 2005;123(5):762-765. https://doi.org/10.1309/UN1AQ2WJU9HDD72F
4. Dulohery MM, Patel RR, Schneider F, Ryu JH. Lung involvement in hypereosinophilic syndromes. Respir Med. 2011;105(1):114-121. https://doi.org/10.1016/j.rmed.2010.09.011
5. Ribeiro L, Souto M, Loureiro A. Angiolymphoid Hyperplasia With Eosinophilia of the Lung. Arch Bronconeumol. 2018;54(6):340-342. https://doi.org/10.1016/j.arbres.2017.12.013
6. Hamaguchi Y, Fujimoto M, Matsushita Y, Kitamura-Sawada S, Kawano M, Takehara K. IgG4-related skin disease, a mimic of angiolymphoid hyperplasia with eosinophilia. Dermatology. 2011;223(4):301-305. https://doi.org/10.1159/000335372
7. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25(9):1181-1192. https://doi.org/10.1038/modpathol.2012.72
8. Moreira LB, Melo AS, Marchiori E. Intrathoracic extramedullary hematopoiesis: a case report [Article in Portuguese]. Radiol Bras 2001;34(3):177-180. https://doi.org/10.1590/S0100-39842001000300013
9. Cellina M, Martinenghi CMA, Panzeri M, Oliva G. Epithelioid hemangioma of the arm: a rare benign vascular lesion. Rheumatol Orthop Med. 2018;3(2):1-3. https://doi.org/10.15761/ROM.1000147

J Bras Pneumol. 2020;46(3):e20190287
https://dx.doi.org/10.36416/1806-3756/e20190287

Pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension and hemoglobinopathies

Ana Cecília Cardoso de Sousa[1], Frederico Thadeu Assis Figueiredo Campos[1,2], Rodrigo de Castro Bernardes[1], Marcelo Braga Ivo[1], Ricardo de Amorim Corrêa[3]

TO THE EDITOR:

We report two cases of patients with sickle cell disease (SCD) and chronic thromboembolic pulmonary hypertension (CTEPH) who underwent pulmonary thromboendarterectomy (PTE), highlighting the scarcity of such cases in Brazil and the special care required during the perioperative period.

Patient 1 was a 38-year-old man with a diagnosis of CTEPH and SCD (homozygous hemoglobin SS) who had a history of recurrent vaso-occlusive crises and was being followed at the Pulmonary Circulation Outpatient Clinic of the Federal University of Minas Gerais *Hospital das Clínicas*, located in the city of Belo Horizonte, Brazil. The patient had been referred to *Hospital Madre Teresa*, located in the same city, with a complaint of progressive dyspnea—World Health Organization Functional Class (WHO-FC) IV—having been receiving anticoagulation with warfarin for 1 year and having been taking tadalafil for 1 month; he had previously been evaluated at that facility with a view to undergoing PTE. On admission, the patient was pale and had increased jugular venous pressure, peripheral cyanosis, mild leg edema, and tachypnea. Physical examination revealed the following: HR = 75 bpm; blood pressure (BP) = 103/60 mmHg; RR = 28 breaths/min; and room-air SpO_2 = 90%. Lung auscultation revealed fine infrascapular crackles. Cardiac auscultation revealed a regular cardiac rhythm with normal heart sounds, accentuation of the second heart sound in its pulmonic component, and no murmurs. His abdomen was painless, and he had hepatomegaly without ascites. After cardiac dysfunction was stabilized, he was reevaluated with a view to undergoing PTE. Previous CT angiography of the chest had shown an extensive filling defect in the lobar, segmental, and subsegmental branches of the right lower lobe, as well as intraluminal filling defects in the anterior segment of the right upper lobe and in the apical posterior segment of the left upper lobe. Ventilation-perfusion lung scintigraphy revealed multiple, bilaterally distributed areas of segmental hypoperfusion, a bilateral parenchymal lung process (probably a sequela of tuberculosis), and an increased cardiac silhouette. An echocardiogram showed that the left ventricle dimensions and contractile function were preserved; the right ventricle dimensions were markedly increased, the ventricle measuring 50 mm in its maximum diastolic diameter, with signs of myocardial hypertrophy and reduced contractility throughout the ventricular wall; the right and left atria were moderately and mildly increased, respectively; tricuspid regurgitation was moderate, with a tricuspid regurgitant jet velocity of 4.87 m/s; and the estimated pulmonary artery systolic pressure was 115 mmHg. Right heart catheterization (RHC) revealed the following: mean pulmonary artery pressure (mPAP) = 42 mmHg; pulmonary artery wedge pressure (PAWP) = 6 mmHg; pulmonary vascular resistance (PVR) = 456.0 dyn/s/cm^{-5}; and cardiac index (CI) = 3.32 L/min/m^2. Pulmonary angiography revealed hypoperfusion of the upper, middle, and lower lobes of the right lung, together with occlusion of a right lower lobe segmental artery. As preoperative preparation, the patient received six exchange transfusions, and his hemoglobin S (HbS) level reached 36% (vs. 68.1% at baseline). The intraoperative period was uneventful. In the postoperative period, the patient had an undefined focus of infection, the size of which was reduced with the use of antibiotics. He was discharged on day 21, without the need for oxygen supplementation. Three months after PTE, the patient was asymptomatic (WHO-FC I). An RHC revealed the following: mPAP = 24 mmHg; PVR = 269.6 dyn/s/cm^{-5}; and CI = 3.22 L/min/m^2 (Table 1). In addition, the six-minute walk distance (6MWD) was 500 m, the SpO_2 decreased from 91% to 85%, and the HR increased from 82 bpm to 128 bpm.

Patient 2 was a 53-year-old woman with SCD (heterozygous hemoglobin SC) and a self-reported one-month history of progressively worsening dyspnea (WHO-FC II) who was diagnosed with acute pulmonary thromboembolism. Having been receiving anticoagulation with warfarin for 5 months, the patient experienced worsening of dyspnea (WHO-FC IV) and had episodes of syncope. On admission to the Pulmonary Circulation Outpatient Clinic of *Hospital Júlia Kubistchek*, located in Belo Horizonte, for evaluation of her condition, she was WHO-FC IV, was acyanotic, had ankle edema, and was intolerant of the supine position. Her vital signs were as follows: HR = 98 bpm; BP = 100/60 mmHg; RR = 26 breaths/min; and room-air SpO_2 = 89%. Her breath sounds were normal, and there was an accentuated second heart sound. An echocardiogram showed that the left ventricle dimensions and systolic function were preserved; the right ventricle measured 37 mm in its maximum diastolic diameter, with normal contraction; tricuspid

1. Hospital Madre Teresa, Belo Horizonte (MG) Brasil.
2. Hospital Júlia Kubitschek, Fundação Hospitalar do Estado de Minas Gerais – FHEMIG – Belo Horizonte (MG) Brasil.
3. Hospital das Clínicas, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.

Table 1. Patient hemodynamic results before and after pulmonary thromboendarterectomy.

Patient	Preoperative period (RHC)				Immediate postoperative period (SG)				Late postoperative period (RHC)			
	PAP(m)	CI	PVR	CO	mPAP	CI	PVR	CO	PAP(m)	CI	PVR	CO
	mmHg	L/min/m^2	dyn/s/cm^{-5}	L/min (Fick)	mmHg	L/min/m^2	dyn/s/cm^{-5}	L/min (thermodilution)	mmHg	L/min/m^2	dyn/s/cm^{-5}	L/min (Fick)
1	70/28 (42)	3.32	456	6.32	27	4.65	145	8.28	46/13 (24)	3.22	269.6	5.94
2	100/25 (50)	2.02	1,010.4	3.33	30	3.09	301	5.49	38/15 (22)	2.05	284.0	4.51

RHC: right heart catheterization; SG: Swan-Ganz; PAP: pulmonary artery pressure; (m): mean; CI: cardiac index; PVR: pulmonary vascular resistance; CO: cardiac output; and mPAP: mean pulmonary artery pressure.

regurgitation was mild; tricuspid regurgitant jet velocity was 4.22 m/s; and the estimated pulmonary artery systolic pressure was 81 mmHg. Chest CT angiography showed that there was a thrombus in the right lower lobe artery; the main pulmonary artery measured 34 mm; there were areas of mosaic attenuation in both lungs; and bronchiectasis and bronchiolectasis were present in the basal lung segments, being accompanied by fibroatelectatic striae. Ventilation-perfusion lung scintigraphy revealed absence of right-lung perfusion in the upper lobe, middle lobe, and anterior basal segment of the lower lobe and absence of left-lung perfusion in the posterior apical portion of the upper lobe. An RHC revealed the following: mPAP = 50 mmHg; PAWP = 8 mmHg; PVR = 1,010.4 dyn/s/cm^{-5}; and CI = 2.02 L/min/m^2. Pulmonary angiography revealed moderate hypoperfusion of the right upper lobe and mild hypoperfusion of the right lower lobe. The 6MWD (with supplemental oxygen) was 278 m; the SpO_2 decreased from 98% to 92%; and the HR increased from 95 bpm to 124 bpm. After a diagnosis of CTEPH was established, the patient was started on bosentan and tadalafil. At the outpatient clinic, the patient was evaluated with a view to undergoing PTE, being referred to the *Hospital Madre Teresa* for the procedure. As preoperative preparation, the patient received four exchange transfusions, and her HbS level reached 16.6% (vs. 46.5% at baseline). The intraoperative period was uneventful. At 3 months after surgery, she was asymptomatic (WHO-FC I). Another RHC showed the following: mPAP = 22 mmHg, PVR = 284 dyn/s/cm^{-5}, and CI = 2.05 L/min/m^2 (Table 1); 6MWD = 465 m; SpO_2 increased from 94% to 97%; and HR increased from 70 bpm to 100 bpm.

As described in the literature,[1-3] CTEPH is characterized by the presence of organized thrombi in the pulmonary arteries after at least three months of full anticoagulation, accompanied by an mPAP > 20 mmHg, a PAWP ≤ 15 mmHg, and a PVR > 3 Woods Units or 240 dyn/s/cm^{-5}, with at least one perfusion defect detected by lung scintigraphy or chest CT angiography. CTEPH and SCD comorbidity has a prevalence of 6-11% and is one of the causes of death in such patients. The pathophysiology of CTEPH in SCD involves factors such as sickling, hemolysis, endothelial inflammation and dysfunction, hypercoagulability, and pulmonary artery thrombosis.[4]

Patients with SCD who are candidates for anesthetic and surgical procedures require special care, given the occurrence of hypoxia, metabolic or respiratory acidosis, hypothermia, infections, and hypovolemia, all of which are associated with surgical trauma. Increased sickling and increased vaso-occlusive crises are common. Patients with SCD can also experience acute chest syndrome, pain crises, priapism, and stroke. Therefore, appropriate preoperative preparation is crucial, and the surgical team should include a hematologist.[5-7]

Studies on the treatment of CTEPH in patients with SCD are scarce. Strategies for treating such patients include optimizing disease treatment and identifying potentially modifiable etiologies. One treatment option, for selected patients, is PTE, which can produce satisfactory outcomes if there is appropriate patient preparation to minimize the effects of cardiopulmonary bypass, hypothermia, and periods of total circulatory arrest that increase the risk of sickling.[3] It has been suggested that HbS levels be maintained between 30% and 10% through exchange transfusions.[5,7] However, there is a risk of recurrent or persistent pulmonary hypertension due to proliferative pulmonary arteriopathy secondary to chronic hemolysis. In addition, there may be *in situ* proximal pulmonary thrombosis, which is difficult to differentiate from new thromboembolic events in the differential diagnosis.[6]

Chief among the largest studies on the treatment of CTEPH in patients with hemoglobinopathies is the study carried out by Mahesh et al.[3] at Papworth Hospital in the United Kingdom. In that study, 19 patients with hemoglobinopathies/hemolytic anemia and CTEPH were retrospectively evaluated regarding treatment with PTE. In that case series, it was decided that HbS levels would be reduced to ≤ 20% through the use of partial exchange transfusions preoperatively and immediately before cardiopulmonary bypass. These measures resulted in significant improvements in PVR, as well as in recovery of FC and 6MWD in the late postoperative period.[3]

In conclusion, PTE is a feasible treatment option for patients with SCD and CTEPH. Given the complexity of the underlying disease and of the surgical treatment, procedures should be performed at facilities that are referral centers for CTEPH and have experience in PTE. Under those conditions, satisfactory outcomes can be achieved.

REFERENCES

1. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT) [published correction appears in Eur Respir J. 2015 Dec;46(6):1855-6]. Eur Respir J. 2015;46(4):903-975. https://doi.org/10.1183/13993003.01032-2015
2. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53(1):1801915. https://doi.org/10.1183/13993003.01915-2018
3. Mahesh B, Besser M, Ravaglioli A, Pepke-Zaba J, Martinez G, Klein A, et al. Pulmonary endarterectomy is effective and safe in patients with haemoglobinopathies and abnormal red blood cells: the Papworth experience. Eur J Cardiothorac Surg. 2016;50(3):537-541. https://doi.org/10.1093/ejcts/ezw062
4. Freeman AT, Ataga KI. Pulmonary endarterectomy as treatment for chronic thromboembolic pulmonary hypertension in sickle cell disease. Am J Hematol. 2015;90(12):E223-E224. https://doi.org/10.1002/ajh.24192
5. Crawford TC, Carter MV, Patel RK, Suarez-Pierre A, Lin SZ, Magruder JT, et al. Management of sickle cell disease in patients undergoing cardiac surgery. J Card Surg. 2017;32(2):80-84. https://doi.org/10.1111/jocs.13093
6. Jerath A, Murphy P, Madonik M, Barth D, Granton J, de Perrot M. Pulmonary endarterectomy in sickle cell haemoglobin C disease. Eur Respir J. 2011;38(3):735-737. https://doi.org/10.1183/09031936.00192910
7. Klings ES, Machado RF, Barst RJ, Morris CR, Mubarak KK, Gordeuk VR, et al. An official American Thoracic Society clinical practice guideline: diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. Am J Respir Crit Care Med. 2014;189(6):727-740.

J Bras Pneumol. 2020;46(3):e20180352
https://dx.doi.org/10.36416/1806-3756/e20180352

Omalizumab: what do we learn from patients in treatment for more than ten years?

Faradiba Sarquis Serpa[1], Joseane Chiabai[1,2], Fernanda Lugão Campinhos[1], Augusto Sarquis Serpa[1], Firmino Braga Neto[1]

TO THE EDITOR:

In recent years, several studies have examined the use of biologic agents in the treatment of asthma. Omalizumab is a humanized anti-IgE monoclonal antibody and the first biologic agent to be approved for use in the treatment of asthma. It is currently licensed for use in adults and children ≥ 6 years of age with severe uncontrolled allergic asthma.[1] By binding to circulating free IgE, omalizumab prevents it from interacting with its high- and low-affinity receptors on mast cells, basophils, and circulating dendritic cells, thus interrupting the inflammatory cascade and the release of proinflammatory mediators.[1] Several studies have confirmed the efficacy and safety of omalizumab in patients with severe allergic asthma, even after long-term use.[2-4]

The present report describes the clinical and functional efficacy of omalizumab, as well as its safety, in two nonsmoking women with severe asthma receiving treatment with the drug for more than 10 years. The diagnosis of asthma was based on clinical criteria (asthma symptoms appearing in childhood and triggered/worsened by aeroallergens and environmental irritants), as well as on positive aeroallergen-specific IgE and expiratory flow limitation, as assessed by an FEV_1/FVC ratio of < 75% of the predicted value. One of the patients (patient 1) showed bronchodilator reversibility during follow-up, albeit only once. Despite receiving regular treatment with high-dose inhaled corticosteroids and a long-acting β_2 agonist, neither patient achieved disease control as defined by Global Initiative for Asthma criteria.[5] Both had at least 5 exacerbations per year and used daily short-acting β_2-agonist medications and long-term systemic corticosteroids. Over the course of 1 year, both patients used systemic corticosteroids on more than 50% of the days, patient 1 using prednisone at a dose of 10 mg/day and patient 2 using betamethasone at least six times a year. All comorbidities potentially contributing to poor asthma control were treated, the exception being obesity. Treatment adherence and inhaler technique were evaluated at each visit. The patients were followed for more than 1 year but failed to achieve disease control with conventional therapy, omalizumab therefore being added to the treatment regimen. The addition of omalizumab reduced exacerbations and eliminated the need for emergency room visits and hospitalizations, systemic corticosteroid therapy therefore being discontinued. Patient clinical and laboratory data, as well as lung function parameters, are shown in Table 1.

Response to omalizumab occurs within the first few months of treatment, and the benefits of omalizumab in reducing exacerbations, emergency room visits, and hospitalizations are well established.[2] Recent studies have shown the safety and efficacy of long-term treatment with omalizumab.[3,4] There is controversy regarding the benefits of omalizumab in reducing the use of inhaled corticosteroids over the course of treatment; there have been reports of small to moderate reductions in use,[2,3,6] as was the case here. In addition, there have been reports of reductions in the use of long-acting β_2 agonists and montelukast after treatment for more than 60 months.[7] The fact that omalizumab results in a more significant reduction in or discontinuation of systemic corticosteroids reinforces the benefits of the drug in controlling inflammation, reducing the risks and adverse effects associated with frequent or prolonged use of systemic corticosteroids.[6] In the two cases reported here, the addition of omalizumab to the treatment regimen allowed the patients to discontinue systemic corticosteroid therapy. With regard to lung function, changes in spirometric parameters are variable. Although some studies have shown an increase of 6.7-11.4% in FEV_1 after 4-6 months of treatment,[2] others have shown a time-dependent response, with increases of 15% and 24% after 36 months and 48 months, respectively.[3,8] However, most studies have shown that FEV_1 increases after approximately 12 months of treatment, at which time omalizumab reaches its peak efficacy, drug efficacy remaining constant or slightly decreasing thereafter. In a study involving 24 severe asthma patients using omalizumab, there was a significant increase in mean FEV_1 (in % of the predicted value), from 37.6% at the beginning of treatment to 44.0% at treatment week 16.[9] In the two cases reported here, FEV_1 and FVC varied over the years, having improved in patient 1. In patient 2, there was an increase in FVC; however, FEV_1 remained unchanged. Nevertheless, despite treatment, severe obstructive lung disease persisted in both patients. Airway remodeling and irreversible airway changes are likely responsible for the lack of functional improvement in some patients. The patients in the present study had been living with asthma and frequent exacerbations for more than 40 years, the latter being a risk factor for airway remodeling.[10] It has been suggested that, by effectively reducing exacerbations, omalizumab can indirectly reverse the structural changes induced by periods of worsening airway inflammation, thus slowing lung function decline.[7]

1. Centro de Referência em Asma, Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória, Vitória (ES) Brasil.
2. Universidade Federal do Espírito Santo, Vitória (ES) Brasil.

ISSN 1806-3713

Table 1. Demographic, clinical, laboratory, and spirometric data for two severe asthma patients receiving treatment with omalizumab for more than 10 years.

Variable	Patient 1	Patient 2
Age, years	65	56
Sex	Female	Female
BMI, kg/m^2	37.1	34.6
Duration of asthma, years	61	41
Duration of treatment with omalizumab, years	11	11
Family history of asthma	No	Yes
Emergency room visits and hospitalizations for asthma in the year preceding treatment	Yes	Yes
ICU admission prior to treatment initiation	Yes (EI)	No
Emergency room visits and hospitalizations for asthma after treatment initiation	No	No
Mean inhaled corticosteroid dose prior to treatment initiation (budesonide, µg/day)	1,200	1,200
Mean inhaled corticosteroid dose after treatment initiation (budesonide, µg/day)	800	800
Continuous systemic corticosteroid use prior to treatment initiation	Yes	Yes
Adverse events during treatment with omalizumab	No	No
Comorbidities	Obesity, rhinitis, GERD, SAH	Obesity, rhinitis, GERD, DM
Peripheral eosinophil count, cells/mm^3	113	248
Total IgE, IU/mL	313	192
Aeroallergen-specific IgE, skin prick test for aeroallergens, or both[a]	Positive for *D. pteronyssinus*, *D. farinae*, *B. tropicalis*	Positive for *D. pteronyssinus*, *D. farinae*, *B. tropicalis*
Pre-BD FVC, L (%P)[b]		
At the initiation of treatment with omalizumab	1.00 (42)	1.79 (58)
After 5 years of treatment	1.19 (51)	2.36 (75)
After 10 years of treatment	1.29 (60)	2.07 (70)
Pre-BD FEV_1, L (%P)[b]		
At the initiation of treatment with omalizumab	0.44 (23)	0.90 (36)
After 5 years of treatment	0.62 (32)	1.38 (54)
After 10 years of treatment	0.62 (37)	0.85 (38)
FEV_1/FVC, n (%P)[b]		
At the initiation of treatment with omalizumab	0.44 (55)	0.50 (62)
After 5 years of treatment	0.52 (64)	0.58 (72)
After 10 years of treatment	0.48 (61)	0.41 (51)
HRCT of the chest	Bronchial wall thickening	Bronchial wall thickening

BMI: body mass index; EI: endotracheal intubation; GERD: gastroesophageal reflux disease; SAH: systemic arterial hypertension; DM: diabetes mellitus; *D.*: *Dermatophagoides*; *B.*: *Blomia*; BD: bronchodilator; and %P: in percentage of the predicted value. [a]Aeroallergens tested: *D. pteronyssinus*, *D. farinae*, *B. tropicalis*, *Aspergillus fumigatus*, dog dander, and cat dander. [b]Long-acting β_2 agonist use was temporarily discontinued at least 12 h before spirometry.

In the present study, neither patient experienced adverse local or systemic effects during treatment with omalizumab, which was shown to be safe. There are conflicting data regarding the adverse effects of omalizumab, most of the data being from earlier studies.[2]

One of the limitations of the present study is that neither clinical disease control nor quality of life was objectively assessed with the use of standardized questionnaires, such as the Asthma Control Test and the Asthma Quality of Life Questionnaire. Observational studies using such instruments have shown a significant improvement in asthma control and quality of life after 1 year of treatment with omalizumab, with a slight but continuous improvement during 4-5 years of follow-up.[2]

In conclusion, long-term treatment with omalizumab appears to be safe and effective. Even after 10 years of treatment, omalizumab produces sustained benefits, including a slowing of the rate of decline in lung function.

REFERENCES

1. Scott HA, Wood LG, Gibson PG. Role of Obesity in Asthma: Mechanisms and Management Strategies. Curr Allergy Asthma Rep. 2017;17(8):53. https://doi.org/10.1007/s11882-017-0719-9
2. Camargo CA Jr, Boulet LP, Sutherland ER, Busse WW, Yancey SW, Emmett AH, et al. Body mass index and response to asthma therapy: fluticasone propionate/salmeterol versus montelukast. J Asthma. 2010;47(1):76-82. https://doi.org/10.3109/02770900903338494
3. Souza ECC, Pizzichini MMM, Dias M, Cunha MJ, Matte DL, Karloh M, Maurici R, Pizzichini E. Body mass index, asthma, and respiratory symptoms: a population-based study. J Bras Pneumol. 2020;46(1):e20190006. https://doi.org/10.1590/1806-3713/e20190006
4. Scott HA, Gibson PG, Garg ML, Wood LG. Airway inflammation is augmented by obesity and fatty acids in asthma. Eur Respir J. 2011;38(3):594-602. https://doi.org/10.1183/09031936.00139810
5. Nijhuis J, Rensen SS, Slaats Y, van Dielen FM, Buurman WA, Greve JW. Neutrophil activation in morbid obesity, chronic activation of acute inflammation. Obesity (Silver Spring). 2009;17(11):2014-2018. https://doi.org/10.1038/oby.2009.113
6. Shah TJ, Leik CE, Walsh SW. Neutrophil infiltration and systemic vascular inflammation in obese women. Reprod Sci. 2010;17(2):116-124. https://doi.org/10.1177/1933719109348252
7. Telenga ED, Tideman SW, Kerstjens HA, Ten Hacken NH, Timens W, Postma DS, et al. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. Allergy. 2012;67(8):1060-1068. https://doi.org/10.1111/j.1398-9995.2012.02855.x
8. Marijsse GS, Seys SF, Schelpe AS, Dilissen E, Goeminne P, Dupont LJ, et al. Obese individuals with asthma preferentially have a high IL-5/IL-17A/IL-25 sputum inflammatory pattern. Am J Respir Crit Care Med. 2014;189(10):1284-1285. https://doi.org/10.1164/rccm.201311-2011LE
9. Chen JH, Qin L, Shi YY, Feng JT, Zheng YL, Wan YF, et al. IL-17 protein levels in both induced sputum and plasma are increased in stable but not acute asthma individuals with obesity. Respir Med. 2016;121:48-58. https://doi.org/10.1016/j.rmed.2016.10.018
10. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. J Appl Physiol (1985). 2010;108(1):206-211. https://doi.org/10.1152/japplphysiol.00694.2009
11. Scott HA, Gibson PG, Garg ML, Pretto JJ, Morgan PJ, Callister R, et al. Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial. Clin Exp Allergy. 2013;43(1):36-49. https://doi.org/10.1111/cea.12004

J Bras Pneumol. 2020;46(3):e20190273
https://dx.doi.org/10.36416/1806-3756/e20190273

Heart-lung transplantation: a necessity

Paulo Manuel Pêgo-Fernandes[1]

TO THE EDITOR:

Heart-lung transplantation (HLT) is a treatment option for patients with end-stage heart and lung failure. The first HLT was performed by Cooley on a child with an atrioventricular septal defect and pulmonary hypertension in the late 1960s in Houston, Texas; however, survival was only 14 h.[1]

In March of 1981, after laboratory tests and shortly after approval of cyclosporine for use in heart transplantation in December of 1980, the first successful HLT was performed in Stanford, California. The patient was a 45-year-old woman with Eisenmenger syndrome who survived for 5 years after the HLT.[2]

The International Society for Heart and Lung Transplantation (ISHLT) has records of more than 4,054 HLTs performed as of 2017. The procedure was most popular in the late 1980s and early 1990s, when it peaked at 284 HLTs performed worldwide.[3]

In 2016, 58 HLTs were performed. That decline reflects advances in other treatments for pulmonary hypertension and heart failure, as well as the use of heart or lung transplantation alone[4,5]; for example, patients with severe pulmonary hypertension and poor right ventricular function usually undergo bilateral lung transplantation and not HLT, because the right ventricle generally improves rapidly following lung transplantation.[6] There are several tests to determine when right ventricular dysfunction becomes irreversible, a condition that is an indication for HLT.[7]

Given the progressive improvement in bilateral lung transplant outcomes, and especially the use of extracorporeal membrane oxygenation in select cases, there is much debate in the international literature about the need and indication for HLT or for heart or lung transplantation alone.[8] For decision-making purposes, certain aspects—anatomy; exacerbation of ventricular failure; hypertension; the clinical and hemodynamic status of the patient; worsening of quality of life; cardiac index; and renal dysfunction—should be taken into consideration.[8]

There are some specialists who contend that HLT is impractical, arguing that the heart could be used for another patient. Nevertheless, despite the decrease, the number of HLTs performed has remained stable, even at centers and in countries where there is access to all other types of technology. The long-term outcomes of HLT are essentially identical to those of lung transplantation.

The postoperative follow-up of HLT recipients should be more similar to that of lung transplant recipients than that of heart transplant recipients.[7] Common causes of death within the first 30 days include graft failure, technical complications, and infection. Bronchiolitis obliterans syndrome and pulmonary allograft dysfunction continue to be the leading causes of death within the first year.[8]

As presented in the 2018 ISHLT report,[3,4] the mean survival following HLT has progressively increased from the early 1980s to the present day, from 2.1 years in the 1982-1993 period to 3.7 years in the 1994-2003 period and 5.8 years in the 2004-2016 period.

The improvement in survival of patients undergoing HLT can be attributed to several factors[8]: the evolution of the surgical technique; advances in organ preservation solutions and in immunosuppression regimens; and a trend toward the preoperative and postoperative use of temporary mechanical circulatory assist devices. In addition, a multidisciplinary approach to patient care and management at all stages is of fundamental importance; integration among the surgical team, the intensive care team, pulmonologists, cardiologists, and pharmacists, as well as the nursing, physical therapy, and nutrition teams, is of fundamental importance for HLT success and for patient rehabilitation.[7]

Although thoracic organ transplantation in Brazil is consolidated, the absolute numbers are far below those estimated to be needed for a population of 210 million people. The latest data from the Brazilian Organ Transplant Association indicate that approximately 400 heart transplants and 100 lung transplants are performed annually. The estimated need is approximately 1,600 for each.[9]

Therefore, we have to continue working on improving these numbers. Over the years that we have worked in the field of heart and lung transplantation, HLT has proved to be a necessity. There are many patients in Brazil who could benefit from HLT for congenital heart disease or pulmonary arterial hypertension of any etiology, which are conditions that cause severe, irreversible impairment.

In Brazil, we have been performing lung transplantation since 1990 and have often encountered patients who could benefit from HLT. However, because that was not an option, those patients died. Certainly, those of us who perform heart transplantation also face this ethical dilemma. In recent years, we have felt that we owe it to Brazilian society to make HLT a treatment option. We have conducted training sessions for a multidisciplinary team, in collaboration with the University of Pennsylvania, all of which were funded by the Brazilian National Ministry of Health through the Unified Health Care System Program to Support Institutional Development (Reference no.

1. Departamento de Cardiopneumologia, Disciplina de Cirurgia Torácica, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

25000.014875/2015-12, linked to Adjustment Term no. 01/2014, published in the Official Gazette of the Federal Republic of Brazil on May 29, 2015), and we have initiated an HLT program to serve the portion of the population that could benefit from the procedure. The initial results are quite promising, and we believe that a new treatment possibility has opened up for these patients in our country.

REFERENCES

1. Webb WR, Howard HS. Cardio-pulmonary transplantation. Surg Forum. 1957;8:313-317.
2. Reitz BA, Wallwork JL, Hunt SA, Penncock JL, Billingham ME, Oyer PE, et al. Heart-lung transplantation: successful therapy for patients with pulmonary vascular disease. N Engl J Med. 1982;306(10):557-564. https://doi.org/10.1056/NEJM198203113061001
3. Khush KK, Cherikh WS, Chambers DC, Goldfarb S, Hayes Jr D, Kucheryavaya AY, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth Adult Heart Transplantation Report-2018; Focus Theme: Multiorgan Transplantation. J Heart Lung Transplant. 2018;37(10):1155-1168. https://doi.org/10.1016/j.healun.2018.07.022
4. Goldfarb SB, Hayes D Jr, Levvey BJ, Cherikh WS, Chambers DC, Khush KK, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth adult lung and heart-lung transplant report-2018; Focus theme: Multiorgan Transplantation. J Heart Lung Transplant. 2018;37(10):1169-1183. https://doi.org/10.1016/j.healun.2018.07.021
5. Brouckaert J, Verleden SE, Verbelen T, Coosemans W, Decaluwé H, De Leyn P, et al. Double-lung versus heart-lung transplantation for precapillary pulmonary arterial hypertension: a 24-year single-center retrospective study. Transpl Int. 2019;32(7):717-729. https://doi.org/10.1111/tri.13409
6. Toyoda Y, Toyoda Y. Heart-lung transplantation: adult indications and outcomes. J Thorac Dis. 2014;6(8):1138-1142.
7. Idrees JJ, Pettersson GB. State of the Art of Combined Heart-Lung Transplantation for Advanced Cardiac and Pulmonary Dysfunction. Curr Cardiol Rep. 2016;18(4):36. https://doi.org/10.1007/s11886-016-0713-1
8. Le Pavec J, Hascoët S, Fadel E. Heart-lung transplantation: current indications, prognosis and specific considerations. J Thorac Dis. 2018;10(10):5946-5952. https://doi.org/10.21037/jtd.2018.09.115
9. Associação Brasileira de Transplante de Órgãos [homepage on the Internet]. São Paulo: Associação Brasileira de Transplante de Órgãos. [cited 2019 Aug 01]. Registro Nacional de Transplantes. Dimensionamento dos Transplantes no Brasil e em cada estado, 2018. Ano XXIV, no. 4. [Adobe Acrobat document, 89p.]. Available from: http://www.abto.org.br/abtov03/Upload/file/RBT/2018/Lv_RBT-2018.pdf

Traumatic pulmonary pseudocyst: an unusual cause of a cavitary pulmonary nodule

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

A previously healthy 34-year-old man presented to the emergency department 1 day after being involved in a motor vehicle accident. He complained of right-sided chest pain, cough, and hemoptysis. Chest CT showed a small cavitary nodule, containing an air-fluid level and surrounded by ground-glass opacities, in the right lower lobe (Figure 1A). A diagnosis of traumatic pulmonary pseudocyst (TPP) was made. The case was managed conservatively, and there were no complications. A follow-up CT scan acquired 12 days later showed that the cystic lesion had evolved to a homogeneous nodule (Figure 1B). Another CT scan acquired three months later showed a marked reduction in the volume of the lesion.

An uncommon lesion associated with traumatic chest injury, TPP occurs as a consequence of traumatic disruption of the lung parenchyma, with subsequent filling of the traumatic intraparenchymal defect with air, blood, or both. The condition is frequently associated with pulmonary contusions.[1-3] Common symptoms include chest pain, dyspnea, cough, and hemoptysis, although some patients are asymptomatic. The most common finding on CT is a round or oval cystic structure, with or without an air-fluid level. The lesion is typically surrounded by ground-glass opacities or consolidations resulting from pulmonary contusion. The management of TPP is conservative, because the clinical course is usually benign.[1-3]

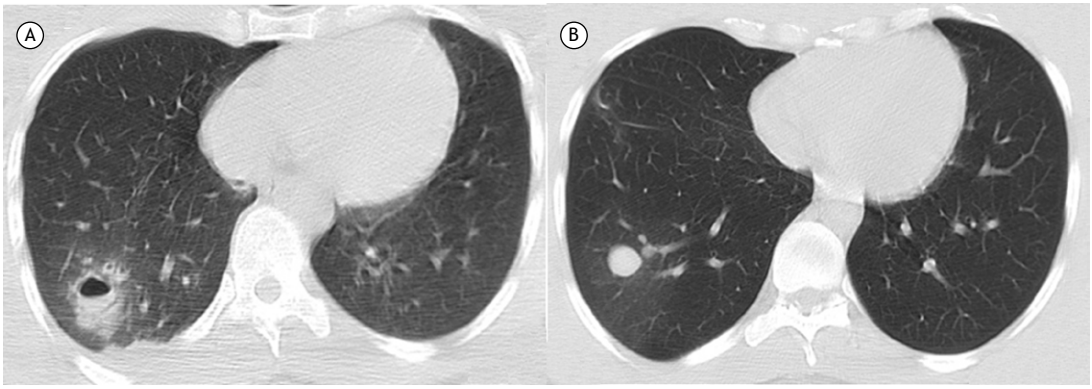


Figure 1. In A, an axial chest CT scan showing a small cavitary lesion, containing an air-fluid level and surrounded by ground-glass opacities, in the right lower lobe. A small pleural effusion is also visible. In B, a follow-up CT scan acquired 12 days later, showing that the cavitary lesion had evolved to a homogeneous nodule with hematic content, together with reabsorption of the ground-glass opacities and of the pleural effusion.

REFERENCES

1. Hazer S, Orhan Söylemez UP. Clinical features, diagnosis, and treatment of traumatic pulmonary pseudocysts. Ulus Travma Acil Cerrahi Derg. 2018;24(1):49–55. https://doi.org/10.5505/tjtes.2017.56023
2. Tsitouridis I, Tsinoglou K, Tsandiridis C, Papastergiou C, Bintoudi A. Traumatic pulmonary pseudocysts: CT findings. J Thorac Imaging. 2007;22(3):247–251. https://doi.org/10.1097/RTI.0b013e3180413e2a
3. Phillips B, Shaw J, Turco L, McDonald D, Carey J, Balters M, et al. Traumatic pulmonary pseudocyst: An underreported entity. Injury. 2017;48(2):214–220. https://doi.org/10.1016/j.injury.2016.12.006

1. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
2. Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre (RS) Brasil.

Pulmonary mucosa-associated lymphoid tissue lymphoma with internal calcifications on positron-emission tomography/CT

Rang Wang[1], Minggang Su[1]

A 68-year-old man with a two-year history of dry cough underwent ^{18}F-fluorodeoxyglucose positron-emission tomography/CT (^{18}F-FDG PET/CT) for the evaluation of lung masses. The results of laboratory tests, which included a complete blood count and determination of serum levels of tumor makers, were unremarkable, except for an elevated serum level of C-reactive protein. The ^{18}F-FDG PET/CT revealed multiple hypermetabolic masses, with scattered internal calcifications, in both lungs (Figure 1A-1C). The maximum diameter was 66 mm, and the standardized uptake value was 4.45. Transbronchial needle aspiration biopsy confirmed the suspected diagnosis of pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma. The patient then received immunotherapy, and a follow-up CT scan showed that the mass decreased in size, although the calcifications remained unchanged (Figure 1D).

The most common diagnosis for a pulmonary mass with internal calcification is granuloma. The differential diagnoses include hamartoma, carcinoid, metastasis, and primary bronchogenic carcinoma.[1] However, calcification is rarely observed in lymphoma. It is almost always associated with previous treatment, including radiation and chemotherapy.[2] Calcification in untreated pulmonary MALT lymphoma has rarely been described in the literature, and the underlying mechanism is unknown. The FDG-avid nature of the lesion described here might be due to its large size.[3] In patients presenting with a hypermetabolic lung mass with scattered internal calcifications on ^{18}F-FDG PET/CT, the differential diagnosis should include MALT lymphoma.

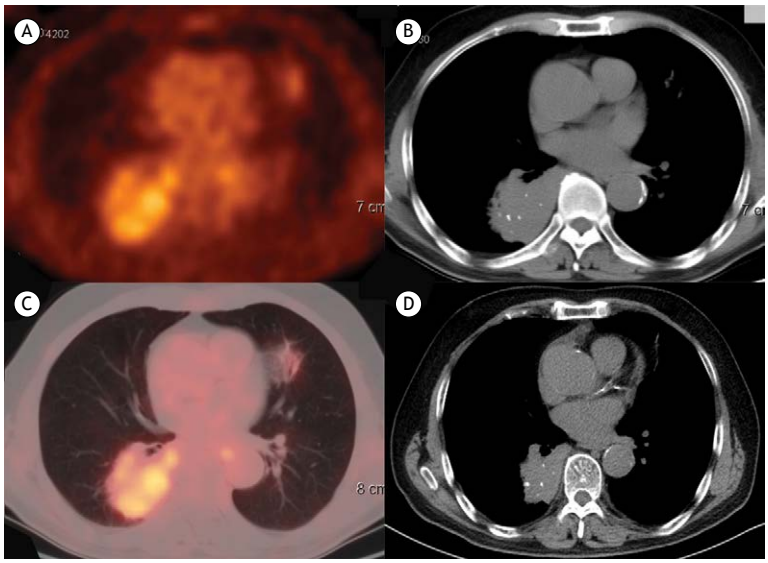


Figure 1. Positron-emission tomography (A), axial CT (B), and fusion images (C), showing multiple fluorodeoxyglucose-avid masses with scattered internal calcifications in both lungs. A follow-up chest CT (D), after treatment, shows that the mass decreased in size, although the calcifications remained unchanged.

REFERENCES

1. Amin SB, Slater R, Mohammed TL. Pulmonary calcifications: a pictorial review and approach to formulating a differential diagnosis. Curr Probl Diagn Radiol. 2015;44(3):267–276. https://doi.org/10.1067/j.cpradiol.2014.12.005
2. Suzuki L, Funari M, Rocha Mde S, Cristofani LM, Odone Filho V, Vieira GS. Calcification in primary lung non-Hodgkin lymphoma. Rev Hosp Clin Fac Med Sao Paulo. 1995;50(4):227–229.
3. Albano D, Borghesi A, Bosio G, Bertoli M, Maroldi R, Giubbini R, et al. Pulmonary mucosa-associated lymphoid tissue lymphoma: 18F-FDG PET/CT and CT findings in 28 patients. Br J Radiol. 2017;90(1079):20170311. https://doi.org/10.1259/bjr.20170311

1. Department of Nuclear Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, China.

ISSN 1806-3713

Pneumomediastinum in a patient with COVID-19

Bernardo Carvalho Muniz[1], Gláucia Zanetti[2], Edson Marchiori[2]

A 36-year-old male patient with no comorbidities was admitted to the ICU with a 14-day history of fever, cough, and intense dyspnea. On admission, his body temperature was 38°C (100.4°F), his RR was 30 breaths/min, and his SpO_2 was 93%. Unenhanced CT of the chest showed predominantly peripheral areas of consolidation in both lungs, as well as pneumomediastinum (Figures 1A to 1C). Real-time fluorescence polymerase chain reaction of his sputum was positive for SARS-CoV-2 nucleic acid. After four days of hospitalization, having been treated exclusively with supportive measures, including oxygen therapy, the patient showed partial improvement of symptoms, and a new CT was performed (Figure 1D), which showed substantial diminution of the areas of consolidation and resorption of the pneumomediastinum.

The major causes of spontaneous pneumomediastinum include those related to the Valsalva maneuver and asthma.[1] The tomographic findings of COVID-19 have already been studied widely and reported in the medical literature.[2] To our knowledge, pneumomediastinum has been rarely associated with the disease.[3] As described in other diseases, the most probable mechanism of pneumomediastinum formation in the context of COVID-19 is the emergence of a pressure gradient between the alveoli and the surrounding structures, leading to alveolar rupture and air leak, which moves along the bronchovascular bundle until it reaches the mediastinum. This pressure gradient seems to be related to heterogeneous involvement of the lung when there are normal parenchymal areas adjacent to those affected by the disease.[1]

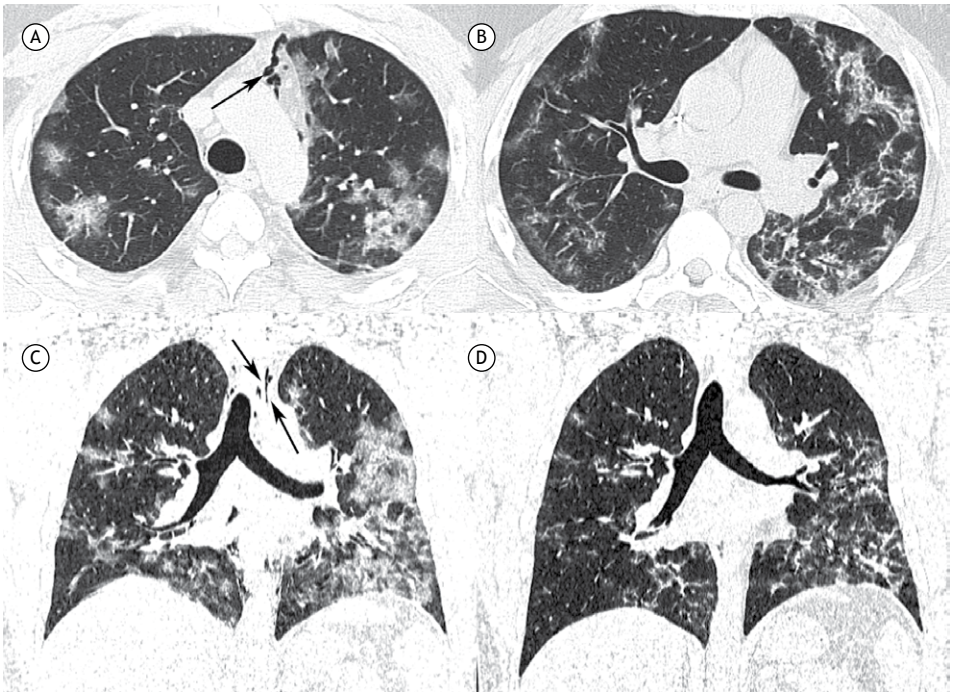


Figure 1. Axial (A and B) and coronal (C) unenhanced CT scans of the chest showing ground-glass opacities in both lungs. Note the presence of pneumomediastinum (arrows). A reconstructed coronal image obtained four days later (D) demonstrated improvement in the areas of ground-glass opacity and resorption of the pneumomediastinum.

REFERENCES

1. Araujo MS, Fernandes FL, Kay FU, Carvalho CR. Pneumomediastinum, subcutaneous emphysema, and pneumothorax after a pulmonary function testing in a patient with bleomycin-induced interstitial pneumonitis. J Bras Pneumol. 2013;39(5):613-619. https://doi.org/10.1590/S1806-37132013000500012
2. Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, et al. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA [published online ahead of print, 2020 Apr 28]. J Thorac Imaging. 2020;10.1097/RTI.0000000000000524. https://doi.org/10.1148/ryct.2020200152
3. Zhou C, Gao C, Xie Y, Xu M. COVID-19 with spontaneous pneumomediastinum. Lancet Infect Dis. 2020;20(4):510. https://doi.org/10.1016/S1473-3099(20)30156-0

1. Hospital Santa Teresa, Departamento de Radiologia, Central Integrada de Imagens – LUMIC – Petrópolis (RJ) Brasil.
2. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.

The Jornal Brasileiro de Pneumologia (J Bras Pneumol, Brazilian Journal of Pulmonology) ISSN-1806-3713, published once every two months, is the official organ of the *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Society) for the publication of scientific papers regarding Pulmonology and related areas.

After being approved by the Editorial Board, all articles will be evaluated by qualified reviewers, and anonymity will be preserved throughout the review process.

Articles that fail to present merit, have significant errors in methodology or are not in accordance with the editorial policy of the journal will be directly rejected by the Editorial Board, with no recourse. Articles may be written in Portuguese, Spanish or English. In the online version of the Journal (www.jornaldepneumologia.com.br, ISSN-1806-3756), all articles will be made available in Spanish or Portuguese, as well as in English. Authors may submit color figures. However, the cost of printing figures in color, as well as any related costs, will be borne by the authors.

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

The *Jornal Brasileiro de Pneumologia* upholds the World Health Organization (WHO) and International Committee of Medical Journal Editors (ICMJE) policies regarding the registration of clinical trials, recognizing the importance of these initiatives for the registration and international, open-access dissemination of information on clinical trials. Therefore, as of 2007, the Journal only accepts clinical trials that have been given an identification number by one of the clinical trials registries meeting the criteria established by the WHO and the ICMJE. This identification number must be included at the end of the abstract.

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

Authorship criteria

An individual may be considered an author of an article submitted for publication only if having made a significant intellectual contribution to its execution. It is implicit that the author has participated in at least one of the following phases: 1) conception and planning of the study, as well as the interpretation of the findings; 2) writing or revision of all preliminary drafts, or both, as well as the final revision; and 3) approval of the final version.

Simple data collection or cataloging does not constitute authorship. Likewise, authorship should not be conferred upon technicians performing routine tasks, referring physicians, doctors who interpret routine exams or department heads who are not directly involved in the research. The contributions made by such individuals may be recognized in the acknowledgements.

The accuracy of all concepts presented in the manuscript is the exclusive responsibility of the authors. The number of authors should be limited to eight, although exceptions will be made for manuscripts that are considered exceptionally complex. For manuscripts with more than six authors, a letter should be sent to the Journal describing the participation of each.

Presentation and submission of manuscripts

All manuscripts must be submitted online from the home-page of the journal. The instructions for submission are available at: www.jornaldepneumologia.com.br/sgp. Although all manuscripts are submitted online, they must be accompanied by a Copyright Transfer Statement and Conflict of Interest Statement signed by all the authors based on the models available at: www.jornaldepneumologia.com.br.

It is requested that the authors strictly follow the editorial guidelines of the journal, particularly those regarding the maximum number of words, tables and figures permitted, as well as the rules for producing the bibliography. Failure to comply with the author instructions will result in the manuscript being returned to the authors so that the pertinent corrections can be made before it is submitted to the reviewers.

Special instructions apply to the preparation of Special Supplements and Guidelines, and authors should consult the instructions in advance by visiting the homepage of the journal.

The journal reserves the right to make stylistic, grammatical and other alterations to the manuscript.

With the exception of units of measure, abbreviations should be used sparingly and should be limited only to those that are widely accepted. These terms are defined in the List of Abbreviations and Acronyms accepted without definition in the Journal. Click here (List of Abbreviations and Acronyms). All other abbreviations should be defined at their first use. For example, use "C-reactive protein (CRP)", and use "CRP" thereafter. After the definition of an abbreviation, the full term should not appear again. Other than those accepted without definition, abbreviations should not be used in titles, and their use in the abstracts of manuscripts should be avoided if possible.

Whenever the authors mention any substance or uncommon piece of equipment they must include the catalogue model/number, name of manufacturer, city and country of origin. For example:

"... ergometric treadmill (model ESD-01; FUNBEC, São Paulo, Brazil) ..."

In the case of products from the USA or Canada, the name of the state or province should also be cited. For example:

"... guinea pig liver tTg (T5398; Sigma, St. Louis, MO, USA) ..."

Manuscript preparation

Title Page: The title page should include the title (in Portuguese and in English); the full names, highest academic degrees and institutional affiliations of all authors; complete address, including telephone number, fax number and e-mail address, of the principal author; and a declaration of any and all sources of funding.

Abstract: The abstract should present the information in such a way that the reader can easily understand without referring to the main text. Abstracts should not exceed 250 words. Abstracts should be structured as follows: Objective, Methods, Results and Conclusion. Abstracts for review articles may be unstructured.

Abstracts for brief communications should not exceed 100 words.

Summary: An abstract in English, corresponding in content to the abstract in Portuguese, should be included.

Keywords: Three to six keywords in Portuguese defining the subject of the study should be included as well as the

corresponding keywords in English. Keywords in Portuguese must be based on the Descritores em Ciência da Saúde (DeCS, Health and Science Keywords), published by Bireme and available at: http://decs.bvs.br, whereas keywords in English should be based on the National Library of Medicine Medical Subject Headings (MeSH), available at: http://www.nlm.nih.gov/mesh/MBrowser.html.

Text:

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

Review and Update articles: Review and Update articles are written at the request of the Editorial Board, which may occasionally accept unsolicited manuscripts that are deemed to be of great interest. The text should not exceed 5000 words, excluding references and illustrations (figures or tables). The total number of illustrations should not exceed eight. The number of references should not exceed 60.

Pictorial essays: Pictorial essays are also submitted only at the request of the Editors or after the authors have consulted and been granted permission by the Editorial Board. The text accompanying such essays should not exceed 3000 words, excluding the references and tables. No more than 12 illustrations (figures and tables) may be used, and the number of references may not exceed 30.

Brief Communications: Brief communications should not exceed 1500 words, excluding references and tables. The total number of tables and figures should not exceed two, and the references should be limited to 20. The text should be unstructured.

Letters to the Editor: Letters to the Editor should be succinct original contributions, not exceeding 800 words and containing a maximum of 6 references. Comments and suggestions related to previously published materials or to any medical theme of interest will be considered for publication.

Correspondence: Authors may submit comments and suggestions related to material previously published in our journal. Such submissions should not exceed 500 words.

Imaging in Pulmonary Medicine: Submissions should not exceed 200 words, including the title, text, and references (no more than three). Authors may include up to three figures, bearing in mind that the entire content will be published on a single page.

Tables and Figures: All tables and figures should be in black and white, on separate pages, with legends and captions appearing at the foot of each. All tables and figures should be submitted as files in their original format. Tables should be submitted as Microsoft Word files, whereas figures should be submitted as Microsoft Excel, TIFF or JPG files. Photographs depicting surgical procedures, as well as those showing the results of exams or biopsies, in which staining and special techniques were used will be considered for publication in color, at no additional cost to the authors. Dimensions, units and symbols should be based on the corresponding guidelines set forth by the Associação Brasileira de Normas Técnicas (ABNT, Brazilian Association for the Establishment of Technical Norms), available at: http://www.abnt.org.br.

Legends: Legends should accompany the respective figures (graphs, photographs and illustrations) and tables. Each legend should be numbered with an Arabic numeral corresponding to its citation in the text. In addition, all abbreviations, acronyms, and symbols should be defined below each table or figure in which they appear.

References: References should be listed in order of their appearance in the text and should be numbered consecutively with Arabic numerals. The presentation should follow the Vancouver style, updated in October of 2004, according to the examples below. The titles of the journals listed should be abbreviated according to the style presented by the List of Journals Indexed in the Index Medicus of the National Library of Medicine, available at: http://www.ncbi.nlm.nih.gov/entrez/journals/loftext.noprov.html. A total of six authors may be listed. For works with more than six authors, list the first six, followed by 'et al.'

Examples: Journal Articles

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

Abstracts

2. Singer M, Lefort J, Lapa e Silva JR, Vargaftig BB. Failure of granulocyte depletion to suppress mucin production in a murine model of allergy [abstract]. Am J Respir Crit Care Med. 2000;161:A863.

Chapter in a Book

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

Official Publications

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

Theses

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

Electronic publications

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

Homepages/URLs

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

Other situations:

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

All correspondence to the Jornal Brasileiro de Pneumologia should be addressed to:

Prof. Dr. Rogério Souza

Editor-Chefe do Jornal Brasileiro de Pneumologia

SCS Quadra 01, Bloco K, Salas 203/204 - Ed. Denasa. CEP: 70.398-900 - Brasília - DF, Brazil

Telefones/Fax: 0xx61-3245-1030, 0xx61-3245-6218

Jornal Brasileiro de Pneumologia e-mail address:

jpneumo@jornaldepneumologia.com.br

(Assistente Editorial - Luana Campos)

Online submission of articles:

www.jornaldepneumologia.com.br

Estaduais da Sociedade Brasileira de Pneumologia e Tisiologia

ASSOCIAÇÃO ALAGOANA DE DOENÇAS DO TÓRAX - AADT

Presidente: Tadeu Peixoto Lopes
Secretário: Artur Gomes Neto
Endereço: Rua Professor José Silveira Camerino, nº 1085/ Sala 501, Pinheiro,
CEP: 57057-250- Maceió – AL
Telefone: (82) 30321967
E-mail: sociedadealagoana.dt@gmail.com tadeupl@hotmail.com

ASSOCIAÇÃO AMAZONENSE DE PNEUMOLOGIA E CIRURGIA TORÁCICA

Presidente: Mário Sergio Monteiro Fonseca
Secretária: Tatiana Minda Herculano Cattebeke
Endereço: Av. Eduardo Ribeiro, nº 520, 12º andar, Sala 1204, Edifício Manaus SH Centro - Centro
CEP: 69020030- Manaus – AM
Telefone: (92) 2101-2586, (92) 98120-4400
E-mail: aapctmanaus@gmail.com ms-fonseca@uol.com.br

ASSOCIAÇÃO CATARINENSE DE PNEUMOLOGIA E TISIOLOGIA - ACAPTI

Presidente: Antônio César Cavallazzi
Vice Presidente: Roger Pirath Rodrigues
Endereço: Rodovia SC, 401 Km 4 – 3854 - Saco Grande
CEP: 88.032 - 005 - Florianópolis – SC
Telefone: (48)32310314
E-mail: acapti@acapti.org.br | acavallazzi@uol.com.br
Site: www.acapti.org.br

ASSOCIAÇÃO DE PNEUMOLOGIA E CIRUGIA TORÁCICA DO RIO GRANDE DO NORTE

Presidente: Suzianne Ruth Hosannah de Lima Pinto
Secretária: Soraia Bernardo Monteiro Cardoso
Endereço: Av. Campos Sales, 762 - Tirol
CEP: 59.020-300 - Natal – RN
Telefone: (84) 99169.9973
E-mail: suzirh@gamil.com | rnapct@gmail.com

ASSOCIAÇÃO MARANHENSE DE PNEUMOLOGIA E CIRURGIA TORÁCICA

Presidente: Maria do Rosario da Silva Ramos Costa
Secretário: João Batista de Sá Filho
Endereço: Travessa do Pimenta, 46 - Olho D'Água
CEP: 65.065-340 - São Luís – MA
Telefone: (98) 32486379/21091295 - (98)999736600
E-mail: rrcosta2904@gmail.com

ASSOCIAÇÃO PARAENSE DE PNEUMOLOGIA E TISIOLOGIA

Presidente: José Tadeu Colares Monteiro
Secretária: Lilian França dos Santos Monteiro Pereira
Endereço: Passagem Bolonha, 134, Bairro Nazaré
CEP: 66053-060 - Belém – PA
Telefone: (91)989346998
E-mail: spapnt@gmail.com | tadeucolares@hotmail.com

ASSOCIAÇÃO PARANAENSE DE PNEUMOLOGIA E TISIOLOGIA (APPT)

Presidente: Irinei Melek
Secretário Áquila Andrade Carneiro
Endereço: Av. Sete de Setembro, 5402 - Conj. 105, 10ª andar Batel
CEP: 80240-000 - Curitiba – PR
Tel/fax: (41) 3342-8889
E-mail: contato@pneumopr.org.br
Site: www.pneumopr.org.br

ASSOCIAÇÃO PERNAMBUCANA DE PNEUMOLOGIA E TISIOLOGIA

Presidente: Adriana Velozo Gonçalves
Secretária: Danielle Cristina Silva Clímaco
Endereço: Rua João Eugênio de Lima , 235 - Boa Viagem
CEP: 51030-360 - Recife – PE
Tel/fax: (81)988817435 -
E-mail: pneumopernambuco@gmail.com adrianavelozo@hotmail.com

SOCIEDADE BRASILIENSE DE DOENÇAS TORÁCICAS

Presidente: Nathali Mireise Costa Ferreira
Secretária: Milena Zamian Danilow
Endereço: Setor de Clubes Sul, Trecho 3, Conj. 6
CEP: 70.200-003 - Brasília – DF
Tel/fax: (61) 3245-8001
E-mail: sbdt@ambr.org.br

SOCIEDADE CEARENSE DE PNEUMOLOGIA E TISIOLOGIA

Presidente: Ricardo Coelho Reis
Secretário: Ivan Guerra De Araújo Freitas
Endereço: Av. Dom Luis, 300, sala 1122, Aldeota
CEP: 60160-230 - Fortaleza – CE
Telefone: (85) 3092-0401/3264-9466
E-mail: assessoria@scpt.org.br ; amc@amc.med.br
Site: www.scpt.org.br

SOCIEDADE DE PNEUMOLOGIA DA BAHIA

Presidente: Rosana Nunes de Abreu Franco
Secretária: Larissa Voss Sadigursky
Endereço: ABM - Rua Baependi,162. Sala 03 - Terreo- Ondina
CEP: 40170-070 - Salvador – BA
Tel/fax: (71) 33326844
E-mail: pneumoba@gmail.com | spba@outlook.com.br

SOCIEDADE DE PNEUMOLOGIA DO ESPÍRITO SANTO - SPES

Presidente: Rafael de Castro Martins
Secretária: Karina Tavares Oliveira
Endereço: Rua Eurico de Aguiar, 130, Sala 514, Ed. Blue Chip, Praia do Campo
CEP: 29.055-280 - Vitória – ES
Telefone: (27) 3345-0564 - (27)999826598
E-mail: rafaelcastromartins@gmail.com

SOCIEDADE DE PNEUMOLOGIA E TISIOLOGIA DO MATO GROSSO - SPMT

Presidente: Carlos Fernando Gossn Garcia
Secretária: Karla de Moura Carlos
Endereço : Av. Miguel Sutil, n 8000, Ed. Santa Rosa Tower, sala 1207
CEP: 78040-400- Cuiabá – MT
Telefone: (65)999681445
E-mail: cfggarcia@yahoo.com.br

SOCIEDADE DE PNEUMOLOGIA E TISIOLOGIA DO MATO GROSSO DO SUL

Presidente: Henrique Ferreira de Brito
Secretário: Luiz Armando Pereira Patusco
Endereço: Rua 15 de novembro,2552, Ed. One Offices, Sala 901
CEP: 79020-300- Campo Grande - MS
Telefone: (67)981628382 – (67)33274110
E-mail: especialidades@amms.com.br

SOCIEDADE DE PNEUMOLOGIA E TISIOLOGIA DO ESTADO DO RIO DE JANEIRO

Presidente: Fernanda de Carvalho de Queiroz Mello
Secretário: Ricardo Luiz de Menezes Duarte
Endereço: Largo do Machado, 21, GR. 08, sala 914, Catete
CEP: 22221-020 - Rio de Janeiro – RJ
Tel/fax: (21) 3852-3677
E-mail: sopterj@sopterj.com.br
Site: www.sopterj.com.br

SOCIEDADE DE PNEUMOLOGIA E TISIOLOGIA DO RIO GRANDE DO SUL

Presidente: Gustavo Chatkin
Vice Presidente: Paulo Roberto Goldenfum
Endereço: Av. Ipiranga, 5.311, sala 403
CEP: 90.610-001 - Porto Alegre – RS
Telefone: (51) 3384-2889
E-mail: sptrs.secretaria@gmail.com
Site: www.sptrs.org.br

SOCIEDADE GOIANA DE PNEUMOLOGIA E TISIOLOGIA

Presidente: Karla Cristina de Moraes Arantes Curado
Secretária: Roseliane de Souza Araújo
Endereço: Galeria Pátio 22, Rua 22 nº 69, Sala 17, Setor Oeste
CEP: 74.120-130 - Goiânia – GO
Telefone: (62)3251-1202 / (62) 3214-1010
E-mail: sgpt2007@gmail.com | karlacurado1@hotmail.com

SOCIEDADE MINEIRA DE PNEUMOLOGIA E CIRURGIA TORÁCICA

Presidente: Marcelo Bicalho de Fuccio
Secretário: Luciana Macedo Guedes
Endereço: Av. João Pinheiro, 161 - sala 203 - Centro
CEP: 30.130-180 - Belo Horizonte – MG
Tel/fax: (31) 3213-3197
E-mail: smpct@smpct.org.br
Site: www.smpct.org.br

SOCIEDADE PARAIBANA DE TISIOLOGIA E PNEUMOLOGIA

Presidente: Maria Enedina Claudino Aquino Scuarcialupi
Secretária: Gerlânia Simplício Sousa
Endereço: Rua José Florentino Jr. 333– Tambauzinho
CEP: 58042-040 – João Pessoa – PB
Telefone: (83)38863700
E-mail: enedinapneumo@enedinapneumo.com

SOCIEDADE PAULISTA DE PNEUMOLOGIA E TISIOLOGIA

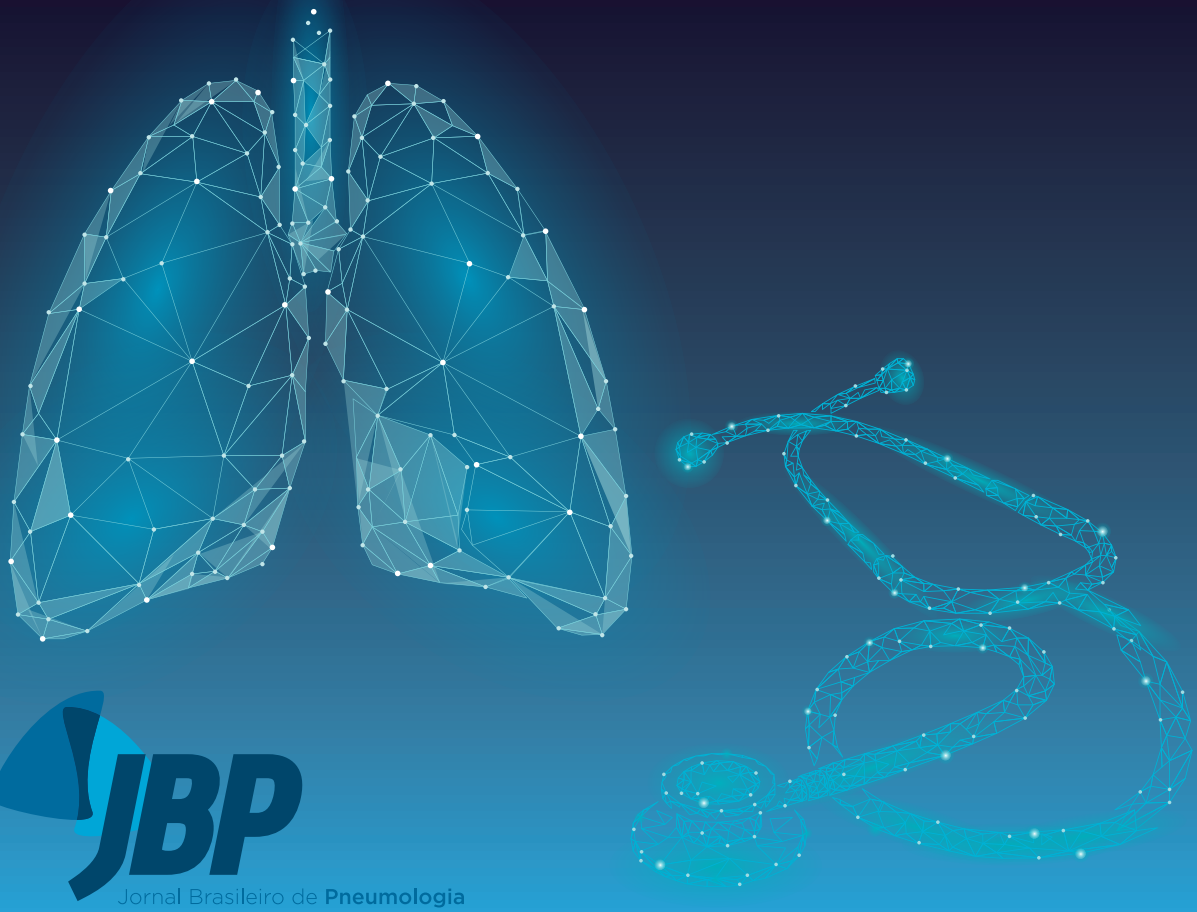
Presidente: Frederico Leon Arrabal Fernandes
Secretário: Rodrigo Abensur Athanazio
Endereço: Rua Machado Bittencourt, 205, 8° andar, conj. 83 - Vila Clementino
CEP: 04.044-000 São Paulo – SP
Telefone: 0800 17 1618
E-mail: sppt@sppt.org.br
Site: www.sppt.org.br

SOCIEDADE PIAUIENSE DE PNEUMOLOGIA E TISIOLOGIA

Presidente: Braulio Dyego Martins Vieira
Secretária: Tatiana Santos Malheiros Nunes
Endereço: Avenida Jose dos Santos e Silva, 1903, Nucleo de Cirurgia Torácica
CEP: 64001-300- Teresina – PI
Telefone: (86)32215068 - (86)999306664
E-mail: brauliodyego@gmail.com

SOCIEDADE SERGIPANA DE PNEUMOLOGIA E TISIOLOGIA

Presidente: Edson Franco Filho
Secretário: Almiro Alves de Oliva Sobrinho
Endereço: Av. Gonçalo Prado Rollemberg, 211, Sala 206-Centro Médico - Bairro São José
CEP: 49050-370- Aracaju - SE
Telefone: (79) 999814482
E-mail: edac@uol.com.br



JBP
Jornal Brasileiro de **Pneumologia**

Jornal Brasileiro de Pneumologia

Novo Fator de Impacto

FATOR DE IMPACTO

1.870

www.jornaldepneumologia.com.br

SOCIEDADE BRASILEIRA DE PNEUMOLOGIA E TISIOLOGIA · 1937 ·

Congresso Brasileiro de Pneumologia e Tisiologia

SBPT Virtual 10 a 12 | Outubro | 2020

40° Congresso Brasileiro de
Pneumologia e Tisiologia

16° Congresso Brasileiro de
Endoscopia Respiratória

11° Congresso Luso-Brasileiro de
Pneumologia

12 a 16 de outubro de 2022
Centro de Convenções Royal Hall
C A M P I N A S / S P