ISSN 1806-3713

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

Volume 46, Number 4
July | August
2020

Volume 46, Number 4 July | August 2020

HIGHLIGHT

Recommendations for the diagnosis and treatment of chronic thromboembolic pulmonary hypertension

Cost-effectiveness of EGFR-tyrosine kinase inhibitors for metastatic non-small cell lung cancer

***Pseudomonas aeruginosa* treatment in cystic fibrosis**

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. 4, July/August 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. 4, July/August 2020

Contents

ISSN 1806-3713

Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 46, n. 4, July/August 2020

Contents

J Bras Pneumol. 2020;46(4):e20200320
https://dx.doi.org/10.36416/1806-3756/e20200320

The Brazilian Journal of Pulmonology and its progress in the major international databases

Bruno Guedes Baldi[1,2], Rogério Souza[1,3]

In recent years, the *Jornal Brasileiro de Pneumologia* (JBP, Brazilian Journal of Pulmonology) has played an important role in disseminating the knowledge produced in the field of respiratory medicine in Brazil and in other countries, which has consolidated its standing in the major international databases. The recent publication of indicators for the JBP by the two major international indexing agencies—Scimago Journal & Country Rank (SJR) and Journal Citation Reports (JCR) Web of Knowledge, Clarivate Analytics—-supports that statement and is a source of pride for our scientific community because JBP has attained its highest levels to date.[1,2]

Since 2012, when the first JBP impact factor was published by the Institute for Scientific Information Web of Knowledge, it has become evident that the international visibility of the Journal is growing, because the participation of authors from other countries in relevant articles and the citations of JBP manuscripts in international publications have been progressively increasing.[3,4]

In the 2020 SJR, whose database includes the greatest number of journals (representing approximately 250 countries), the two-year citation index of the JBP was 1.805, corresponding to a 26.7% increase in relation to the previous cycle. In addition, the JBP ranking in the SJR rose from 91st to 83rd among the 147 journals in the area of pulmonary and respiratory medicine and from 66th to 46th among the 404 Brazilian journals. It is also noteworthy that international collaboration has increased from 20% to 24%.[1] According to the JCR, the JBP impact factor for 2020 was 1.870, corresponding to a 36.4% increase in relation to the previous year. Consequently, the JBP ranking in the JCR rose from 57th to 50th among the 64 journals in the area of respiratory medicine and from 28th to 13th among the 129 Brazilian journals. Given these newly issued indicators, we envision that the JBP will move up to category B1 in Medicine I in the journal ranking system of the Brazilian Office for the Advancement of Higher Education, a system known as Qualis.[2]

The articles with the highest number of citations, which influenced our indicators, were primarily those on tuberculosis, lung cancer, and sleep disorders, some of which were produced exclusively by researchers in Brazil, whereas others involved international collaboration.[5-7]

Another relevant aspect is that, according to the JCR database, 43% of the articles published in 2017 and 2018 were cited in 2019. In addition, in accordance with the objectives proposed at the beginning of the current editorship, efforts have been made to increase the numbers of guidelines and recommendations for the major respiratory diseases, as well as the number of editorials by international authors and the number of articles with a greater impact on clinical practice, which will certainly contribute to a greater visibility of the Journal, nationally and internationally.[3]

It is obvious that the impact factor is only one of the relevant indicators of the performance and international influence of a journal. Other principles that should be valued and that are not included in the isolated analysis of the impact factor, although relevant to the JBP, include the composition of the editorial board and of the team of reviewers, with an emphasis on the inclusion of participants from other countries, the proportion of articles rejected (currently about 65%), the transparency throughout the editorial process, and the quality of reviews. In addition, the number of times that JBP articles are accessed via websites and are cited on social networks should be taken into consideration.

Finally, the voluntary participation of associate editors and reviewers in the evaluation and refinement of the articles submitted should be highlighted. These professionals have played an essential role in the success achieved in recent years. There are other aspects that represent challenges for maintaining the continuity of the growth of the JBP, such as streamlining the process of reviewing articles and publishing them online, expanding the team of reviewers, encouraging the submission of articles in English, and disseminating well-respected, well-structured studies and opinions. The preparation for each of these steps is our contribution to improving research in respiratory medicine in Brazil.[8,9]

We hope to continue improving the production of articles and providing high-quality points of view that are relevant to the day-to-day approach to pulmonology and related areas. By doing so, we will gradually improve the indicators for our Journal in the major international databases.

REFERENCES

1. Scimago Journal & Country Rank [homepage on the Internet]. Scimago Lab; c2017-2020 [cited 2020 26 Jun]. Available from http://www.scimagojr.com
2. Journal Citation Reports [homepage on the Internet]. Clarivate Analytics; c2020 [cited 2020 Jun 26]. 2019 Journal Impact Factor. Available from: https://clarivate.com/webofsciencegroup/solutions/journal-citation-reports/

1. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo – HCFMUSP – São Paulo (SP), Brasil.
2. Editor-Chefe do Jornal Brasileiro de Pneumologia – JBP – Brasília (DF) Brasil
3. Vice-Editor do Jornal Brasileiro de Pneumologia - JBP - Brasília (DF) Brasil

3. Baldi BG, Chatkin JM. Jornal Brasileiro de Pneumologia and Sociedade Brasileira de Pneumologia e Tisiologia: perspectives for the next four years. J Bras Pneumol. 2019;45(1):e20190028. https://doi.org/10.1590/1806-3713/e20190028
4. Carvalho CR, Baldi BG, Jardim CV, Caruso P. Publication of the impact factor of the Brazilian Journal of Pulmonology: a milestone on a long and arduous journey. J Bras Pneumol. 2012;38(4):417-418. https://doi.org/10.1590/S1806-37132012000400001
5. Migliori GB, Centis R, D'Ambrosio L, Silva DR, Rendon A. International collaboration among medical societies is an effective way to boost Latin American production of articles on tuberculosis. J Bras Pneumol. 2019;45(2):e20180420. https://doi.org/10.1590/1806-3713/e20180420
6. Araujo LH, Baldotto C, Castro G Jr, Katz A, Ferreira CG, Mathias C, et al. Lung cancer in Brazil. J Bras Pneumol. 2018;44(1):55-64. https://doi.org/10.1590/s1806-37562017000000135
7. Silva RPD, Martinez D, Bueno KSDS, Uribe-Ramos JM. Effects of exercise on sleep symptoms in patients with severe obstructive sleep apnea. J Bras Pneumol. 2019;45(3):e20180085. https://doi.org/10.1590/1806-3713/e20180085
8. Souza R. The importance of strong fundamentals in scientific methodology. J Bras Pneumol. 2018;44(5):350-351. https://doi.org/10.1590/s1806-37562018000500005
9. Souza R. JBP and bibliometric índices. J Bras Pneumol. 2017;43(4):247-248. https://doi.org/10.1590/s1806-37562017000400002

J Bras Pneumol. 2020;46(4):e20200317
https://dx.doi.org/10.36416/1806-3756/e20200317

EDITORIAL

Thrombosis and anticoagulation in COVID-19

Roberta Pulcheri Ramos[1], Jaquelina Sonoe Ota-Arakaki[1]

Coronavirus disease 2019 (COVID-19) has recently been described, and it has been reported that 15% of patients with the disease develop the severe form.[1] Because the lungs are the organs most often affected, clinical deterioration can occur, with progression to hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS), within a few days after symptom onset. In the context of a pandemic that has important prognostic implications, the investigation of new treatments is justified.

Studies on pharmacological treatment, including systemic corticosteroid therapy, have recently been published. The practices employed in patients with ARDS should also be prioritized in the supportive care of patients with COVID-19 in the ICU, such as protective strategies for mechanical ventilation, neuromuscular blocks, prone positioning, and conservative fluid administration. However, although COVID-19 is pathologically similar to ARDS, most patients with COVID-19 present with slightly impaired ventilatory mechanics and reduced potential of recruitment, despite significant hypoxemia.[2,3] The discrepancy between changes in gas exchange, radiological findings, and findings regarding respiratory mechanics might indicate a vascular component of the disease, as evidenced by a high shunt fraction[4] and the presence of thrombi in the microcirculation, which have been identified in autopsy studies.[5]

In this context, a state of hypercoagulability and hematological changes have been described in up to one third of the patients, the increase in D-dimer levels being an important marker of unfavorable outcomes.[6] Therefore, some retrospective studies have investigated the occurrence of venous thromboembolism (VTE) in patients with COVID-19, identifying it in up to 40% of those patients.[7] If an active search for VTE, by means of ultrasound venous mapping of the lower limbs, is performed, that rate is nearly 70% among ICU patients with COVID-19.[8]

It is of note that D-dimer is a fibrin degradation product that might be elevated due to the simultaneous activation of fibrinolysis during the formation of thrombi. The determination of D-dimer levels is nonspecific, and those levels might be increased in other situations, such as in cancer, after surgery, in infections, or during pregnancy. As described above, an increase in the levels of this marker is common in patients with COVID-19, which makes it difficult to use in the investigation of VTE in those patients. Therefore, in patients with COVID-19 and a high pre-test probability of thrombotic events, especially in those with disproportionate hypoxemia, D-dimer levels should not contribute to the clinical decision-making to continue the investigation, because this test is more important for excluding the disease in populations with a low prevalence of VTE (< 10%). Likewise, because this test has low specificity in populations with a high prevalence of VTE (> 50%), it should not influence the diagnosis in this situation.

Although there is clear evidence of an increased risk of VTE in COVID-19, the use of full anticoagulation in all COVID-19 patients has been questioned and is not currently recommended by international societies.[9] In suspected cases of VTE, it is suggested that the use of empirical anticoagulation be carefully evaluated, especially when we consider the risk-benefit ratio according to the clinical probability, and the diagnosis should be made as soon as possible to minimize the risk of bleeding. More importantly, the determination of D-dimer levels is of little use for the diagnosis of VTE when analyzed in isolation, especially in this high-risk population, in which the positive predictive value of the test is low. This is even more relevant in ICU patients who have a high inflammatory response. However, for patients in whom the clinical probability is higher (e.g., in those with worsened hypoxemia despite improved radiological findings and infection control), the determination of D-dimer levels can be useful. It is possible that future studies will identify higher cutoff points that might increase the specificity of this test for COVID-19. It is important to highlight the association between increased levels of D-dimer and systemic inflammation, as demonstrated by the correlation between high serum C-reactive protein levels and high D-dimer levels, even in patients with COVID-19.[10]

If the empirical treatment of macrovascular events is controversial, there is even less evidence to support its use in the treatment of microthrombi. A procoagulant state has been widely described in patients with sepsis and ARDS, as well as in those with other types of viral pneumonia, such as that caused by influenza. In fact, vascular lesions have been identified in patients with ARDS, not only in autopsy studies but also in ICU patients by means of pulmonary angiography. Patients with microthrombosis are not necessarily diagnosed with disseminated intravascular coagulation, and there is no evidence to support the use of full anticoagulation in this clinical situation.

Although some researchers recommend the prophylactic use of moderate doses of anticoagulants, that approach has not been shown to be beneficial in reducing mortality in patients without cancer. As expected, the incidence of VTE is lower when that therapy is employed, although there might be a greater chance of adverse hemorrhagic

1. Grupo de Circulação Pulmonar, Disciplina de Pneumologia – Unifesp – São Paulo (SP) Brasil.

events.[11] In patients with COVID-19, this can be aggravated by the presence of other risk factors for bleeding, such as renal dysfunction and stroke, even in young patients.[12]

To date, the best approach to treat patients with COVID-19 is to underscore the approach recommended for diseases with a high thrombotic risk: performing routine thromboprophylaxis in all hospitalized patients and increasing surveillance and clinical suspicion, especially in patients with gas exchange alterations disproportionate to the degree of systemic inflammation and the radiological findings. While we await the results of clinical trials studying the use of higher doses of anticoagulants in COVID-19, we recommend greater surveillance and screening in the presence of additional risk factors, such as the use of mechanical ventilation.

Results of studies on anticoagulation in COVID-19 are expected to be published soon; however, we cannot stop to wait for good evidence to guide us if it is still unavailable. Appropriate, personalized clinical judgment supersedes "cookie-cutter" solutions and helps ensure that the patient receives high-quality care. However, clinical decision-making must be based on the best evidence available for similar diseases, rather than on just any evidence, taking into consideration not only the benefits but also the risks that that chosen course of action might carry.

REFERENCES

1. 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
2. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes?. Intensive Care Med. 2020;46(6):1099-1102. https://doi.org/10.1007/s00134-020-06033-2
3. Pan C, Chen L, Lu C, Zhang W, Xia JA, Sklar MC, et al. Lung Recruitability in COVID-19-associated Acute Respiratory Distress Syndrome: A Single-Center Observational Study. Am J Respir Crit Care Med. 2020;201(10):1294-1297. https://doi.org/10.1164/rccm.202003-0527LE
4. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not?. Crit Care. 2020;24(1):154. https://doi.org/10.1186/s13054-020-02880-z
5. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, da Silva LFF, de Oliveira EP, Saldiva PHN, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. J Thromb Haemost. 2020;18(6):1517-1519. https://doi.org/10.1111/jth.14844
6. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal [published correction appears in BMJ. 2020 Jun 3;369:m2204]. BMJ. 2020;369:m1328. https://doi.org/10.1101/2020.03.24.20041020
7. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089-1098. https://doi.org/10.1007/s00134-020-06062-x
8. Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients [published online ahead of print, 2020 Apr 22]. J Thromb Haemost. 2020;10.1111/jth.14869. https://doi.org/10.1111/jth.14869
9. Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, et al. Prevention, Diagnosis, and Treatment of VTE in Patients With COVID-19: CHEST Guideline and Expert Panel Report [published online ahead of print, 2020 Jun 2]. Chest. 2020;S0012-3692(20)31625-1. https://doi.org/10.1016/j.chest.2020.05.559
10. Yu B, Li X, Chen J, Ouyang M, Zhang H, Zhao X, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis [published online ahead of print, 2020 Jun 10]. J Thromb Thrombolysis. 2020;1-10. https://doi.org/10.1007/s11239-020-02171-y
11. Eck RJ, Bult W, Wetterslev J, Gans ROB, Meijer K, Keus F, et al. Intermediate Dose Low-Molecular-Weight Heparin for Thrombosis Prophylaxis: Systematic Review with Meta-Analysis and Trial Sequential Analysis. Semin Thromb Hemost. 2019;45(8):810-824. https://doi.org/10.1055/s-0039-1696965
12. Kremer S, Lersy F, de Sèze J, Ferré JC, Maamar A, Carsin-Nicol B, et al. Findings in Severe COVID-19: A Retrospective Observational Study [published online ahead of print, 2020 Jun 16]. Radiology. 2020;202222. https://doi.org/10.1148/radiol.2020202222

J Bras Pneumol. 2020;46(4):e20200282
https://dx.doi.org/10.36416/1806-3756/e20200282

COVID-19 pandemic and mechanical ventilation: facing the present, designing the future

Marcelo Alcantara Holanda[1,2], Bruno Valle Pinheiro[3,4]

Mechanical ventilation (MV) is essential for sustaining life in cases of severe respiratory failure. The origins of MV date back to the 16th century, when Vesalius described the technique in the book *De Humani Corporis Fabrica*. Negative pressure ventilators were developed in the late 19th century, whereas invasive MV, as we know it, emerged in response to the 1952 poliomyelitis pandemic in Denmark. At that time, anesthesiologist Bjorn Ibsen used tracheostomy and manual positive pressure ventilation in patients with severe forms of the disease and respiratory muscle paralysis, reducing the lethality from 97% to 40%.[1,2] Thereafter, MV came to be recognized as a life-saving technique, and its history is comingled with that of ICUs.[1,2] It has since evolved from a support basically aimed at normalizing gas exchange to a technique capable of doing so, without damaging the lungs, without compromising the physiology of the cardiovascular system or that of other organs, and without causing diaphragmatic dysfunction, thus ensuring the resolution of the underlying disease, providing good patient-ventilator synchrony, and reducing the need for sedation.[1] After almost 70 years, MV is now facing its biggest challenge: the new coronavirus disease 2019 (COVID-19) pandemic. Poliomyelitis was accompanied by respiratory acidosis due to neuromuscular failure, whereas pneumonia by the new coronavirus causes severe damage to the lung parenchyma and severe hypoxemia, which is often refractory to usual interventions, in 10-20% of the cases.[3]

A few months after the first case of COVID-19 was reported in China, the disease was declared a pandemic, and more than 6.9 million confirmed cases and 400,469 deaths had been reported as of June 8, 2020.[4] By that same date, 645,771 confirmed cases and 35,026 deaths had been reported in Brazil, which thus came to rank third in terms of absolute number of deaths worldwide.[4] These numbers, which had been reached in such a short time, show the high contagiousness of the virus that causes COVID-19, designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although severe forms of the disease occur in only a small fraction of patients, the absolute numbers of such patients are considerable and could eventually cause the collapse of health care systems. The most critical structural limitation is the shortage of ICU beds and mechanical ventilators, ventilatory support being at the heart of the problem. In addition, there are restrictions on the use of noninvasive ventilation and high-flow nasal cannulas due to the risk of aerosolizing the virus into the environment and infecting members of the multidisciplinary team or other patients. Patients with COVID-19 can require MV for two to four weeks. In addition, complications, such as ventilator-associated pneumonia, pulmonary thromboembolism, delirium, and patient-ventilator asynchrony that is difficult to resolve, can increase morbidity and mortality.[3,5] The challenges for providing MV safely include maintaining the supply of materials, such as personal protective equipment, MV accessories (such as filters and circuits), and medications (for sedation, analgesia, and neuromuscular blocks), as well as the need for support from clinical engineering services.

Errors in adjusting the mechanical ventilator can cause serious iatrogenic complications and increase the risk of death, whereas the use of MV with the appropriate settings reduces mortality, the occurrence of complications, the number of days on MV, the length of ICU stay, and hospital costs.[6] In recent decades, technological advances, including the emergence of equipment incorporating microprocessors, different ventilation modes, and advanced features, have led to significant improvements in mechanical ventilators, although such ventilators have human-machine interfaces that are more complex, which has complicated their use.[7] Along with these advances, the learning process and management of these machines have become more difficult for students, residents, and other health professionals.[7,8] Because of the COVID-19 pandemic, thousands of new ICU beds have been created and similar numbers of new ventilators have been acquired throughout the country. Consequently, there is a shortage of staff specialized to work in that context. Although recent graduates have been called in to work on the front lines, they lack the necessary knowledge, training, and experience to manage different types of ventilators in complex cases. It is to be expected that inexperienced professionals feel insecure and have difficulty applying the best evidence-based practices and interventions recommended in protocols and guidelines by the major medical societies. Therefore, there is a high risk of deviations from established practices.[3,8]

Coping with this wartime scenario is characterized by a set of measures taken in order to mitigate the risks and reduce the lethality of COVID-19. Such measures include promoting broad access to digital training (courses and virtual simulators) on using MV[9]; enabling access to telemedicine; supporting the development and manufacture of mechanical ventilators with technology that is more accessible, making them easier to use, and that are not dependent on components and materials

1. Disciplinas de Pneumologia e de Terapia Intensiva, Universidade Federal do Ceará, Fortaleza (CE) Brasil.
2. Escola de Saúde Pública do Ceará Paulo Marcelo Martins Rodrigues, Fortaleza (CE) Brasil.
3. Disciplina de Pneumologia, Universidade Federal de Juiz de Fora, Juiz de Fora (MG) Brasil.
4. Coordenação da UTI, Hospital Universitário, Universidade Federal de Juiz de Fora, Juiz de Fora (MG) Brasil.

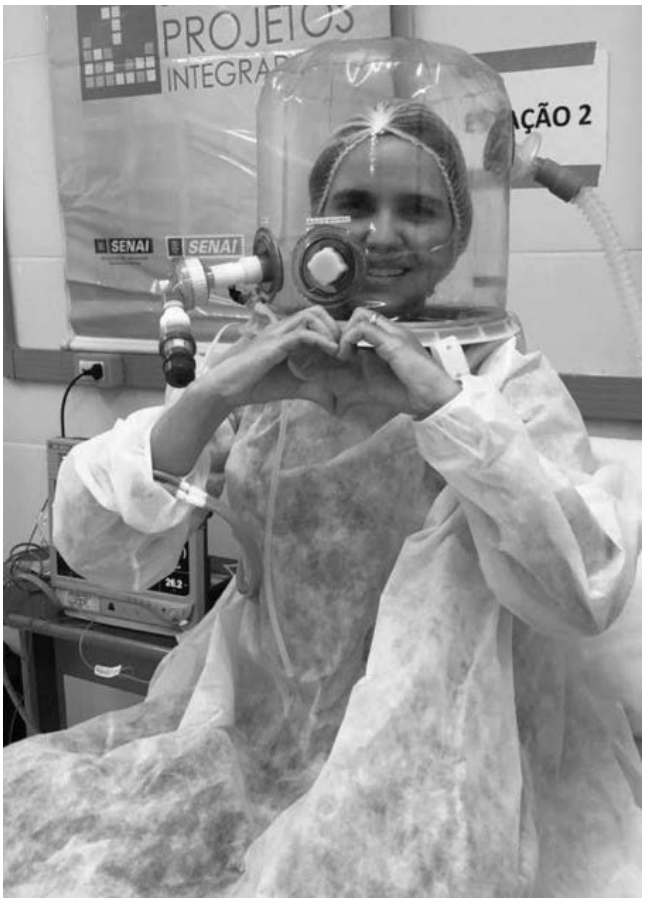


Figure 1. A physiotherapist wearing a prototype of a helmet-type system developed specifically for coping with COVID-19. The helmet allows the application of positive pressure around the head by means of a mixture of high flows of compressed air and oxygen, enabling an FiO_2 of up to 100% and continuous positive airway pressure of up to 18-20 cmH_2O, minimizing the risk of air leakage into the environment. Source: Personal archive of Holanda MA.

that must be acquired from the international market; making efforts to restore old, inoperative ventilators and to adapt portable ventilators or ventilators used in anesthesiology; creating safe hospital environments for the use of noninvasive ventilation and high-flow nasal cannulas in negative-pressure isolation rooms, if possible; and searching for alternatives to noninvasive ventilatory support, reducing the risk of infection of the health care team and the pressure for indicating tracheal intubation as the first treatment option in the event of oxygen therapy failure (Figure 1).[10] Research funding agencies, universities, industry sectors, medical societies, and other entities have united around these measures, quite often in a supportive and altruistic way, and that is commendable.

This is a historical moment because awareness has been raised and there have been paradigm shifts regarding the role of mechanical ventilatory support in health care systems. Accessibility, expertise, technology, innovation, usability, training, excellence, safety, effectiveness, low cost, equity, and universality are some of the concepts that permeate the role of MV in health care policies worldwide.[11,12] It is certain that there will be new catastrophes and pandemics in the future and that the health of millions, perhaps billions of people, will be seriously affected. Contingency plans for current and future threats to global health, especially infections and respiratory diseases, should guide and enable universal access to safe, high-quality ventilatory support, even in regions with limited financial resources.[11,12] The challenges have been set; it is up to us to face them in the present as we build the foundations for a promising future for MV in Brazil and in the world.

REFERENCES

1. Slutsky AS. History of Mechanical Ventilation. From Vesalius to Ventilator-induced Lung Injury. Am J Respir Crit Care Med. 2015;191(10):1106-1115. https://doi.org/10.1164/rccm.201503-0421PP
2. LASSEN HC. A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. Lancet. 1953;1(6749):37-41. https://doi.org/10.1016/S0140-6736(53)92530-6

3. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19 [published online ahead of print, 2020 May 15]. N Engl J Med. 2020;10.1056/NEJMcp2009575. https://doi.org/10.1056/NEJMcp2009575
4. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [cited 2020 Jun 8]. Coronavirus disease (COVID-19) pandemic [about 9 screens]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=Cj0KCQjvvv_f2BRC-ARIsAP3zarGPN3jVnt36qWvYS5TZ54HLi_8KsVwBpxNq4sEQsXCJ6_Vb7b_zsRoaArIBEALw_wcB
5. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area [published correction appears in doi: 10.1001/jama.2020.7681]. JAMA. 2020;323(20):2052-2059. https://doi.org/10.1001/jama.2020.7681
6. 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
7. Kacmarek RM. The mechanical ventilator: past, present, and future. Respir Care. 2011;56(8):1170-1180. https://doi.org/10.4187/respcare.01420
8. Tallo FS, de Campos Vieira Abib S, de Andrade Negri AJ, Cesar P Filho, Lopes RD, Lopes AC. Evaluation of self-perception of mechanical ventilation knowledge among Brazilian final-year medical students, residents and emergency physicians. Clinics (Sao Paulo). 2017;72(2):65-70. https://doi.org/10.6061/clinics/2017(02)01
9. Lino JA, Gomes GC, Sousa ND, Carvalho AK, Diniz ME, Viana Junior AB, et al. A Critical Review of Mechanical Ventilation Virtual Simulators: Is It Time to Use Them?. JMIR Med Educ. 2016;2(1):e8. https://doi.org/10.2196/mededu.5350
10. Patel BK, Kress JP, Hall JB. Alternatives to Invasive Ventilation in the COVID-19 Pandemic [published online ahead of print, 2020 Jun 4]. JAMA. 2020;10.1001/jama.2020.9611. https://doi.org/10.1001/jama.2020.9611
11. Guérin C, Lévy P. Easier access to mechanical ventilation worldwide: an urgent need for low income countries, especially in face of the growing COVID-19 crisis. Eur Respir J. 2020;55(6):2001271. https://doi.org/10.1183/13993003.01271-2020
12. World Health Organization. Medical devices: managing the mismatch: an outcome of the priority medical devices project. Geneva: World Health Organization; 2010.

J Bras Pneumol. 2020;46(4):e20200363
https://dx.doi.org/10.36416/1806-3756/e20200363

Telemedicine, legal certainty, and COVID-19: where are we?

Marcos Vinicius Fernandes Garcia[1], Marco Aurélio Fernandes Garcia[2]

In Brazil, telemedicine activities were exceptionally authorized due to the recent coronavirus disease 2019 (COVID-19), being valid only while the pandemic lasts.[1] The necessary regulation of telemedicine is still being discussed and was subjected to a presidential veto, on the grounds that the regulation of medical activities by means of telemedicine after the end of the current pandemic is a matter that should be regulated by law.[2]

Telemedicine has been a successful tool and was the major international technological innovation implemented during the pandemic[3]; however, legal uncertainty on the topic is still common among health care professionals and institutions.[4]

COVID-19 spread across all continents in weeks, overcoming the ability of health care systems to test individuals, as well as to track and contain the disease.[5] Telemedicine activities prevent close contact, decreasing the chance of infection with the COVID-19 virus, accelerate the dissemination of accurate information by making teaching platforms available, and promote access to the opinions of experts in remote locations.[3]

Various countries severely affected by the pandemic have developed and implemented telemedicine platforms. The government of the Chinese province of Shandong, one of the most affected regions, established a comprehensive telemedicine program in March of 2020. The program has provided guidance on prevention and treatment directly to the patients, training for health care professionals, and remote consultation with specialists for medical staff in different locations. This platform has been a great success and a model for other Chinese cities.[6]

Italy, however, encountered various barriers to telemedicine amidst a large number of critical patients and low availability of ICU beds. The limited availability of large-scale telemedicine solutions, the heterogeneity of the tools available, the poor interconnection among telemedicine services operating in different locations, the lack of a multidisciplinary approach to the management of patients, and the absence of clear legal guidelines were factors that limited the wide use of telemedicine.[7]

Telemedicine is not a novelty in the world. The World Medical Association statement, also known as the Tel Aviv Statement, one of the most important telemedicine documents worldwide, was created in 1999.[8] This phenomenon soon arrived in Brazil. In 2002, the Brazilian *Conselho Federal de Medicina* (CFM, Federal Council of Medicine)[9] formulated a resolution that defined what telemedicine service is, established the minimal infrastructure required, and addressed medical responsibilities and the registration of telemedicine service providers.

This resolution remained dormant for 15 long years, but made sure that "telemedicine, even in a timid way, already existed and worked."[10] Incredibly, CFM new attempt to regulate the topic resulted in the alleged ban on telemedicine nationally. Between the end of 2018 and the beginning of 2019, CFM prepared Resolution no. 2,227,[11] which introduced several innovations applicable to telemedicine and finally provided a robust legal framework for the provision of telemedicine services in Brazil. According to the resolution, these would be the modalities of telemedicine: teleconsultation, teleinterconsultation, telediagnosis, telesurgery, telescreening, telemonitoring (or telesurveillance), teleorientation, and teleconsulting. The legal wording reinforced that each of the eight different modalities of telemedicine would deserve a different approach instead of establishing general rules for telemedicine as a whole. It is important to note that this resolution formally revoked the previous CFM resolution of 2002, and it would only come into force 90 days after its publication.

Resolution no. 2,227[11] had a very short life because it was revoked even before it came into force. Because of the immediate reaction of the medical community, CFM rushed to publish Resolution no. 2,228,[12] which completely revoked Resolution no. 2,227,[11] but expressly reestablished Resolution no. 1,643.[9] Therefore, an unusual legal confusion was created. If Resolution no. 2,228[12] had only revoked Resolution no. 2,227,[11] with nothing else to add, the understanding would be that telemedicine was no longer authorized in Brazil. However, by expressly reestablishing the validity of the 2002 Resolution[9] on telemedicine, Resolution no. 2,228[12] did not effectively prohibit the practice of telemedicine in Brazil.

This resulted in a legal imbroglio. Technically, Resolution no. 1,643[9] remains in effect today. This fact still generates doubts and uncertainties in the medical community and in the media; however, it is understood that CFM regulations have never prohibited telemedicine in Brazil. This position is clear considering that the law of telemedicine and the subsequent Brazilian Ministry of Health Ordinance no. 467[13] made it clear that telemedicine would be authorized in Brazil. However, the Code of Medical Ethics,[14] published in 2019, maintains the prohibition of prescribing treatment and procedures without the direct examination of the patient or by any other means of communication or mass media. Therefore, even the greatest enthusiast of telemedicine would be reluctant to rely on the outdated and incomplete Resolution no. 1,643.[9]

1. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo – HCFMUSP – São Paulo (SP) Brasil.
2. Costa e Garcia Advogados Associados. São Paulo (SP) Brasil.

ISSN 1806-3713

It is evident that telemedicine needs to be properly regulated in order to become available after the end of the COVID-19 pandemic. To this end, all interested parties in its approval should be convened to create an adequate legal framework for telemedicine activities.

Given the very favorable results of telemedicine obtained in a very short time in Brazil and worldwide, it is natural to expect that there will be no setbacks, such as the prohibition of telemedicine services in Brazil. Telemedicine has become a critical component during the pandemic and improved the efficacy of health care services, multiplying the capacity of the health care system to cope with COVID-19. We believe that telemedicine plays a fundamental role in defeating the pandemic and should not be considered just an option or a complement to react against a crisis. Therefore, the dissemination of telemedicine is a path of no return. The regulation of telemedicine will be remembered as a historic landmark for the Brazilian Unified Health Care System in the future.

AUTHOR CONTRIBUTIONS

MVFG and MAFG were responsible for preparing the text, revising the references, and writing the final text.

REFERENCES

1. Brasil. Presidência da República. Lei no. 13.989, de 15 de abril de 2020, Artigos 1 e 2. Diário Oficial da União. 16 de abril de 2020;73:(1):1
2. Brasil. Presidência da República. Secretaria Geral. Subchefia para Assuntos Jurídicos. Mensagem no. 191, de 15 de abril de 2020. Diário Oficial da União. 16 de abril de 2020;73(6).
3. Hollander JE, Carr BG. Virtually Perfect? Telemedicine for Covid-19. N Engl J Med. 2020;382(18):1679-1681. https://doi.org/10.1056/NEJMp2003539
4. Gonçalves C. Jurídico: A busca pela regulamentação da telemedicina. Rev Hosp Brasil [serial on the Internet]. 2014 Apr [cited 2020 Jul 15;66(4):[about 3p.]. Available from: https://telemedicina.fm.usp.br/portal/wp-content/uploads/2015/01/Revista_Hospitais_Brasil_66_Abr2014_.pdf
5. Keesara S, Jonas A, Schulman K. Covid-19 and Health Care's Digital Revolution. N Engl J Med. 2020;382(23):e82. https://doi.org/10.1056/NEJMp2005835
6. Song X, Liu X, Wang C. The role of telemedicine during the COVID-19 epidemic in China-experience from Shandong province. Crit Care. 2020;24(1):178. https://doi.org/10.1186/s13054-020-02884-9
7. Omboni S. Telemedicine During The COVID-19 in Italy: A Missed Opportunity? [published online ahead of print, 2020 Apr 22]. Telemed J E Health. 2020;10.1089/tmj.2020.0106. https://doi.org/10.1089/tmj.2020.0106
8. World Medical Association [homepage on the Internet]. Ferney-Voltaire, France :World Medical Association; [updated 2017 Mar 23; cited 2020 Jul 15]. Archived: Statement on Accountability, Responsibilities and Ethical Guidelines in the Practice of Telemedicine [about 11 screens]. Available from: https://www.wma.net/policies-post/wma-statement-on-accountability-responsibilities-and-ethical-guidelines-in-the-practice-of-telemedicine/
9. Brasil. Conselho Federal de Medicina. Resolução CFM no. 1.643/2002. Diário Oficial da União. 26 de agosto de 2002;164(1):205.
10. França GV. Direito Médico, 12th ed. Rio de Janeiro: Forense; 2014. p.54.
11. Brasil. Conselho Federal de Medicina. Resolução CFM no. 2.227/2018. Diário Oficial da União. 6 de fevereiro de 2019;26(1):58.
12. Brasil. Conselho Federal de Medicina. Resolução CFM no. 2.228/2019. Diário Oficial da União. 6 de março de 2019;44(1):91.
13. Brasil. Ministério da Saúde. Portaria no. 467. Diário Oficial da União. 23 de março de 2020;56-B(1-extra):1.
14. Brasil. Conselho Federal de Medicina. Código de Ética Médica. Resolução CFM no. 2.217, de 27 de setembro de 2018, modificada pelas Resoluções CFM nos. 2.222/2018 e 2.226/2019. Brasília: Conselho Federal de Medicina; 2019.

J Bras Pneumol. 2020;46(4):e20200388
https://dx.doi.org/10.36416/1806-3756/e20200388

Challenging scenarios in the treatment of lung cancer

Ana Caroline Zimmer Gelatti[1,2,3], Vinicius Lorandi[1,2,4]

Lung cancer continues to be a global health problem. Since the 1980s, it has been the leading cause of death from cancer, as well as accounting for approximately 13% of all new cases of cancer.[1] In Brazil, it is the most lethal type of cancer among males and the second most lethal among females, being responsible for a total of 28,717 deaths in 2018.[2]

Given that smoking is the main risk factor, lung cancer is one of the main avoidable causes of death. Due to a reduction in smoking rates, the lung cancer mortality rate began to decline in 2011. Nevertheless, nearly 75% of lung cancer patients are still diagnosed with either locally advanced or metastatic cancer. In the advanced disease scenario, fewer than 20% have a life expectancy of five years and systemic treatment is still the main therapeutic option available. In contrast, 50-90% of those diagnosed in the initial stages have survival rates of five years.[1,2]

Access to diagnostic procedures to obtain tissue samples, which are linked to advances in surgical and systemic treatments, still differs between public and private institutions. In the public system, diagnostic procedures that are less invasive, such as imaging-guided percutaneous needle biopsy and bronchoscopy, are scarce and result in delays in the treatment timeline for patients with lung cancer.[3]

In the last ten years, thoracic surgery has evolved rapidly, with the development and assimilation of minimally invasive techniques in the management of lung cancer. According to the Brazilian Society of Thoracic Surgery database, 52% of patients diagnosed with lung cancer between August of 2015 and December of 2016 underwent anatomical lung resection. This number is higher than that reported by European societies.[4] The use of robot-assisted thoracic surgery has also recently been adopted, although access to the technology is still very limited. Lobectomy continues to be the surgical procedure most commonly performed.[5]

Despite the advances in surgical techniques, only a small portion of lung cancer patients undergo surgery with curative intent. Data suggest that only a quarter of such patients undergo surgical treatment. Access to curative surgery is probably influenced by socioeconomic differences, performance status, comorbidities, geographic distribution, and advanced age.[6] Data from the Brazilian National Cancer Institute indicate that more than 45% of lung cancer deaths occurring between 2010 and 2018 were in patients over 70 years of age.[2] Studies that evaluate special populations are scarce. One retrospective study conducted at a center in Portugal showed that, among patients over 70 years of age, the relapse and mortality rates were similar between those undergoing sublobar resection and those undergoing traditional lobectomy.[7] Data from the São Paulo State Department of Health show that the probability of undergoing surgery is lower among individuals with a lower level of education.[8]

In another retrospective study, Younes et al.[9] evaluated data collected from 2,673 patients with metastatic non-small cell lung cancer treated at two cancer treatment centers between 1990 and 2008. Only 10% of the patients had a Karnofsky performance status (KPS) score > 90, and half of the patients had a score of ≤ 70, reflecting the delayed access of these patients to cancer treatment centers. Although it is known that the KPS is influenced by multiple factors, anorexia and weight loss might be some of the main factors. Franceschini et al.[10] addressed that theme, reporting that weight loss and anorexia are independent factors for mortality in patients with lung cancer, even before the initiation of treatment.

In one recent study,[11] real-life data were collected from 1,256 patients in seven countries, including 175 in Brazil. All the patients in the Brazilian cohort received at least first-line treatment. Only 58% of the patients were tested for the *EGFR* mutation (identified in 17% of those patients), and the *ALK* rearrangement test was applied in only 11% (no positive results). Most patients were treated with platinum doublet therapy. These results may reflect the fact that most patients diagnosed with advanced/metastatic non-small cell lung cancer in Brazil and showing a good KPS score are being treated with platinum doublet therapy because of their access to the public health care system.

The diagnosis of tumor-induced mutations is essential for the selection of the most appropriate treatment. Wider access to the genomic profiling of tumors and the respective corresponding molecularly targeted therapy is a high priority in Brazil. Restrictions and financial barriers are among the possible reasons why the clinical use of tyrosine kinase inhibitors and checkpoint inhibitors is so low in patients treated via the public health care system in the country.

Although anti-EGFR drugs have been incorporated into the Brazilian public health care system since 2015, neither the test for the *EGFR* mutation nor the medication is readily available or routinely provided to patients in the country. The first ALK inhibitor approved for use in Brazil was crizotinib, which was approved in February of

1. Grupo Oncoclínicas, Porto Alegre (RS) Brasil.
2. Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.
3. Grupo Brasileiro de Oncologia Torácica – GBOT – Porto Alegre (RS) Brasil.
4. Hospital Mãe de Deus, Porto Alegre (RS) Brasil.

ISSN 1806-3713

2016. It is estimated that the delay in the approval of crizotinib resulted in the premature deaths of more than 700 patients due to a lack of access to the medication. Despite conflicting data on the cost-effectiveness of tyrosine kinase inhibitor use in Brazil, Aguiar et al.[12] stated that there are different models for the analysis of these data in the Brazilian Unified Health Care System and showed that the use of anti-EGFR drugs can indeed be cost-effective.

The lack of local data in many sectors highlights the need for regional studies to help develop programs that are effective in the prevention, diagnosis, and treatment of lung cancer, as well as fostering the creation of algorithms and guidelines for triage in Brazil.

Over the last decade, in addition to new drugs, technological innovations in treatment to allow the individualization of cancer treatment have appeared rapidly. However, the accessibility of such innovations has not kept pace with their evolution because of their cost. Because the population of patients with lung cancer is quite heterogeneous, it is essential that we be able to analyze the various scenarios and propose courses of treatment that can meet all of the challenges encountered in clinical practice.

REFERENCES

1. Araujo LH, Baldotto C, Castro G Jr, Katz A, Ferreira CG, Mathias C, et al. Lung cancer in Brazil. J Bras Pneumol. 2018;44(1):55-64. http://dx.doi.org/10.1590/S1806-37562017000000135
2. Instituto Nacional de Câncer [homepage on the Internet]. Rio de Janeiro: INCA; c2020 [updated 2020 May 8; cited 2020 Aug 1]. Estatísticas de câncer. Available from: https://www.inca.gov.br/numeros-de-cancer
3. Mathias C, Prado GF, Mascarenhas E, Ugalde PA, Gelatti ACZ, Carvalho ES, et al. Lung Cancer in Brazil. J Thorac Oncol. 2020;15(2):170-175. https://doi.org/10.1016/j.jtho.2019.07.028
4. Falcoz PE, Puyraveau M, Thomas PA, Decaluwe H, Hürtgen M, Petersen RH, et al. Video-assisted thoracoscopic surgery versus open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. Eur J Cardiothorac Surg. 2016;49(2):602-609. https://doi.org/10.1093/ejcts/ezv154
5. Tsukazan MTR, Terra RM, Vigo Á, Fortunato GA, Camargo SM, Oliveira HA, et al. Video-assisted thoracoscopic surgery yields better outcomes than thoracotomy for anatomical lung resection in Brazil: a propensity score-matching analysis using the Brazilian Society of Thoracic Surgery database. Eur J Cardiothorac Surg. 2018;53(5):993-998. https://doi.org/10.1093/ejcts/ezx442
6. Araujo LH, Baldotto CS, Zukin M, Vieira FM, Victorino AP, Rocha VR, et al. Survival and prognostic factors in patients with non-small cell lung cancer treated in private health care. Rev Bras Epidemiol. 2014;17(4):1001-1014. https://doi.org/10.1590/1809-4503201400040017
7. Afonso M, Branco C, Alfaro TM. Sublobar resection in the treatment of elderly patients with early-stage non-small cell lung cancer. J Bras Pneumol. 2020;46(4):e20190145.
8. Fundação Oncocentro de São Paulo (FOSP) [homepage on the Internet]. São Paulo: FOSP [cited 2020 Aug 1]. Acesso ao TABNET. Available from: http://www.fosp.saude.sp.gov.br/publicacoes/tabnet
9. Younes RN, Pereira JR, Fares AL, Gross JL. Chemotherapy beyond first-line in stage IV metastatic non-small cell lung cancer. Rev Assoc Med Bras (1992). 2011;57(6):686-691. https://doi.org/10.1590/S0104-42302011000600017
10. Franceschini JP, Jamnik S, Santoro IL. Role that anorexia and weight loss play in patients with stage IV lung cancer. J Bras Pneumol. 2020;46(4):e20190420. https://doi.org/10.1590/1806-3713/e20190412
11. de Castro J, Tagliaferri P, de Lima VCC, Ng S, Thomas M, Arunachalam A, et al. Systemic therapy treatment patterns in patients with advanced non-small cell lung cancer (NSCLC): PIvOTAL study. Eur J Cancer Care (Engl). 2017;26(6):e12734. https://doi.org/10.1111/ecc.12734
12. Aguiar P Jr, Roitberg F, Lopes G Jr, Giglio AD. Distinct models to assess the cost-effectiveness of EGFR-tyrosine kinase inhibitors for the treatment of metastatic non-small cell lung cancer in the context of the Brazilian Unified Health Care System. J Bras Pneumol. 2020;46(4):e20180255. https://doi.org/10.36416/1806-3756/e20180255

J Bras Pneumol. 2020;46(4):e20200443
https://dx.doi.org/10.36416/1806-3756/e20200443

Maneuvers and strategies in respiratory physical therapy: time to revisit the evidence

Marcella Musumeci Fagundes de Almeida[1,2,3], Renata de Jesus Teodoro[1,4,5,6], Luciana Dias Chiavegato[1,2]

Respiratory physical therapy has always sought to prove the efficiency of techniques,[1-3] such as chest vibration/percussion and changes in inspiratory/expiratory flow, in bronchial hygiene. However, this has failed to be proven because of methodological differences among the studies and the fact that these techniques depend on being properly performed by the physical therapist, as well as, in many cases, on the collaboration of the patients.[4]

We believe that studies that corroborate the use of bronchial hygiene techniques are important, since they are necessary to prevent atelectasis and pulmonary infections, as well as to reduce the length of hospital stay. In this context, Chicayban et al.,[5] in the present issue of the *Jornal Brasileiro de Pneumologia*, contemplate us with a study comparing two bronchial hygiene techniques that can be used in clinical practice.

Postural drainage, tapotement and chest vibration, acceleration of expiratory flow, positive end-expiratory pressure–zero end-expiratory pressure maneuvers,[6] bag squeezing,[7] and manual hyperinflation performed with an artificial manual breathing unit (AMBU) are among the most frequently studied techniques. Bag squeezing and manual hyperinflation, when compared with the stimulation of cough or tracheal aspiration without the prior use of physical therapy maneuvers, have so far been shown not to be effectively capable of demonstrating an increase in the mobilization and in the amount of fluid.[8]

Cough depends on inspiratory and expiratory muscles being preserved; however, after prolonged ICU stays and use of mechanical ventilation, in addition to the evolution of various diseases, these muscles might become impaired and end up compromising effective coughing.[8] In this context, maneuvers that improve the patient's ability to perform deep and sustained inhalations are very important to make coughing more effective, revert possible areas of atelectasis, and prevent other pulmonary complications due to accumulation of secretions.[8]

A recent study[8] evaluated the major bronchial hygiene techniques used by physical therapists: vibrocompression, hyperinflation, postural drainage, tracheal aspiration, and motor physical therapy. The authors found that the most frequent reason for using one or the other maneuver was the personal experience of the professional (not scientific evidence), which demonstrates the need for further studies on this topic because techniques/maneuvers have always been used and recommended in the routine of such professionals.[8] Based on these findings, interventions were started to help improve or simulate the physiological mechanisms of fluid clearance.

Breath stacking techniques, which include voluntary and involuntary breath stacking, have the physiological principle of increasing lung volume and elastic recoil. These techniques are intended to reexpand collapsed areas and assist coughing, which are mechanisms that can be impaired in various diseases. For this reason, we believe that the study by Chicayban et al.[5] is valuable because it scientifically supports physical therapy approach using viable, comprehensive resources in clinical practice. In addition, breath stacking techniques have demonstrated a solid scientific basis as to their effectiveness.[9-13] These techniques have been well-established in the treatment of neuromuscular diseases and, in practice, are aided by AMBU, which increases inspiratory volume above three liters. This acts on lung elastic recoil, and it makes coughing more effective during forced expiration, whether associated with thoracoabdominal restriction or not. The major function of involuntary breath stacking is not related to mobilizing fluid, as is observed in conventional maneuvers. In fact, it simulates cough mechanisms, increases PEF and peak cough flow, carrying fluid to the upper airways. Therefore, it is a technique that should applied and studied in other diseases, besides neuromuscular diseases.[12] The voluntary breath stacking technique has good results in terms of improving oxygenation in patients with atelectasis.[14] However, the effects of this technique on respiratory mechanics in patients with severely impaired lung function should be further evaluated to contribute to decision-making in clinical practice. It is of note that voluntary breath stacking depends more on the muscle contraction of the patient to generate tidal volume, whereas involuntary breath stacking relies on the volume generated by AMBU (bag-valve-mask).

Although both techniques can be used easily and independently,[5] involuntary breath stacking appeared to be more effective in generating inspiratory volume and increasing static compliance when compared with voluntary breath stacking. In the study by Chicayban et al.,[5] 85% of the patients needed fluid aspiration due to coughing during the performance of involuntary breath stacking. Because this increases elastic recoil, we can strategically think that there was an effect of "sudden decompression" that, when associated with more vigorous

1. Disciplina de Pneumologia, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil.
2. Serviço de Fisioterapia, Hospital São Paulo, Disciplina de Pneumologia, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil.
3. Hospital Vila Nova Star, São Paulo (SP) Brasil.
4. Universidade Nove de Julho, São Paulo (SP) Brasil.
5. Liga da Fisiointensiva, São Paulo (SP) Brasil.
6. Clinica Play Edu, São Paulo (SP) Brasil.
7. Programa de Mestrado e Doutorado, Universidade Cidade de São Paulo – UNICID – São Paulo (SP) Brasil.

ISSN 1806-3713

expiratory efforts, could generate a more productive and effective cough, carrying secretions more easily, which was well discussed and demonstrated by the authors.[5]

Regarding the safety of the maneuvers,[5] these were repeated in 4-5 consecutive cycles, which seemed not to cause adverse effects, such as hemodynamic instability, patient discomfort, or increased airway resistance. This corroborates the studies by Sarmento et al.[13] and Naue et al.,[15] who compared different bronchial hygiene techniques, combined and isolated, and concluded that the techniques were safe and that, when combined, they appeared to be more efficient in reducing the frequency of aspiration and the duration of mechanical ventilation.

Although the authors[5] do not mention the level of awareness and cooperation of the patients at the time that interventions were performed, we believe that more cooperative patients can benefit more from such maneuvers, especially when they receive orientation on how to perform the maneuvers themselves after hospital discharge.

In conclusion, we found that both techniques promote bronchial hygiene by increasing inspiratory volume, inspiratory capacity, and complacency, favoring a greater peak cough flow. The study by Chicayban et al.[5] helps support the use of reexpansion techniques based on evidence and applicability in an attempt to supply the absence of well-evidenced studies with proper methodology on this topic.

REFERENCES

1. Peruzzi WT, Smith B. Bronchial hygiene therapy. Crit Care Clin. 1995;11(1):79-96. https://doi.org/10.1016/S0749-0704(18)30086-1
2. Varekojis SM, Douce FH, Flucke RL, Filbrum DA, Tice JS, McCoy KS, et al. A comparison of the therapeutic effectiveness of and preference for postural drainage and percussion, intrapulmonary percussive ventilation, and high-frequency chest wall compression in hospitalized cystic fibrosis patients. Respir Care. 2003;48(1):24-28.
3. Florêncio RB, Aliverti A, Fagundes MLLC, Batista IPDS, Nóbrega AJS, Resqueti VR, et al. Acute effects of three pulmonary reexpansion modalities on thoracoabdominal motion of healthy subjects: Randomized crossover study. PLoS One. 2019;14(3):e0213773. https://doi.org/10.1371/journal.pone.0213773
4. Walton JR, Shapiro BA. Appropriate utilization of bronchial hygiene therapy: development and evaluation of a cost-effective respiratory therapy program. QRB Qual Rev Bull. 1981;7(1):21-25.
5. Chicayban LM, Hemétrio AC, Azevedo LTR. Comparison of the effects of voluntary and involuntary breath stacking techniques on respiratory mechanics and lung function patterns in tracheostomized patients: a randomized crossover clinical trial. J Bras Pneumol. 2020;46(4):e20190295. https://doi.org/10.36416/1806-3756/e20190295
6. Santos FR, Schneider Júnior LC, Forgiarini Junior LA, Veronezi J. Effects of manual rib-cage compression versus PEEP-ZEEP maneuver on respiratory system compliance and oxygenation in patients receiving mechanical ventilation. Rev Bras Ter Intensiva. 2009;21(2):155-161. https://doi.org/10.1590/S0103-507X2009000200007
7. Windsor HM, Harrison GA, Nicholson TJ. "Bag squeezing": a physiotherapeutic technique. Med J Aust. 1972;2(15):829-832. https://doi.org/10.5694/j.1326-5377.1972.tb103565.x
8. Matilde INE, Eid RAC, Nunes AF, Ambrozin ARP, Moura RH, Carnieli-Cazati D, et al. Bronchial hygiene techniques in patients on mechanical ventilation: what are used and why? Einstein (Sao Paulo). 2018;16(1):eAO3856. https://doi.org/10.1590/s1679-45082018ao3856
9. Toussaint M, Pernet K, Steens M, Haan J, Sheers N. Cough Augmentation in Subjects With Duchenne Muscular Dystrophy: Comparison of Air Stacking via a Resuscitator Bag Versus Mechanical Ventilation. Respir Care. 2016;61(1):61-67. https://doi.org/10.4187/respcare.04033
10. Camela F, Gallucci M, Ricci G. Cough and airway clearance in Duchenne muscular dystrophy. Paediatr Respir Rev. 2019;31:35-39. https://doi.org/10.1016/j.prrv.2018.11.001
11. Iskandar K, Sunartini, Nugrahanto AP, Ilma N, Kalim AS, Adistyawan G, et al. Use of air stacking to improve pulmonary function in Indonesian Duchenne muscular dystrophy patients: bridging the standard of care gap in low middle income country setting. BMC Proc. 2019;13(Suppl 11):21. https://doi.org/10.1186/s12919-019-0179-4
12. Brito MF, Moreira GA, Pradella-Hallinan M, Tufik S. Air stacking and chest compression increase peak cough flow in patients with Duchenne muscular dystrophy. J Bras Pneumol. 2009;35(10):973-979. https://doi.org/10.1590/S1806-37132009001000005
13. Sarmento A, de Andrade AF, Lima ÍN, Aliverti A, de Freitas Fregonezi GA, Resqueti VR. Air Stacking: A Detailed Look Into Physiological Acute Effects on Cough Peak Flow and Chest Wall Volumes of Healthy Subjects. Respir Care. 2017;62(4):432-443. https://doi.org/10.4187/respcare.05189
14. Marini JJ, Rodriguez RM, Lamb VJ. Involuntary breath-stacking. An alternative method for vital capacity estimation in poorly cooperative subjects. Am Rev Respir Dis. 1986;134(4):694-698. https://doi.org/10.1164/arrd.1986.134.5.902
15. Naue WDS, Herve BB, Vieira FN, Deponti GN, Martins LF, Dias AS, et al. Comparison of bronchial hygiene techniques in mechanically ventilated patients: a randomized clinical trial. Rev Bras Ter Intensiva. 2019;31(1):39-46. https://doi.org/10.5935/0103-507X.20190005

Branching tubular opacities

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

A 58-year-old male patient presented with difficult-to-control bronchial asthma and a productive cough. During the investigation, a chest CT scan showed branching tubular opacities at the lung bases (Figure 1).

Branching tubular opacities, also known as the "finger-in-glove" sign, are seen in vascular/bronchial processes or in thickened portions of the peribronchovascular sheath. Branching tubular opacities arising from vessels can be caused by congenital malformations, such as arteriovenous malformations, or by neoplastic vascular infiltration, such as that occurring in endovascular metastasis. Peribronchovascular thickening can be identified in diseases with a lymphatic distribution, such as sarcoidosis and lymphangitic carcinomatosis. The most common possibility, however, is filling of the bronchi with material that is denser than air.

A finding of branching tubular opacities can be indicative of a number of conditions. In bronchial atresia, mucoid impaction is seen when secretion accumulates in the distal segment of the atretic bronchus. A similar aspect can be seen in patients with bronchiectasis, cystic fibrosis, bronchial obstruction by a foreign body, endobronchial neoplasms, broncholithiasis, or allergic bronchopulmonary aspergillosis (ABPA). The CT scan of our patient had a very useful aspect for the differential diagnosis among these diseases: the branching opacities were denser than were the adjacent soft tissue structures, such as the heart and aorta. This finding of high-density branching opacities is characteristic of ABPA.

The cause of ABPA is a hypersensitivity reaction to fungal species of the genus *Aspergillus*. This form of aspergillosis is caused by the presence of plugs of thickened, fungus-containing mucus. Clinically, it presents as recurrent wheezing, cough with expectoration of mucus plugs, fever, and weight loss. Patients with chronic ABPA may also present with recurrent pneumonia.[1,2]

The radiological manifestations of ABPA include central bronchiectasis, most often involving segmental and subsegmental bronchi, and mucoid impaction, associated with "plugging" of the airways with hyphal masses, which are characterized on imaging as branching, "finger-in-glove" tubular opacities involving mainly the upper lobes. Isolated lobar or segmental atelectasis occurs in some cases. The mucus plugs in ABPA are usually hypodense. However, in approximately 30% of patients, the impacted mucus has high attenuation or shows frank calcification on CT. The high-attenuation mucus plugs contain macrophages, eosinophils, fungal hyphae, desquamated epithelium, and calcium oxalate crystals. The hyperdensity is attributed to the presence of calcium oxalate crystals.[1,2]

In conclusion, the presence of branching tubular opacities, corresponding to dilated bronchi containing hyperdense mucus, is considered a characteristic—if not pathognomonic—finding of ABPA.

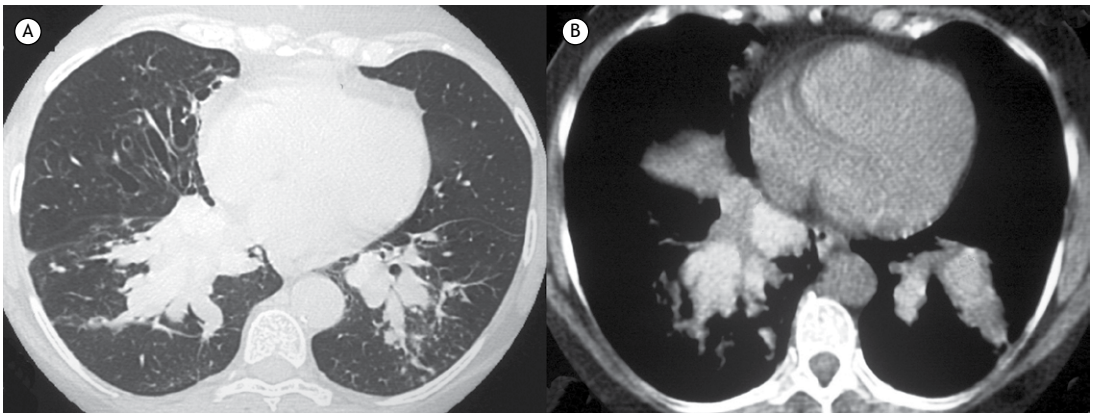


Figure 1. Chest CT scan in lung and mediastinal windows (A and B, respectively) showing branching tubular opacities in both lower lobes. Bronchiectasis is also seen anteriorly. Note in B that the density of the branching opacities is greater than is that of the heart.

REFERENCES

1. Franquet T, Müller NL, Giménez A, Guembe P, de La Torre J, Bagué S. Spectrum of pulmonary aspergillosis: histologic, clinical, and radiologic findings. Radiographics. 2001;21(4):825-837. https://doi.org/10.1148/radiographics.21.4.g01jl03825
2. Agarwal R. High attenuation mucoid impaction in allergic bronchopulmonary aspergillosis. World J Radiol. 2010;2(1):41-43. https://doi.org/10.4329/wjr.v2.i1.41

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.

ISSN 1806-3713

J Bras Pneumol. 2020;46(4):e20200352
https://dx.doi.org/10.36416/1806-3756/e20200352

Pitfalls in the interpretation of pulmonary function tests in neuromuscular disease

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

BACKGROUND

Dyspnea is a common complaint of patients with neuromuscular disease (NMD). Accordingly, these patients are frequently referred for lung function assessment. Some of the abnormalities brought by NMD, however, are prone to misinterpretation causing potential negative clinical consequences.

OVERVIEW

The director of a pulmonary function test (PFT) laboratory was questioned by a family physician about the interpretation of a PFT indicating that, despite the absence of airflow limitation, an 81-year-old, never-smoker woman with normal chest CT had "severe air trapping and a trend toward lung hyperinflation and low carbon monoxide transfer coefficient (K_{CO})." Under the assumption that the results indicated airway disease, she was empirically treated with a combination of bronchodilators which had no impact on her exertional dyspnea and fatigability. The patient repeated the test with the addition of a simplified protocol for NMD assessment. Results indicated a borderline decrease in static and dynamic MIPs but severe expiratory muscle weakness (including a low PEF), which was associated with a marked increase in RV and RV/TLC ratio (Figure 1). She was referred to the neurology department, being eventually diagnosed with a motor neuron disease (amyotrophic lateral sclerosis).

Depending on the relative contribution of inspiratory vs. expiratory muscle weakness, abnormalities on lung and/or chest wall compliance, underlying comorbidities (e.g., atelectasis and lung scarring predisposing to restriction vs. airway disease causing obstruction), and body habitus (obesity vs. underweight), the final pattern of dysfunction may vary substantially in NMD.[1] For instance, whereas RV in healthy elderly subjects is mainly determined by the volume at which the small airways close at low lung volumes,[2] RV becomes strongly dependent on the ability of those with expiratory muscle weakness to "squeeze" the airways near the end of expiration.[1,3] If RV—and, to a lesser extent, functional residual capacity (FRC)—increases in a patient with severe expiratory muscle weakness, but only with mildly impaired inspiratory muscle strength (i.e., preserved inspiratory capacity), TLC might be normal or, as seen in our lean patient, slightly increased (Figure 1).[4] In this context, a preserved TLC associated with a high RV/TLC ratio might be easily misinterpreted as indicative of air trapping due to airway disease. Because her diaphragm was only mildly impaired, FVC did not significantly decrease from a seated position to a supine position. Patients with clinically relevant expiratory muscle weakness

Measurement	Values
Spirometry	
FVC seated (%pred)	82
FVC supine (Δ from seated, %)	-6
FEV_1(%pred)	76
FEV_1/FVC	0.77
PEF (%pred)	57
Lung volumes	
TLC (%pred)	115
IC (%pred)	94
FRC (%pred)	118
RV (%pred)	152
RV/TLC	0.55
Gas exchange	
K_{co} (%pred)	83
DLCO (%pred)	74
Respiratory pressures	
MIP (%pred)	77
SNIP (%pred)	82
MEP (%pred)	41

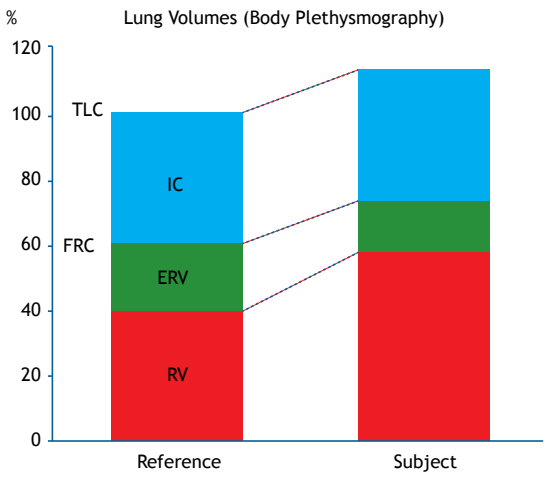


Figure 1. Standard respiratory function tests with measurements of maximal respiratory pressures (plus forced expiration with the patient in seated and supine positions) in an 81-year-old woman (body mass index = 19.6 kg/m²) under investigation for exertional dyspnea. Abnormal test results are marked in red. See text for discussion. %pred: % of the predicted value; IC: inspiratory capacity, FRC: functional residual capacity, K_{CO}: carbon monoxide transfer coefficient, SNIP: sniff nasal inspiratory pressure, ERV: expiratory reserve volume.

1. Pulmonary Function Laboratory and Respiratory Investigation Unit, Division of Respirology, 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.

may present with unequal distribution of ventilation and perfusion[3] which, in addition to microatelectasis, may decrease lung diffusing capacity at a given (low) alveolar volume, reducing K_{CO} (Figure 1).[5]

CLINICAL MESSAGE

The pattern of "extraparenchymal restriction" (low TLC and increased K_{CO}), coupled with low FRC and preserved RV, is commonly seen in patients with isolated inspiratory muscle weakness.[1] Such a pattern, however, might change in the presence of associated/dominant expiratory muscle weakness, leading to increased RV, normal-to-high TLC and FRC, and a trend toward low K_{CO}.[3] The interpretation of lung volumes and K_{CO} should therefore take into consideration the inspiratory and expiratory muscle strength in subjects with unclear "out-of-proportion" dyspnea in whom an NMD is suspected.

REFERENCES

1. Gibson GJ. Neuromuscular Disease. In: Gibson GJ. Clinical Tests of Respiratory Function. 3rd ed. London: Hodder-Arnold; 2009. p.324-50.
2. Macklem PT. The physiology of small airways. Am J Respir Crit Care Med. 1998;157(5 Pt 2):S181-S183. https://doi.org/10.1164/ajrccm.157.5.rsaa-2
3. Hart N, Cramer D, Ward SP, Nickol AH, Moxham J, Polkey MI, et al. Effect of pattern and severity of respiratory muscle weakness on carbon monoxide gas transfer and lung volumes. Eur Respir J. 2002;20(4):996-1002. https://doi.org/10.1183/09031936.00.00286702
4. De Troyer A, Borenstein S, Cordier R. Analysis of lung volume restriction in patients with respiratory muscle weakness. Thorax. 1980;35(8):603-610. https://doi.org/10.1136/thx.35.8.603
5. Neder JA, Berton DC, O'Donnell DE. Integrating measurements of pulmonary gas exchange to answer clinically relevant questions. J Bras Pneumol. 2020;46(1):e20200019. https://doi.org/10.1590/1806-3713/e20200019

Case series: an essential study design to build knowledge and pose hypotheses for rare and new diseases

Carlos Arturo Torres-Duque[1,2,3], Cecilia Maria Patino[1,4], Juliana Carvalho Ferreira[1,5]

PRACTICAL SCENARIO

At the end of December of 2019, a pneumonia outbreak of unknown origin appeared in China. Soon afterwards, the causative virus was identified—SARS coronavirus 2 (SARS-CoV-2), and the disease was named coronavirus disease 2019 (COVID-19). In January of 2020, Chinese investigators published a detailed case series describing the characteristics and outcomes of 41 adults with confirmed COVID-19.[1] The study showed that 15% of those patients died during the study period. That case series[1] was extremely important because it was the first published description of the impact of the new disease, helping clinicians around the world to face a new pandemic.

CONCEPTS AND APPLICATION

A case series includes a description of the characteristics and outcomes among a group of individuals with either a disease or an exposure (which can be an intervention) over a period of time and without a control group. Data are collected retrospectively or prospectively, and there is no randomization. The objective is to describe the population and outcomes, rather than compare risks across groups. Therefore, a case series differs from cohort studies because the latter compares the risk between two groups (exposed and unexposed) and allows for the estimation of an absolute risk for the occurrence of a given outcome in the exposed group and of a relative risk in comparison with the unexposed group.

The case series design is not considered the strongest source of evidence due to the absence of a control group and the risk of bias, in particular selection bias, since typical or severe cases of the disease are more easily identified, and rare presentations or mild cases may not be included. In the Chinese report,[1] for example, patients with less severe COVID-19 were not hospitalized and therefore were not included in the case series. However, case series are particularly important when a new disease or treatment emerges, because it provides descriptive information and contributes to building knowledge and generating hypotheses. Case series is also an appropriate study design to describe new treatments, previously unknown medication adverse events, and rare diseases.[2]

METHODOLOGY AND QUALITY OF CASE SERIES STUDIES

- Inclusion criteria - A precise operational definition of a "case" is crucial for the reliability of the study.
- Sampling - Two strategies are possible: 1) based on disease or exposure; 2) based on a specific outcome.
- Selection of variables of interest - A detailed selection and a clear definition of predictive variables of interest are necessary, as well as test results, interventions, complications, adverse events, and outcomes.
- Systematic collection of data and robust analysis - They assure the quality of a case series study.

Table 1 presents a tool for evaluating the methodological quality of case series.[2]

Table 1. A tool for evaluating the methodological quality of case series.

Domains	Leading explanatory questions
Selection	1. Were all the potentially eligible patients included or is the selection method unclear to the extent that other patients with similar presentations may not have been reported?
Definition of exposure and outcomes	2. Was the exposure adequately and clearly defined? 3. Was the outcome adequately and clearly defined?
Causality	4. Were other alternative causes that may explain the observation ruled out? 5. Was there a challenge/rechallenge phenomenon? 6. Was there a dose-response effect? 7. Was follow-up long enough for outcomes to occur?
Reporting	8. Are the cases described with sufficient details to allow other investigators to replicate the research or to allow practitioners to make inferences related to their own practice?

Adapted from Murad et al.[2] Questions 4, 5 and 6 are more relevant for adverse drug events.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet. 2020 Jan 30]. Lancet. 2020;395(10223):497-506. https://doi.org/10.1016/S0140-6736(20)30183-5
2. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med. 2018;23(2):60-63. https://doi.org/10.1136/bmjebm-2017-110853

1. Methods in Epidemiologic, Clinical, and Operations Research–MECOR–program, American Thoracic Society/Asociación Latinoamericana del Tórax, Montevideo, Uruguay.
2. CINEUMO Research Center, Fundación Neumológica Colombiana, Bogota, Colombia.
3. Universidad de la Sabana, Bogota, Colombia.
4. Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA.
5. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

J Bras Pneumol. 2020;46(4):e20180237
https://dx.doi.org/10.36416/1806-3756/e20180237

ORIGINAL ARTICLE

The Richards-Campbell Sleep Questionnaire and Sleep in the Intensive Care Unit Questionnaire: translation to Portuguese and cross-cultural adaptation for use in Brazil

Samia Khalil Biazim[1], Daniela Almeida Souza[2], Hipólito Carraro Junior[3], Kathy Richards[4], Silvia Valderramas[5]

1. Programa de Pós-Graduação em Medicina Interna, Universidade Federal do Paraná, Curitiba (PR) Brasil.
2. Serviço de Fisioterapia, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba (PR) Brasil.
3. UTI Adulto, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba (PR) Brasil.
4. School of Nursing, University of Texas at Austin, Austin (TX) USA.
5. Departamento de Prevenção e Reabilitação em Fisioterapia, Universidade Federal do Paraná, Curitiba (PR) Brasil.

Submitted: 1 August 2018.
Accepted: 6 May 2019.

Study carried out under the auspices of the Programa de Pós-Graduação em Medicina Interna, Universidade Federal do Paraná, Curitiba (PR) Brasil.

ABSTRACT

Objective: To translate the Richards-Campbell Sleep Questionnaire (RCSQ) and Sleep in the Intensive Care Unit Questionnaire (SICUQ) to Portuguese, making the appropriate cross-cultural adaptations for their use in Brazil, as well as to determine the interobserver reliability of the instruments. **Methods:** In this study, we evaluated medical and surgical patients admitted to the adult ICU of the Federal University of Paraná *Hospital de Clínicas*, in the city of Curitiba, Brazil, between June of 2017 and January of 2018. The translation and cross-cultural adaptation of the questionnaires involved the following steps: translation, synthesis, back-translation, revision by an expert panel, approval of the back-translation by the original authors, pretesting, and creation of the final versions. Two researchers applied the Portuguese-language versions in the evaluation of critically ill patients. Interobserver reliability was assessed by calculating the intraclass correlation coefficient (ICC) and 95% CI. **Results:** The sample comprised 50 patients, of whom 27 (54%) were women. The mean age was 47.7 ± 17.5 years. The main reason for ICU admission, in 10 patients (20%), was cancer. The interobserver reliability of the questionnaires ranged from good to excellent. For the RCSQ, the ICC was 0.84 (95% CI: 0.71-0.90). For SICUQ domains 1-5 (sleep quality and daytime sleepiness), the ICC was 0.75 (95% CI: 0.55-0.86), whereas it was 0.86 (95% CI: 0.76-0.92) for SICUQ domains 6 and 7 (causes of sleep disruption). **Conclusions:** The cross-culturally adapted, Portuguese-language versions of the RCSQ and SICUQ appear to have good interobserver reliability.

Keywords: Sleep; Intensive care units; Sleep deprivation; Surveys and questionnaires; Translations; Cross-cultural comparison.

INTRODUCTION

Sleep plays an important role in restoring the health of individuals who are ill or injured. Sleep disruption is associated with immune system dysfunction, decreased resistance to infection, changes in nitrogen balance, and impaired wound healing, as well as with neurological and cardiopulmonary adverse events.[1] In hospitalized patients, pain, anxiety, medication effects, and environmental stimuli, as well as medical and health care interventions, together with the acute illness itself, can affect the quantity and quality of sleep.[2,3]

Significant changes in sleep architecture are seen in ICU patients, including severely fragmented sleep, circadian rhythm sleep disorders, prolonged sleep latency, frequent awakenings, and reduced nighttime sleep efficiency.[4,5] Sleep disorders constitute an often overlooked complication, the prevalence of which is greater than 50% in critically ill patients, especially very critically ill patients and septic patients.[6-11]

Clinical evaluation, objective methods, and subjective methods can be used in order to investigate sleep disorders. Polysomnography is the gold standard method of objective sleep evaluation, providing information on sleep stages and cycles.[12] However, polysomnography requires appropriate facilities and specially trained personnel, meaning that the costs are high and the availability is limited in the hospital setting, particularly in the ICU.[5,13,14]

Methods of subjective sleep evaluation include questionnaires that are routinely used in clinical practice and research. They are used for diagnostic purposes and to assess treatment response, as well as being used in epidemiological studies and clinical trials. In clinical practice, questionnaires are often the only option for daily bedside assessment of sleep quality because of their low cost, practicality, and rapidity.[9,15,16] Of the sleep quality questionnaires that are most commonly used in the ICU setting, the Richards-Campbell Sleep

Correspondence to:
Silvia Valderramas. Avenida Coronel Heráclito dos Santos, 100, Centro Politécnico, Jardim das Américas, CEP 81531-980, Curitiba, PR, Brasil.
Tel.: 55 41 3361-1744. E-mail: svalderramas@uol.com.br
Financial support: None.

ISSN 1806-3713

Questionnaire (RCSQ) and the Sleep in the Intensive Care Unit Questionnaire (SICUQ) have advantages in terms of their applicability and content.[17,18]

The RCSQ and the SICUQ are original English-language questionnaires developed for use in English-speaking populations. In order to be used in Brazil, they must be translated to Portuguese and culturally adapted for use in the country. The translation and cross-cultural adaptation of a questionnaire should be done with great care, with the use of methods recommended in the literature.[19-21]

The objective of the present study was to translate the RCSQ and the SICUQ to Portuguese and adapt them for use in Brazil, as well as to determine the interobserver reliability for assessing sleep quality with the two instruments.

METHODS

The present study was approved by the Research Ethics Committee of the *Hospital de Clínicas da Universidade Federal do Paraná* (HC/UFPR, Federal University of Paraná *Hospital de Clínicas*), located in the city of Curitiba, Brazil (Ruling no. 2,342,453). The study was conducted between June of 2017 and January of 2018 in the HC/UFPR adult ICU, which is a 14-bed ICU with private rooms.

The RCSQ[17] is used in order to assess sleep quality in eligible ICU patients. It has been validated against polysomnographic recordings, showing excellent internal consistency and moderate correlation. The RCSQ is a five-item self-report questionnaire that is used in order to assess perceived sleep depth, sleep latency (time to fall asleep), and number of awakenings, as well as sleep efficiency and quality. The original RCSQ was subsequently adapted to include a sixth item, namely, perceived nighttime noise.[22-24] Each RCSQ item is scored on a visual analog scale ranging from 0 mm to 100 mm, with higher scores representing better sleep. The mean score of the five items is known as the total score and represents the overall perception of sleep.

The SICUQ[18] is used in order to assess sleep quality in critically ill patients, as well as for collecting data on factors affecting sleep in the ICU, including environmental factors and routine patient care activities. On a scale of 1 to 10 (with 1 being "poor" and 10 being "excellent"), patients rate the overall quality of their sleep at home and in the ICU, rating the overall quality of their sleep on the first night in the ICU, during the middle of their ICU stay, and at the end of their ICU stay. Also on a scale of 1 to 10 (with 1 being "unable to stay awake" and 10 being "fully alert and awake"), patients rate the overall degree of daytime sleepiness during their ICU stay, rating the overall degree of daytime sleepiness on the first day in the ICU, during the middle of their ICU stay, and at the end of their ICU stay. Again on a scale of 1 to 10 (with 1 being "no disruption" and 10 being "significant disruption"), patients rate how disruptive environmental stimuli were to their sleep during their ICU stay, including noise, light, nursing interventions (baths), testing (chest X-rays), assessment of vital signs, collection of blood samples, and administration of medications. As in another study,[25] participants in the present study rated how disruptive pain was to their sleep during their ICU stay. Finally (and yet again on a scale of 1 to 10, with 1 being "no disruption" and 10 being "significant disruption"), patients rate how disruptive certain noises were to their sleep during their ICU stay, including the following: heart monitor alarm; ventilator sounds and alarms; sounds of pulse oximetry; communications between staff members; intravenous pump alarms; nebulizer sounds; suctioning sounds; television sounds; and telephone sounds.

The present methodological study was approved by Dr. Kathy Richards, first author of the original RCSQ, and Dr. Neil Freedman, first author of the original SICUQ.[17,18] Both questionnaires were originally developed in English, in the USA.[17,18] The RCSQ has been translated to and validated for use in German, Chinese, and Farsi.[26-28]

The RCSQ and SICUQ were translated to Portuguese and adapted for use in Brazil in accordance with internationally accepted guidelines.[21,29-31] The protocol included the following steps: 1) permission and rights of use granted by the original authors of the questionnaires, followed by translation from English to Brazilian Portuguese by two independent translators (T1 and T2), native speakers of Portuguese and fluent in English, with one of the translators being familiar with the original questionnaires and aware of the objectives of the study and the other being unfamiliar with the original questionnaires and unaware of the objectives of the study; 2) synthesis of the translations: T1 and T2, together with our research group, analyzed the two translations and used a consensus approach to resolve discrepancies; 3) back-translation: the consensus version was back-translated to English by two independent translators, native speakers of English and fluent in Portuguese, both of whom were unfamiliar with the original versions of the questionnaires; 4) review and revision by an expert panel: a multidisciplinary expert panel consisting of one specialist in methodological research, physicians, physical therapists, and all translators compared the original questionnaires and the back-translations in order to identify discrepancies and make the necessary adjustments, thus arriving at the final versions of the back-translations of the questionnaires; 5) approval from the original authors: the final versions of the back-translations of the questionnaires were sent to the original authors for verification and comments, which were subsequently reviewed by the expert panel, the pretest versions of the questionnaires being thus arrived at; 6) pretesting among the target population and final versions of the questionnaires: two raters (R1 and R2), both of whom were ICU physical therapists, underwent standardized training in using and scoring the pretest versions of the questionnaires. Subsequently, 11 patients participated in a pilot study, in which the

questionnaires were administered in accordance with the methods described in the original papers.[17,18] This was done in order to identify difficulties in administering the questionnaires and arrive at the final Brazilian Portuguese versions of the questionnaires (Figure 1).

All data were collected blindly and independently. The questionnaire administration time was approximately 30 min, and the functions of rater and observer were swapped every 5 patients. Each rater was responsible for half of the evaluations. In an attempt to avoid bias, the scoring sheets were separate and there was no communication between the raters. The collected data included age, sex, reason for ICU admission, length of ICU stay, use of mechanical ventilation, use of vasoactive drugs, and Acute Physiology and Chronic Health Evaluation II scores.[29]

Ours was a convenience sample of medical and surgical patients. The inclusion criteria were as follows: being 18 years of age or older, having stayed in the HC/UFPR ICU for at least 72 h, and having given written informed consent. The exclusion criteria were as follows: presenting with delirium, as assessed by the Confusion Assessment Method for Intensive Care Unit[30]; having a Glasgow Coma Scale score of < 15 or < 11T (using an endotracheal tube or having a tracheostomy)[31]; having a Richmond Agitation-Sedation Scale score of < 0 (being sedated) or > 0 (being nonsedated)[32]; and being unable to understand Portuguese, write, or score the answers. Screening for eligible patients and data collection were performed by R1 one hour before the administration of the questionnaires, at approximately 9:00 a.m.

All statistical analyses were performed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA). The normality and homogeneity of the data were checked with the Kolmogorov-Smirnov test. Participant clinical and demographic characteristics were expressed as frequency, mean, and standard deviation, or as median and interquartile range. Interobserver reliability and reproducibility were assessed by the intraclass correlation coefficient (ICC) and 95% CI for the RCSQ (mean total scores), as well as for SICUQ domains 1-5 and SICUQ domains 6 and 7 (mean domain scores). With regard to interobserver reliability, an ICC of < 0 indicated no reliability; an ICC of 0.00-0.20 indicated poor reliability; an ICC of 0.21-0.40 indicated fair reliability; an ICC of 0.41-0.60 indicated moderately good reliability; an ICC of 0.61-0.80 indicated good reliability; and an ICC of 0.81-1.00 indicated excellent reliability.[33] The level of significance was set at $p < 0.05$.

Sample size was calculated by using the methodology set forth by Terwee et al.,[34] who recommend a total of 4-10 patients for each questionnaire item in a sample of at least 50 patients.

RESULTS

The RCSQ and the SICUQ were initially translated to Brazilian Portuguese by two independent translators (T1 and T2). A consensus approach was used in order to resolve discrepancies, which were found to be few and minor. A decision was made to prioritize terms and phrases familiar to the Brazilian population. For

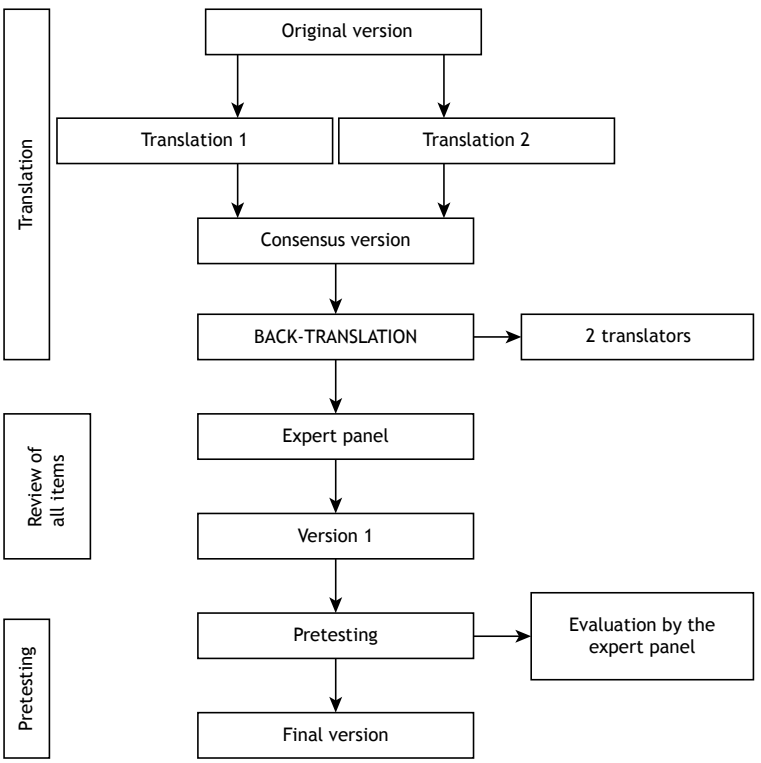


Figure 1. Flow chart of the process of translation and cross-cultural adaptation of the questionnaires.

instance, RCSQ term "noise" was translated as *barulho* rather than as *ruído*; SICUQ terms "poor", "stay", and "disruption" were translated as *ruim*, *permanência*, and *interrupção*, respectively, rather than as *pobre*, *estadia*, and *disruptivo*, respectively. The original authors of the RCSQ and SICUQ made very few changes to the back-translations because they were found to be very similar to the original versions of the questionnaires.

During the expert panel meeting, there was a high level of agreement regarding most of the items on the pretest versions of the questionnaires. Special attention was given to RCSQ item 2, namely, sleep latency. Although the term can be literally translated as *latência do sono*, a decision was made to use the term *tempo para dormir* (time to fall asleep) because patients might not understand the term *latência* (latency). SICUQ item 3 can be rated from 0 to 10, with 1 being "no sleep" and 10 being "excellent". The terms refer to the overall quality of sleep in the ICU on specific days, and although the term "no sleep" can be translated as *não durmo* or *não consigo dormir*, the expert panel suggested that the term be translated as *ruim* (poor, as in "poor quality of sleep"). The same was done for SICUQ items 1 and 2, which also rate the quality of sleep from 0 to 10, with 1 being "no sleep" and 10 being "excellent". All items are summarized in Tables 1 and 2.

During pretesting, raters reported no difficulty administering the questionnaires, reporting that patients had no difficulty understanding the questions. Therefore, no additional changes were made to the final versions of the questionnaires. The RCSQ and SICUQ were rapidly administered (administration time, 2-3 min and 4-5 min, respectively).

A total of 50 patients met the criteria for inclusion in the present study. Of those 50 patients, 27 (54%) were female. The mean age of the participants was 47.7 ± 17.5 years, with cancer being the most common reason for ICU admission, in 10 patients (20%). Of the 50 participants, 1 (2%) was on mechanical ventilation, 2 (4%) underwent tracheostomy, and 2 (4%) were on sedatives at the time of evaluation but met the eligibility criteria, as assessed by the Richmond Agitation-Sedation Scale[32] and the Confusion Assessment Method for Intensive Care Unit.[30] Table 3 shows the demographic and clinical characteristics of the study participants, and Table 4 shows the questionnaire scores.

RCSQ scores were similar between R1 and R2. Interobserver reliability was excellent (ICC = 0.84; 95% CI: 0.71-0.90; $p < 0.001$).

SICUQ scores were similar between R1 and R2. Interobserver reliability was good for SICUQ domains 1-5 (ICC = 0.75; 95% CI: 0.55-0.86; $p < 0.001$) and excellent for SICUQ domains 6 and 7 (ICC = 0.86; 95% CI: 0.76-0.92; $p < 0.001$).

DISCUSSION

There has been an increasing number of studies evaluating sleep quality in the ICU because of increasing concerns with the quality of ICU stay and its impact on the mental, cognitive, and physical health of patients surviving a critical illness.[35] Questionnaires have been developed in order to assess sleep quality in ICU patients. Questionnaires allow short- and long-term evaluation of a larger number of patients than does polysomnography, as well as allowing the implementation of effective interventions to improve sleep quality.[5]

The present study provides health professionals in Brazil with access to two questionnaires that can improve the quality of the care provided to critically ill patients in the ICU and be used in order to compare results across studies.[21]

In the present study, the RCSQ and SICUQ were translated to Portuguese and adapted for use in Brazil, and every effort was made to maintain the reliability of the original instruments.[36] Simple literal translations are insufficient for health questionnaires because of relevant cultural and socioeconomic differences across target populations.[19] According to Behling & Law,[37] cross-cultural adaptation is a process that should be approached with care and address technical, linguistic, and semantic issues.

Interobserver reliability was excellent for the Brazilian Portuguese version of the RCSQ, with an ICC of 0.84. This finding is consistent with those of Chen et al.,[24] who found excellent interobserver reliability for the Chinese version of the questionnaire, with an ICC of 0.91. The Farsi version of the RCSQ was found to have good reliability, with an ICC of 0.71.[25]

The original RCSQ was validated against polysomnography in a sample of 70 critically ill patients, and the data supported the reliability and validity of the questionnaire.[17] Patients in the ICU can present with delirium, receiving intense sedative regimens; this limits the applicability of the RCSQ and can reduce the potential sample size by half.[22] This can partially explain the small sample size of our study.

Although the SICUQ has yet to be validated against polysomnography and via reproducibility studies, the original study in which the SICUQ was developed[18] examined 203 patients and factors contributing to sleep disruption. The SICUQ assesses quality of sleep at home, daytime sleepiness, sleep disruption caused by patient care activities, and sleep disruption caused by environmental factors, none of which are assessed by the RCSQ. Studies using this questionnaire[24,37,38] have shown positive results regarding the implementation of protocols for sleep promotion in the ICU setting and post-ICU evaluation, confirming its utility in clinical practice.

One issue to be addressed is the lack of strict criteria for the use of assessment instruments developed for use elsewhere. Failure to adapt the contents to the target population can undermine the quality of the data being collected and, consequently, invalidate study results.[39,40]

The present study has some limitations that should be noted. Our sample size was small because patients

Table 1. Translations performed by translators 1 and 2, together with the final version of the Richards-Campbell Sleep Questionnaire for use in Brazil.

Item	Original version		Translator 1		Translator 2		Final version	
	Measure	Question	Measure	Question	Measure	Question	Measure	Question
1	Sleep depth	My sleep last night was: light sleep (0) deep sleep (100)	Profundidade do sono	Meu sono na última noite foi: sono leve (0) sono profundo (100)	Profundidade do sono	Meu sono ontem à noite foi: sono leve (0) sono profundo (100)	Profundidade do sono	Meu sono na última noite foi: sono leve (0) sono profundo (100)
2	Sleep latency	Last night, the first time I got to sleep, I: just never could fall asleep (0) fell asleep almost immediately (100)	Latência do sono	Na última noite, a primeira vez que adormeci, eu: não consegui adormecer (0) adormeci quase imediatamente (100)	Latência do sono	Nesta noite, a primeira vez que adormeci, eu: não consegui adormecer (0) adormeci quase imediatamente (100)	Latência do sono Tempo para dormir[a]	Na última noite, a primeira vez que adormeci, eu: não consegui adormecer (0) adormeci quase imediatamente (100)
3	Awakenings	Last night, I was: awake all night long (0) awake very little (100)	Despertar	Na última noite, eu estava: acordado(a) a noite inteira (0) acordei muito pouco (100)	Despertar	Nesta noite, eu estava: acordado(a) a noite inteira (0) despertei muito pouco (100)	Despertar	Na última noite, eu estava: acordado(a) a noite toda (0) acordei muito pouco (100)
4	Returning to sleep	Last night, when I woke up or was awakened, I: couldn't get back to sleep (0) got back to sleep immediately (100)	Voltando ao sono	Na última noite, quando acordei ou fui despertado(a), eu: não consegui voltar a dormir (0) voltei a dormir imediatamente (100)	Retorno ao sono	Nesta noite, quando acordei ou fui acordado(a), eu: não consegui voltar a dormir (0) voltei a dormir imediatamente (100)	Retorno ao sono	Na última noite, quando eu acordei ou fui acordado(a): não consegui voltar a dormir (0) voltei a dormir imediatamente (100)
5	Sleep quality	I would describe my sleep last night as: a bad night's sleep (0) a good night's sleep (100)	Qualidade do sono	Eu descreveria meu sono na última noite como: uma noite ruim de sono (0) uma boa noite de sono (100)	Qualidade do sono	Eu descreveria meu sono na última noite como: ruim noite de sono (0) boa noite de sono (100)	Qualidade do sono	Eu descreveria meu sono na última noite como: ruim noite de sono (0) boa noite de sono (100)
6	Noise	I would describe the noise level last night as: very noisy (0) very quiet (100)	Ruído	Eu descreveria o nível de ruído na última noite como: muito barulhento (0) muito silencioso (100)	Barulho	Eu descreveria o nível de barulho desta noite como: muito barulhento (0) muito quieto (100)	Barulho	Eu descreveria o nível de barulho na última noite como: muito barulhento (0) muito quieto (100)

[a]Change made after a meeting with the expert panel.

Table 2. Translations performed by translators 1 and 2, together with the final version of the Sleep in the Intensive Care Unit Questionnaire for use in Brazil.

Item	Original version	Translator 1	Translator 2	Final version
1	Rate the overall quality of your sleep at home. Use a scale of 1 to 10 (1 is poor; 10 is excellent)	Avalie a qualidade geral do seu sono em casa. Use uma escala de 1 a 10 (1 = pobre, 10 = excelente)	Classifique a qualidade global do seu sono em casa. Utilize uma escala de 1 a 10 (1 = ruim, 10 = excelente)	Classifique a qualidade global do seu sono em casa. Utilize uma escala de 1 a 10 (1 = ruim, 10 = excelente)
2	Rate the overall quality of your sleep in the ICU. Use a scale of 1 to 10 (1 is poor; 10 is excellent)	Avalie a qualidade geral do seu sono na UTI. Use uma escala de 1 a 10 (1 = pobre, 10 = excelente)	Classifique a qualidade global do seu sono na UTI. Utilize uma escala de 1 a 10 (1 = ruim, 10 = excelente)	Classifique a qualidade global do seu sono na UTI. Utilize uma escala de 1 a 10 (1 = ruim, 10 = excelente)
3	Rate the overall quality of your sleep in the ICU on the following days: (1 is no sleep; 10 is excellent) - On the first night in the ICU - During the middle of your ICU stay - At the end of your ICU stay	Avalie a qualidade geral do seu sono na UTI nos dias seguintes: (1 = não dorme, 10 = excelente) - Na primeira noite na UTI - Durante a metade da sua estadia na UTI - No final da sua estadia na UTI	Classifique a qualidade global do seu sono na UTI nos seguintes dias: (1 = não dorme, 10 = excelente) - Na primeira noite na UTI - Durante a metade da sua permanência na UTI - No final da sua permanência na UTI	Classifique a qualidade global do seu sono na UTI nos seguintes dias: (1 não dorme /[a]1 = ruim, 10 = excelente) - Primeira noite na UTI - Durante a metade da sua permanência na UTI - No final da sua permanência na UTI
4	Rate the overall degree of daytime sleepiness during your ICU stay: (1 is unable to stay awake; 10 is fully alert and awake)	Avalie o grau geral de sonolência diurna durante sua estadia na UTI: (1 = incapaz de ficar acordado/a, 10 = totalmente alerta e acordado/a)	Classifique o nível global de sonolência diurna durante sua permanência na UTI: (1 = incapaz de ficar acordado/a, 10 = totalmente alerta e acordado/a)	Classifique o nível global de sonolência diurna durante sua permanência na UTI: (1 = incapaz de ficar acordado/a, 10 = totalmente alerta e acordado/a)
5	Rate the overall degree of daytime sleepiness during your ICU stay on the following days: (1 is unable to stay awake; 10 is fully alert and awake) - On the first night in the ICU - During the middle of your ICU stay - At the end of your ICU stay	Avalie o grau geral de sonolência diurna durante sua estadia na UTI nos dias seguintes: (1 = incapaz de ficar acordado/a; 10 = totalmente alerta e acordado/a) - Na primeira noite na UTI - Durante a metade da sua estadia na UTI - No final da sua estadia na UTI	Classifique o nível global de sonolência diurna durante sua permanência na UTI nos seguintes dias: (1 = incapaz de ficar acordado/a; 10 = totalmente alerta e acordado/a) - Na primeira noite na UTI - Durante a metade da sua permanência na UTI - No final da sua permanência na UTI	Classifique o nível global de sonolência diurna durante sua permanência na UTI nos seguintes dias: (1 = incapaz de ficar acordado/a; 10 = totalmente alerta e acordado/a) - Primeira noite na UTI - Durante a metade da sua permanência na UTI - No final da sua permanência na UTI
6	Rate how disruptive the following activities were to your sleep during your ICU stay. Use a scale of 1 to 10 (1 is no disruption; 10 is significant disruption) - Pain - Noise - Light - Nursing Interventions (i.e. baths) - Diagnostic Testing (i.e. chest x-rays) - Vital Signs (blood pressure, pulse, temperature) - Blood Samples - Administration of Medications	Avalie o grau de disruptiva as seguintes atividades foram para seu sono durante sua estadia na UTI. Use uma escala de 1 a 10 (1 = não interrompe, 10 =- interrupção significativa) - Dor - Barulho - Luz - Intervenções da enfermagem (ou seja, banhos) - Testes de diagnóstico (ou seja, radiografias de tórax) - Sinais vitais (pressão sanguínea, pulso, temperatura) - Amostras de sangue - Administração de medicamentos	Classifique o nível de interrupção do seu sono para as seguintes atividades durante sua permanência na UTI. Use uma escala de 1 a 10 (1 = sem interrupção, 10 = interrupção significativa) - Dor - Barulho - Luminosidade - Intervenções da enfermagem (isto é, banhos) - Testes de diagnóstico (isto é, radiografias de tórax) - Sinais vitais (pressão arterial, pulso, temperatura) - Amostras de sangue - Administração de medicamentos	Classifique o nível de interrupção do seu sono para as seguintes atividades durante sua permanência na UTI. Use uma escala de 1 a 10 (1 = sem interrupção, 10 = interrupção significativa) - Dor - Barulho - Luminosidade - Cuidados de enfermagem (banhos) - Exames (radiografias de tórax) - Sinais vitais (pressão arterial, pulso, temperatura) - Coletas de sangue - Administração de medicamentos

[a]Change made after a meeting with the expert panel.

Table 2. Continued...

Item	Original version	Translator 1	Translator 2	Final version
7	Rate how disruptive the following noises were to your sleep during your ICU stay. (1 is no disruption; 10 is significant disruption) - Heart Monitor Alarm - Ventilator Alarm - Ventilator - Oxygen Finger Probe - Talking - I.V. Pump Alarm - Suctioning - Nebulizer - Doctor's Beepers - Television - Telephone	Avalie o grau de disruptivo os seguintes ruídos foram para seu sono durante sua estadia na UTI. (1 = não interrompe, 10 = interrupção significativa) - Alarme do monitor cardíaco - Alarme do ventilador - Ventilador - Oximetria de pulso - Conversas - Alarme da bomba de infusão - Sucção - Nebulizador - Telefone do médico - Televisão - Telefone	Classifique o nível de interrupção do seu sono para os seguintes barulhos durante sua permanência na UTI. (1 = sem interrupção, 10 = interrupção significativa) - Alarme do monitor cardíaco - Alarme do ventilador - Ventilador - Oximetria de pulso - Conversas - Alarme da bomba infusora - Vácuo de sucção - Nebulizador - Telefone do médico - Televisão - Telefone da unidade	Classifique o nível de interrupção do seu sono para os seguintes barulhos durante sua permanência na UTI. (1 = sem interrupção, 10 = interrupção significativa) - Alarme do monitor cardíaco - Alarme do ventilador - Ventilador - Oximetria de pulso - Conversas - Alarme da bomba infusora - Vácuo de sucção - Nebulização - Telefone do médico - Televisão - Telefone da unidade

[a]Change made after a meeting with the expert panel.

Table 3. Demographic and clinical characteristics of patients completing the Brazilian Portuguese versions of the Richards-Campbell Sleep Questionnaire and Sleep in the Intensive Care Unit Questionnaire (N = 50).[a]

Variable	Result
Age, years	47.7 ± 17.5
Female sex	27 (54)
APACHE II	14.9 ± 8.5
Reason for ICU admission	
Cancer	10 (20)
Respiratory disease	8 (16)
Gastrointestinal disease	6 (12)
Neurological disease	5 (10)
Heart disease	5 (10)
Liver disease	4 (8)
Kidney disease	3 (6)
Pregnancy	3 (6)
Poisoning	2 (4)
Neuromuscular disease	2 (4)
Endocrine disease	1 (2)
Infectious disease	1 (2)
Charlson comorbidity index	1.3 ± 1.7
Smokers	10 (20)
Length of previous ICU stay, days	2.2 ± 4.4
Total length of ICU stay, days	3.5 [3-7]
Use of mechanical ventilation	1 (2)
Duration of mechanical ventilation, days	0 [0-1]
Tracheostomy	2 (4)
Drugs used in the ICU	
Analgesics	44 (88)
Sedatives	2 (4)
Anxiolytics	4 (8)
Vasoactive drugs	11 (22)
Level of consciousness/agitation and sedation at the time of evaluation	
GCS score = 15 or = 11T	48 (96)
RASS score = 0	2 (4)

APACHE II: Acute Physiology and Chronic Health Evaluation; GCS: Glasgow Coma Scale; and RASS: Richmond Agitation-Sedation Scale. [a]Values expressed as mean ± SD, n (%), or median [interquartile range].

Table 4. Total scores on the Brazilian Portuguese versions of the Richards-Campbell Sleep Questionnaire and Sleep in the Intensive Care Unit Questionnaire for raters 1 and 2.[a]

Questionnaire/rater	Score
RCSQ	
R1	34.3 [23.6-49.8]
R2	37.9 [21.5-52.3]
SICUQ	
R1-Domains 1 to 5	6.2 ± 2.0
R2-Domains 1 to 5	6.1 ± 2.3
R1-Domains 6 and 7	3.1 ± 1.5
R2-Domains 6 and 7	3.2 ± 1.7

RCSQ: Richards-Campbell Sleep Questionnaire; SICUQ: Sleep in the Intensive Care Unit Questionnaire; R1: rater 1; and R2: rater 2. [a]Values expressed as median [interquartile range] or mean ± SD.

must remain awake and be cognitively capable of understanding the questions in order to complete the questionnaires. These criteria make it difficult to identify eligible ICU patients. Another limitation is that questionnaires are not the gold standard for assessing sleep quality in the ICU; however, methods such as polysomnography are highly complex and expensive. Therefore, questionnaires are an alternative method for assessing sleep quality in critically ill patients and implementing interventions to improve it. Future studies should examine the psychometric properties of the RCSQ and SICUQ, testing their construct validity and internal consistency.

In summary, the Brazilian Portuguese versions of the RCSQ and SICUQ have good inter-rater reliability and can therefore be used in order to assess sleep quality in adult ICU patients in Brazil.

ACKNOWLEDGMENTS

We would like to thank Dr. Kathy Richards and Dr. Neil Freedman for giving us permission to use their questionnaires.

REFERENCES

1. Parthasarathy S, Tobin MJ. Sleep in the intensive care unit. Intensive Care Med. 2004;30(2):197-206. https://doi.org/10.1007/s00134-003-2030-6
2. Bano M, Chiaromanni F, Corrias M, Turco M, De Rui M, Amodio P, et al. The influence of environmental factors on sleep quality in hospitalized medical patients. Front Neurol. 2014;5:267. https://doi.org/10.3389/fneur.2014.00267
3. Park MJ, Yoo JH, Cho BW, Kim KT, Jeong WC, Ha M. Noise in hospital rooms and sleep disturbance in hospitalized medical patients. Environ Health Toxicol. 2014;29:e2014006. https://doi.org/10.5620/eht.2014.29.e2014006
4. Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. Am J Respir Crit Care Med. 2001;163(2):451-457. https://doi.org/10.1164/ajrccm.163.2.9912128
5. Beltrami FG, Nguyen XL, Pichereau C, Maury E, Fleury B, Fagondes S. Sleep in the intensive care unit. J Bras Pneumol. 2015;41(6):539-546. https://doi.org/10.1590/s1806-37562015000000056
6. Kamdar BB, Needham DM, Collop NA. Sleep deprivation in critical illness: its role in physical and psychological recovery. J Intensive Care Med. 2012;27(2):97-111. https://doi.org/10.1177/0885066610394322
7. McKinley S, Fien M, Elliott R, Elliott D. Sleep and psychological health during early recovery from critical illness: an observational study. J Psychosom Res. 2013;75(6):539-545. https://doi.org/10.1016/j.jpsychores.2013.09.007
8. Altman MT, Knauert MP, Pisani MA. Sleep Disturbance after Hospitalization and Critical Illness: A Systematic Review. Ann Am Thorac Soc. 2017;14(9):1457-1468. https://doi.org/10.1513/AnnalsATS.201702-148SR
9. Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D, Coleman Jr J, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep. 2005;28(4):499-521. https://doi.org/10.1093/sleep/28.4.499
10. Practice parameters for the indications for polysomnography and related procedures. Polysomnography Task Force, American Sleep Disorders Association Standards of Practice Committee. Sleep. 1997;20(6):406-422. https://doi.org/10.1093/sleep/20.6.406
11. Elliott R, McKinley S, Cistulli P, Fien M. Characterisation of sleep in intensive care using 24-hour polysomnography: an observational study. Crit Care. 2013;17(2):R46. https://doi.org/10.1186/cc12565
12. Bourne RS, Minelli C, Mills GH, Kandler R. Clinical review: Sleep measurement in critical care patients: research and clinical implications. Crit Care. 2007;11(4):226. https://doi.org/10.1186/cc5966
13. Hoey LM, Fulbrook P, Douglas JA. Sleep assessment of hospitalised patients: a literature review. Int J Nurs Stud. 2014;51(9):1281-1288. https://doi.org/10.1016/j.ijnurstu.2014.02.001
14. Richards KC, O'Sullivan PS, Phillips RL. Measurement of sleep in critically ill patients. J Nurs Meas. 2000;8(2):131-144. https://doi.org/10.1891/1061-3749.8.2.131
15. Freedman NS, Kotzer N, Schwab RJ. Patient perception of sleep quality and etiology of sleep disruption in the intensive care unit. Am J Respir Crit Care Med. 1999;159(4 Pt 1):1155-1162. https://doi.org/10.1164/ajrccm.159.4.9806141
16. Reichenheim ME, Moraes CL. Operationalizing the cross-cultural adaptation of epidemiological measurement instruments [Article in Portuguese]. Rev Saude Publica. 2007;41(4):665-673. https://doi.org/10.1590/S0034-89102006005000035
17. Turci AM, Bevilaqua-Grossi D, Pinheiro CF, Bragatto MM, Chaves TC. The Brazilian Portuguese version of the revised Maastricht Upper Extremity Questionnaire (MUEQ-Br revised): translation, cross-cultural adaptation, reliability, and structural validation. BMC Musculoskelet Disord. 2015;16:41. https://doi.org/10.1186/s12891-015-0497-2
18. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine (Phila Pa 1976). 2000;25(24):3186-3191. https://doi.org/10.1097/00007632-200012150-00014
19. Frisk U, Nordström G. Patients' sleep in an intensive care unit--patients' and nurses' perception. Intensive Crit Care Nurs. 2003;19(6):342-349. https://doi.org/10.1016/S0964-3397(03)00076-4
20. Kamdar BB, Shah PA, King LM, Kho ME, Zhou X, Colantuoni E, et al. Patient-nurse interrater reliability and agreement of the Richards-Campbell sleep questionnaire. Am J Crit Care. 2012;21(4):261-269. https://doi.org/10.4037/ajcc2012111
21. Li SY, Wang TJ, Vivienne Wu SF, Liang SY, Tung HH. Efficacy of controlling night-time noise and activities to improve patients' sleep quality in a surgical intensive care unit. J Clin Nurs. 2011;20(3-4):396-407. https://doi.org/10.1111/j.1365-2702.2010.03507.x
22. Bihari S, Doug McEvoy R, Matheson E, Kim S, Woodman RJ, Bersten AD. Factors affecting sleep quality of patients in intensive care unit. J Clin Sleep Med. 2012;8(3):301-307. https://doi.org/10.5664/jcsm.1920
23. Krotsetis S, Richards KC, Behncke A, Köpke S. The reliability of the German version of the Richards Campbell Sleep Questionnaire. Nurs Crit Care. 2017;22(4):247-252. https://doi.org/10.1111/nicc.12275
24. Chen LX, Ji DH, Zhang F, et al. Richards-Campbell sleep questionnaire: psychometric properties of Chinese critically ill patients. Nurs Crit Care. 2019;24(6):362–368. doi: https://doi.org/10.1111/nicc.12357
25. Rahimi A, Ahmadali A, Feizi F, Siratinir M. The Psychometric Properties of Richard Campbell Sleep Questionnaire in Patients in Intensive Care Unit. Crit Care Nurs J. 2018;11(1):e65483. https://doi.org/10.5812/ccn.65483
26. Guillemin F. Measuring health status across cultures. Rheum Eur.

1995(Suppl 2):102-3.

27. Sperber AD. Translation and validation of study instruments for cross-cultural research. Gastroenterology. 2004;126(1 Suppl 1):S124-S128. https://doi.org/10.1053/j.gastro.2003.10.016
28. Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. J Clin Epidemiol. 1993;46(12):1417-1432. https://doi.org/10.1016/0895-4356(93)90142-N
29. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-829. https://doi.org/10.1097/00003246-198510000-00009
30. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286(21):2703-2710. https://doi.org/10.1001/jama.286.21.2703
31. Nassar Junior AP, Pires Neto RC, Figueiredo WB de, Park M. Validity, reliability and applicability of Portuguese versions of sedation-agitation scales among critically ill patients. São Paulo Med J. 2008;126(4):215–219. https://doi.org/10.1590/S1516-31802008000400003
32. Sessler CN, Gosnell M, Grap MJ, Brophy GT, O'Neal PV, Keane KA, Tesoro EP, Elswick RK. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care patients. Am J Respir Crit Care Med. 2002;166(10):1338-1344. https://doi.org/10.1164/rccm.2107138
33. Sarwal A, Parry SM, Berry MJ, et al. Interobserver Reliability of Quantitative Muscle Sonographic Analysis in the Critically Ill Population. J Ultrasound Med. 2015;34(7):1191-1200. https://doi.org/10.7863/ultra.34.7.1191
34. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007;60(1):34-42. https://doi.org/10.1016/j.jclinepi.2006.03.012
35. Jutte JE, Erb CT, Jackson JC. Physical, Cognitive, and Psychological Disability Following Critical Illness: What Is the Risk?. Semin Respir Crit Care Med. 2015;36(6):943-958. https://doi.org/10.1055/s-0035-1566002
36. Pilz B, Vasconcelos RA, Marcondes FB, Lodovichi SS, Mello W, Grossi DB. The Brazilian version of STarT Back Screening Tool - translation, cross-cultural adaptation and reliability. Braz J Phys Ther. 2014;18(5):453-461. https://doi.org/10.1590/bjpt-rbf.2014.0028
37. Behling O, Law KS. Translating questionnaires and other research instruments: problems and solutions. Thousand Oaks: Sage; 2000. https://doi.org/10.4135/9781412986373
38. Patel J, Baldwin J, Bunting P, Laha S. The effect of a multicomponent multidisciplinary bundle of interventions on sleep and delirium in medical and surgical intensive care patients. Anaesthesia. 2014;69(6):540-549. https://doi.org/10.1111/anae.12638
39. Kamdar BB, King LM, Collop NA, Sakamuri S, Colantuoni E, Neufeld KJ, et al. The effect of a quality improvement intervention on perceived sleep quality and cognition in a medical ICU. Crit Care Med. 2013;41(3):800-809. https://doi.org/10.1097/CCM.0b013e3182746442
40. Herdman M, Fox-Rushby J, Badia X. A model of equivalence in the cultural adaptation of HRQoL instruments: the universalist approach. Qual Life Res. 1998;7(4):323-335. https://doi.org/10.1023/A:1008846618880

J Bras Pneumol. 2020;46(4):e20180325
http://dx.doi.org/10.36416/1806-3756/e20180325

ORIGINAL ARTICLE

Protocol implementation for venous thromboembolism prophylaxis: a before-and-after study in medical and surgical patients*

Lisiane Freitas Leal[1,2], Maicon Falavigna[3], Marcelo Basso Gazzana[3,4], Juçara Gasparetto Maccari[3], Flávia Ghizzoni[3], Danielle Alves[3], Bruce Bartholow Duncan[1,2], Rodrigo Antonini Ribeiro[2,5]

1. Programa de Pós-Graduação em Ciências da Saúde Cardiologia e Ciências Cardiovasculares, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.
2. Programa de Pós-Graduação em Epidemiologia, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.
3. Associação Hospitalar Moinhos de Vento, Porto Alegre (RS) Brasil.
4. Programa de Pós-Graduação em Ciências Pneumológicas, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.
5. Escola de Medicina, Faculdade Meridional, Passo Fundo (RS) Brasil.

Submitted: 24 October 2018.
Accepted: 13 August 2019.

Study carried out in the Programa de Pós-Graduação em Ciências da Saúde Cardiologia e Ciências Cardiovasculares, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.

* Study was performed in the Hospital Moinhos de Vento as a result of master degree's thesis of Lisiane Leal in the Programa de Pós-Graduação em Cardiologia.

ABSTRACT

Objective: This study aimed to assess the adequacy of venous thromboembolism (VTE) prophylaxis prescription after a protocol implementation. **Methods:** This was a before-and-after study conducted in a tertiary care hospital in Rio Grande do Sul, Southern Brazil. Medical and surgical inpatients aged 18 years or older were assessed for VTE risk and subsequently for thromboprophylaxis adequacy, according to their risk. The evaluations occurred before and after the protocol strategy implementation; it consisted of an online platform to access the protocol, a public posting of the protocol diagram, clinical alerts on the medical staff TV, e-mail alerts, and pop-up alerts on the computerized physician order entry system. The main outcome measure was the adequacy of VTE prophylaxis prescription according to the protocol. **Results:** A total of 429 patients were evaluated for thromboprophylaxis adequacy (213 before and 216 after). The prevalence of adequacy increased from 54% to 63% (pre and post-intervention, respectively), and after adjustment for patient type and phase of the study, the prevalence ratio reached (PR)=1.20, 95% confidence interval (CI) 1.02-1.42. **Conclusion:** The results showed that the overall appropriateness of thromboprophylaxis prescription was weakly improved. Despite these results, this study provides evidence to date a bunch of strategies for protocol implementations in private institutions in middle-income countries with an open medical staff, as there are few studies investigating these simple and pragmatic interventions.

Keywords: Venous thromboembolism; Guideline adherence; Prevention; Thromboprophylaxis.

INTRODUCTION

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common condition in populations with chronic diseases, especially in hospitalized patients.[1] Epidemiologic studies report that about 900,000 people are affected each year in the United States.[2] The mortality in the United Kingdom is estimated in 25,000 deaths from preventable hospital-acquired VTE every year,[3] while in Brazil the estimates are probably underreported: less than 2,000 deaths due to DVT and PE in 2015.[4]

In hospitals, VTE is a major cause of morbidity and mortality[5] and, despite efforts to guide evidence-based practice,[3,6] thromboprophylaxis rates remain low worldwide.[7,8] Factors related to healthcare resources, medical staff and reimbursement patterns have been associated with low protocol adherence and, consequently, VTE prophylaxis inadequacy.[9]

In this regard, quality improvement (QI) strategies to engage hospital staff and increase prescription of prophylaxis[6,8,10] have been tested, though methods such as multifaceted interventions still require further study.[11] Kahn et al.[5,7] have suggested that multifaceted interventions with an alert component may be the most effective initiative to improve thromboprophylaxis in hospitalized patients, highlighting the importance of context with respect to the adoption of specific QI interventions.[12] Thus, this study aimed to describe a pragmatic intervention for a protocol implementation, which included a computerized alert for prescribers and assess the adequacy of the prescriptions to thromboprophylaxis before and after this implementation.

Correspondence to:
Lisiane Freitas Leal. Programa de Pós-Graduação em Epidemiologia, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2400, CEP 90035-003, Porto Alegre, RS, Brasil.
Tel.: 1 438 866-1729. E-mail: lisianeleal@gmail.com
Financial support: None.

METHODS

Design

This was a before and after study performed at Hospital Moinhos de Vento (HMV), a 380-bed private non-profit tertiary hospital in Rio Grande do Sul, Brazil.

Participants

In both phases, patients were prospectively interviewed according to their availability to answer the questionnaire. Eligible participants included those admitted for one day or longer for medical or surgical conditions. Patients were not eligible if they met any of the following exclusion criteria: (1) age younger than 18 years old; (2) VTE diagnosis at admission; (3) anticoagulant treatment at admission; (4) direct admission to an intensive care unit; (5) length of stay above 120 days; or (6) pregnancy. Patients were classified as medical or surgical based on the reason for admission.

Procedures

Data regarding VTE risk factors such as, bleeding risk, admitting specialty and surgical procedure were obtained through interviews and chart reviews, and recorded on a data collection form. Pharmacological prophylaxis data were abstracted from the electronic medical record (EMR) system.

Physicians with management VTE expertise and clinical research participated in planning all phases of the study, including testing the form before its application. The interviews were conducted by pharmacists and nurses previously trained. The same form was used for both phases of the study. The baseline collection occurred in 2014, before the protocol implementation.

The local VTE prophylaxis protocol was developed based on the 9th Edition of the American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines.[13] For VTE risk evaluation, the protocol applies the Padua Prediction Score risk assessment model[14] for medical patients, while for surgical patients risk is assessed according to patient-specific characteristics, incorporating surgery-specific risk in addition to medical factors.[15] According to the local protocol, pharmacologic prophylaxis must be considered for patients at risk for VTE who are not at high risk for major bleeding complications. For medical patients, the thromboprophylaxis was considered adequate when patients were at high risk for VTE, without risk of bleeding, and received the first prescription of anticoagulant up to 24 hours of their admission. For surgical patients, the appropriate prescription was defined when they were at intermediate or at high risk of VTE, without risk of bleeding, and received the first prescription of anticoagulation up to 24 hours after surgery.

Risk of bleeding was considered present if a patient had multiple risk factors such as (1) active gastroduodenal ulcer; (2) bleeding (episodes that required transfusion, hospitalization or surgical intervention for control, excluding dental, nasal and skin-related, and hemorrhoids) over the 3 months before admission; or (3) had a platelet count <50,000 per mm^3.[13] An International Normalized Ratio (INR) >1.5 was considered as an additional risk factor for bleeding. If no platelet count or INR test were available (or requested) and no risk factors identified during the interview, the risk of bleeding was assumed as low or absent. Recommended thromboprophylaxis is presented in Table 1. The protocol does not recommend an adjusted-dose vitamin K antagonist or aspirin for thromboprophylaxis. Mechanical prophylaxis was recommended only if pharmacological prophylaxis was contra-indicated.

The protocol development was the first component of the intervention. All recommendations previously described were implemented through a web-based platform called IPROTOCOLOS that allows easy access to clinical pathways. The strategies described in Table 2 were developed and implemented along with IPROTOCOLOS tool.

The second phase of the data collection was performed in 2015, after the implementation of all components of the intervention.

In both phases, the enrollment stopped when the exact number of patients defined in the sample size calculation was achieved.

Table 1. Pharmacological thromboprophylaxis recommended.

Type of patient		Recommendation
Medical and surgical	**LMWH**	Enoxaparin 40mg, subcutaneously, every 24h; 40mg, subcutaneously, every 12h if patient >140kg
		OR
	UFH	Sodium heparin 5,000IU subcutaneously every 12h; 5,000IU subcutaneously every 8h if patient >140kg
		OR
	Fondaparinux	2.5mg every 24h (just for patients under risk for thrombocytopenia induced by heparin)
Orthopedic surgery only	**Direct thrombin inhibitors**	Rivaroxaban 10mg, every 24h
		OR
		Dabigatran 220mg, every 24h

LMWH: Low molecular weight heparin; UFH: Unfractionated heparin.

Sample size calculation and statistics

The sample size was calculated considering a *p*-value of 0.05, 90% power, a 50% rate of VTE thromboprophylaxis adequacy prior to protocol implementation, and an expected absolute increase of 16% in adequacy following protocol implementation.[16] These parameters required 396 patients. In order to ensure the required sample, we planned a 10% enrollment increase, considering possible inadequate information provided by participants that would leave to withdraws. Therefore, the final sample size was 436 patients (218 in each of the study's phases).

Patient characteristics are expressed as mean and standard deviation or median and interquartile range for continuous variables, and frequency and percentage for categorical variables. Group comparisons between the two study phases were made using the *t*-test or a non-parametric test for continuous variables, and the chi-square test for categorical variables. Chi-square testing was used to detect differences in adequacy between 2014 and 2015 (before and after implementation).

Poisson regression with robust variance was used to calculate prevalence ratio (PR) of adequacy (95% confidence interval) when controlled by phase and type of patient (medical or surgical).

All reported *p*-values are two-tailed. p<0.05 was considered statistically significant. The data were analyzed using Stata/IC 15 (StataCorp LLC, TX).

Ethics approval

The study was approved by the HMV Ethics Research Board under number 700.551. All procedures were in accordance with national ethics guidelines[17] and with the 1964 Helsinki declaration.[18] All patients provided written informed consent prior to involvement in this study.

RESULTS

We interviewed a total of 454 patients, 227 patients in each phase (before and after implementation). Of these, we excluded 25 patients (14 in the first phase and 11 in the second phase): 4 patients who had been previously included during the ongoing hospitalization (duplicated), 3 with a length of stay above 120 days and 18 admitted for the treatment of VTE or receiving anticoagulant treatment on admission. At the end of the study, we assessed a total of 429 patients for thromboprophylaxis adequacy (213 before protocol implementation and 216 after).

Table 3 summarizes the characteristics of patients included in the two phases. The main differences between patients included in both phases were the length of stay (two days more in the second phase than in the first phase, $p < 0.05$), the type of patient according to admission service (greater proportion of surgical patients in the first phase, $p < 0.01$), and proportion of acute infection or rheumatologic disorder (which was almost doubled in the second phase, $p < 0.01$). Considering the VTE risk factors, reduced mobility and age over 70 years old were the more prevalent in both phases.

Patients at intermediate or high risk of VTE represented more than three quarters of the patients evaluated in both phases. Considering the contraindication to pharmacological prophylaxis, active ulcer and bleeding at hospital admission were the only variables evaluated, since the platelet count and INR were unavailable for 43.5% and 87.5% of the patients, respectively.

The thromboprophylaxis more frequently prescribed was unfractionated heparin before and after the protocol implementation (Table 4), followed by low molecular weight heparin. In our sample, we did not find either oral anticoagulants prescribed for VTE prophylaxis or mechanical prophylaxis.

Overall thromboprophylaxis adequacy was 54% before the intervention and 63% after the intervention, a 9% increase in the appropriateness of thromboprophylaxis prescription which did not achieve statistical significance (p=0.06). Table 5 demonstrates the prevalence by type of patient, showing that the increase in thromboprophylaxis was due to surgical patients (PR=1.33; 95% CI 1.09-1.62). The prevalence ratio of after vs before intervention overall adequacy of

Table 2. Pragmatic strategy.

Component	Description
Clinical Practice Guideline flowchart	Three simplified flowcharts for orthopedic and non-orthopedic surgical and medical patients were developed. Protocols were posted in the physician common area. Another flowchart with the complete protocol information for surgical patients was posted at the surgical facility.
Clinical alerts on medical staff television	Televisions used for physician updates were used to convey information about the VTE protocol. The information consisted of a visual model of a flowchart with the following text: *Venous thromboembolism: your engagement is key to reduce this risk - Access the platform*
E-mail alerts	E-mail alerts were sent to medical staff informing about the protocol and the link for its access.
Computerized alerts for prescribers	This strategy consisted of a pop-up alert upon the first prescription and at 24h, 48h, and 7 days after admission (for any prescriber accessing the computerized physician order entry system). The alert was shown only for patients aged 18 or more with the following information: "Dear Doctor (name of the attending physician): it is essential that you assess venous thromboembolism risk for your patient and prescribe appropriate prophylaxis."

VTE: Venous Thromboembolism.

Table 3. Characteristics of patients included in the two phases of the study.

Variable	Before (n=213)	After (n=216)	p-value*
Age, median years (Q1; Q3)	64 (46;77)	67.5 (50.5;79.5)	0.135
Female sex, n (%)	131 (61.5)	131 (60.6)	0.856
Body-mass index (kg/m^2), mean (SD)	26.5 (4.9)	26.1 (4.8)	0.387
Length of stay,[a] median days (Q1, Q3)	9 (3;19)	11 (6;22)	<0.05
Admission service			
Medical, n (%)	82 (38.5)	120 (55.1)	<0.01
Surgical, n (%)	132 (61.5)	98 (44.9)	
Risk factors for VTE			
Active cancer,[b] n (%)	47 (22.1)	43 (19.9)	0.583
Previous VTE, n (%)	22 (10.3)	16 (7.4)	0.287
Reduced mobility,[c] n (%)	130 (61.0)	145 (67.1)	0.188
Thrombophilia, n (%)	2 (0.94)	4 (1.8)	0.421
Age ≥70 years, n (%)	88 (41.3)	99 (45.8)	0.345
Heart and/or respiratory failure, n (%)	41 (19.2)	44 (20.4)	0.771
Acute myocardial infarction or ischemic stroke, n (%)	5 (2.3)	6 (2.8)	0.778
Acute infection or rheumatologic disorder, n (%)	50 (23.5)	91 (42.1)	<0.01
Obesity (BMI ≥ 30 Kg/m^2), n (%)	43 (20.2)	46 (21.3)	0.777
Hormonal treatment, n (%)	23 (10.8)	17 (7.9)	0.297
Patients at intermediate or high risk of VTE[d]	181 (85.0)	171 (79.2)	0.117
Contraindication to pharmacological prophylaxis[e]			
Active gastroduodenal ulcer, n (%)	8 (3.8)	6 (2.8)	0.569
Bleeding at hospital admission, n (%)	29 (13.5)	17 (7.9)	0.060

Q1: first quartile; Q3: third quartile; SD: standard deviation; VTE: Venous Thromboembolism; BMI: Body Mass Index. *p value of Pearson χ2 test for categorical variables and of Wilcoxon rank-sum test for numerical variables; [a]Calculated based as the day of the discharge minus the day of admission; [b]Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous 6 months, including hormonal blockade; [c]Bedrest with bathroom privileges, more than half of the day; [d]Assesment according to protocol definition, Padua prediction score >=4 for medical patients and type of surgery + individual risc factors for surgical patients; [e]Contraindications defined in accordance with local protocol based on the 9th ACCP.[19]

Table 4. Type of prophylaxis prescribed at the day of the evaluation.

Prophylaxis	Before the intervention (n=213)	After the intervention (n=216)
Unfractionated heparin	84 (57.5)	105 (59.7)
Low molecular weight heparin	62 (42.5)	70 (39.8)
Fondaparinux	-	1 (0.6)
Total	146 (100.0)	176 (100.0)

Table 5. Prevalence and prevalence ratio of thromboprophylaxis adequacy before and after intervention.

	Before (n=213) n (%)	After (n=216) n (%)	p-value*	Prevalence Ratio (CI 95%)	Prevalence Ratio adjusted** (CI 95%)
All patients	115 (54.0)	136 (63.0)	0,06	1.17 (0.99-1.37)	1.20 (1.02-1.42)
Medical	43 (52.4)	65 (54.6)	0,76	1.04 (0.80-1.35)	
Surgical	72 (55.0)	71 (73.2)	<0.05	1.33 (1.09-1.62)	

CI 95%: 95% confidence interval. *p value of Pearson χ^2 test; **Adjusted through Poisson regression (robust variance) for type of patient (medical or surgical) and phase of the study.

thromboprophylaxis increase significantly (PR=1.20; 95% CI 1.02-1.42), just when adjusted for patient type and phase of the study.

DISCUSSION

We describe the results of a pragmatic intervention for a protocol implementation in a tertiary hospital in Southern Brazil. The intervention started through a web-based platform allowing easy access to clinical pathways, followed by other simple initiatives, together with an electronic alert for prescribers physicians. Although there are limitations to assume that the changes in adequacy are exclusively due to the strategies applied,[20] the results found suggest some future considerations for the decision making using such simple interventions. The findings of our implementation are discussed as follows.

First, the main result regarding the overall appropriateness of thromboprophylaxis prescription, after protocol

implementation, showed significant improvement just for adjusted analyses, supported by a significant increase in adequacy for surgical patients after the intervention. This result is sustained by previous evidence in which thromboprophylaxis adequacy is greater in surgical patients and remains inadequate in medical hospitalized patients.[21-23] Nevertheless, this was a stratified analysis which was conducted in order to improve the efficiency of the estimation.[24]

Second, this humble improvement in overall adequacy must be analyzed in depth in further studies conducted using this type of intervention. The current literature shows that just a protocol implementation should be responsible for increasing around 15% in adequacy.[16] In fact, for years cross-sectional studies around the world have documented underprescription of thromboprophylaxis, with adequacy ranging from 10% to 70%,[9,19,21,25] and our overall appropriateness for VTE prophylaxis was similar to previous data.[9,26-28] A recent systematic review of randomized trials showed that electronic alerts were associated with an improvement in prophylaxis prescription (risk difference=16%; 95% CI 12% to 20%).[7] However, it is still unclear how multifaceted interventions (education, reminders, audit and feedback), including electronic alerts, are associated with an increase in the proportion of patients receiving prophylaxis and even for the reduction in symptomatic VTE.[7] On the other hand, studies have demonstrated that the percentage of patients with adequate prophylaxis may reach 90% or more when the protocol is enhanced by other QI and high-reliability strategies, for example the integration of the VTE protocol into order sets.[6,8,19] Additional strategies, such as engagement of multidisciplinary teams and well-structured QI institutional initiatives are described as responsible for changes in culture and reduction of VTE events.[6,8] Facing these controversies, we agree that the success of different approaches depends on the adaptation of the strategies to differences in the context in which the QI initiative takes place.[12]

Third, our implementation strategies did not engage multidisciplinary teams, being directed only to the medical staff. If, on the one hand, we expected only a slight improvement in adequacy, on the other, we felt it is important to attempt a simple set of strategies to evaluate protocol adherence before implementing other initiatives. Many studies have demonstrated the impact of electronic tools and other QI strategies,[8,29-32] but none in a setting characterized by an "open" medical staff, a reality that may negatively impact protocol adherence.

Fourth, the inadequacy of thromboprophylaxis prescription highlights a great concern in which the frequency of underutilization of prophylaxis was large in medical patients. Besides, anticoagulant prescription in both low-risk patients and in those with high-risk of bleeding confirmed overprescription in our scenario. Other studies have already described this problem, in which high-risk patients are undertreated and low-risk patients are overtreated.[23,29] Further, as platelet counts and INR results were unavailable for almost half of the interviewed patients (43.5% without platelet counts and 87.5% without INR results), it is possible to assume that the inadequacy is even greater than documented.

Finally, according to our results, several additional actions should be planned to achieve protocol adherence and consequently better appropriateness of thromboprophylaxis. When we compare our results with those from other low- and middle-income countries, it is possible to observe that, despite our better hospital infrastructure, our results are not better.[21,23,26,27]

The current study has a number of limitations. First, we used an uncontrolled before and after study design to investigate while pragmatic interventions were able to achieve adequacy of thromboprophylaxis in hospitalized patients. These studies are a relatively weak method of distinguishing cause and effect, since any observed change might plausibly be attributed to other causes, such as secular trends. However, these were the first results of a culture change and here we are generating hypothesis about a set of strategies used for this implementation. In general, there are no measures for this type of intervention since a more rigorous design was not practical in our situation.[33] Second, this study was carried out in a single private hospital, which may reduce the generalizability of our results, with additional studies being necessary to better understand if the same strategy would be effective in other settings. There are several characteristics, including physician's behavior that were not accounted for in our study. Third, the prescribing physicians were not interviewed, so we cannot exclude the possibility that in some cases additional clinical information obtained prior to admission had been taken into account in making decisions which in this study appeared inadequate on the basis of hospital data alone. In fact, we assumed that a lack of platelet count would be included as known just by physicians, mainly for surgical patients whose tests are performed outside hospital previous to the procedure. Nevertheless, we assumed no misclassification of the risk of bleeding, even if platelet count or INR values were missing, considering both medical records review and interviews were conducted. Moreover, requesting coagulation tests routinely if a patient presents a negative bleeding history is still questionable and it is not a consensus among physicians.[34,35]

In summary, after a protocol implementation, the results showed that the overall appropriateness of thromboprophylaxis prescription was weakly improved, despite the efforts. Although the study was performed at a single institution, it may provide the best evidence to date a bunch of strategies for the protocol implementation in private institutions in middle-income countries with an open medical staff, as there are few studies investigating these simple and pragmatic interventions. The lessons learned and the data obtained will support other institutional initiatives such as engaging multidisciplinary teams and elaborating a plan to adopt a computerized clinical decision support tool in future efforts to improve VTE prophylaxis.

ACKNOWLEDGEMENTS

We would like to thank Sabrina Zimmer, Fabiane Rocca, Lolita Rushel, Deoclecio Martini and Paulo Martins, the Technology of Information staff, for all support to the development of this project; Carisi Polankzyk for advice about the execution; Anna Costa for providing information regarding marketing initiatives; Maria Cláudia Schardosim for initial data analysis in the first phase; Luciano Hammes for idealizing the platform IPROTOCOLOS; and Claudia Buchweitz for her invaluable review.

REFERENCES

1. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):3-14. http://dx.doi.org/10.1007/s11239-015-1311-6. PMid:26780736.
2. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. Am J Prev Med. 2010;38(4, Suppl.):S495-501. http://dx.doi.org/10.1016/j.amepre.2009.12.017. PMid:20331949.
3. NICE: National Institute for Health and Care Excellence. Venous thromboembolism: reducing the risk for patients in hospital [Internet]. London: NICE; 2010 [cited 2017 Nov 13]. Available from: https://www.nice.org.uk/Guidance/CG92
4. Brasil. Ministério da Saúde. Sistema de Informações sobre Mortalidade - SIM - por Unidade da Federação - Brasil [Internet]. Brasília: DATASUS; 2017 [cited 2017 Nov 13]. Available from: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sim/cnv/obt10uf.def
5. Kahn SR, Morrison DR, Cohen JM, Emed J, Tagalakis V, Roussin A, et al. Interventions for implementation of thromboprophylaxis in hospitalized medical and surgical patients at risk for venous thromboembolism. Cochrane Database Syst Rev. 2013;7(7):CD008201. http://dx.doi.org/10.1002/14651858.CD008201.pub2. PMid:23861035.
6. Maynard G. Preventing hospital-associated venous thromboembolism: a guide for effective quality improvement [Internet]. 2nd ed. Rockville: Agency for Healthcare Research and Quality; 2015. (AHRQ Publication; 16-0001-EF) [cited 2015 Nov 29]. Available from: http://www.ahrq.gov/professionals/quality-patient-safety/patient-safety-resources/resources/vtguide/index.html
7. Kahn SR, Morrison DR, Diendéré G, Piché A, Filion KB, Klil-Drori AJ, et al. Interventions for implementation of thromboprophylaxis in hospitalized patients at risk for venous thromboembolism. Cochrane Database Syst Rev. 2018;4:CD008201. http://dx.doi.org/10.1002/14651858.CD008201.pub3. PMid:29687454.
8. Streiff MB, Carolan HT, Hobson DB, Kraus PS, Holzmueller CG, Demski R, et al. Lessons from the Johns Hopkins Multi-Disciplinary Venous Thromboembolism (VTE) Prevention Collaborative. BMJ. 2012;344(6):e3935-3935. http://dx.doi.org/10.1136/bmj.e3935. PMid:22718994.
9. Cohen AT, Tapson VF, Bergmann J-F, Goldhaber SZ, Kakkar AK, Deslandes B, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet. 2008;371(9610):387-94. http://dx.doi.org/10.1016/S0140-6736(08)60202-0. PMid:18242412.
10. Fuzinatto F, Waldemar FS, Wajner A, Elias CAA, Fernandez JF, Hopf JLS, et al. A clinical decision support system for venous thromboembolism prophylaxis at a general hospital in a middle-income country. J Bras Pneumol. 2013;39(2):138-46. http://dx.doi.org/10.1590/S1806-37132013000200004. PMid:23670498.
11. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients. Chest. 2012;141(2, Suppl.):e227S-77S. http://dx.doi.org/10.1378/chest.11-2297. PMid:22315263.
12. Kaplan HC, Brady PW, Dritz MC, Hooper DK, Linam WM, Froehle CM, et al. The influence of context on quality improvement success in health care: a systematic review of the literature. Milbank Q. 2010;88(4):500-59. http://dx.doi.org/10.1111/j.1468-0009.2010.00611.x. PMid:21166868.
13. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, Cook DJ, Balekian AA, Klein RC, Le H, Schulman S, Murad MH. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(4):e195S-226S. http://dx.doi.org/10.1378/chest.11-2296.
14. Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost. 2010;8(11):2450-7. http://dx.doi.org/10.1111/j.1538-7836.2010.04044.x. PMid:20738765.
15. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ. Executive Summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2):7S-47S. http://dx.doi.org/10.1378/chest.1412S3.
16. Maynard G. Preventing hospital: associated venous thromboembolism: a guide for effective quality improvement [Internet]. 2nd ed. Rockville: AHRQ; 2016 [cited 2017 Oct 14]. Available from: https://www.ahrq.gov/sites/default/files/publications/files/vteguide.pdf
17. Brasil. Conselho Nacional de Saúde. Resolução nº 466, de 12 de dezembro de 2012 [Internet]. Diário Oficial da União; Brasília; 13 jul. 2012 [cited 2017 Nov 10]. Available from: http://www.conselho.saude.gov.br/web_comissoes/conep/index.html
18. WMA: World Medical Association. WMA declaration of Helsinki: ethical principles for medical research involving human subjects [Internet]. France: World Medical Association; 2017 [cited 2017 Aug 1]. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
19. Maynard GA, Morris TA, Jenkins IH, Stone S, Lee J, Renvall M, et al. Optimizing prevention of hospital-acquired venous thromboembolism (VTE): prospective validation of a VTE risk assessment model. J Hosp Med. 2010;5(1):10-8. PMid:19753640.
20. Sedgwick P. Before and after study designs. BMJ. 2014;349(2):g5074. http://dx.doi.org/10.1136/bmj.g5074. PMid:25106742.
21. Bâ SA, Badiane SB, Diop SN, Diouf FS, Fall D, Ka MM, et al. A cross-sectional evaluation of venous thromboembolism risk and use of venous thromboembolism prophylaxis in hospitalized patients in Senegal. Arch Cardiovasc Dis. 2011;104(10):493. http://dx.doi.org/10.1016/j.acvd.2011.05.007. PMid:22044701.
22. Singh K, Wright A. Clinical decision support. In: Finnell JT, Dixon BE, editors. Clin inform study guide. Cham: Springer International Publishing; 2016. p. 111-33. http://dx.doi.org/10.1007/978-3-319-22753-5_6.
23. Mokhtari M, Attarian H, Norouzi M, Kouchek M, Kashani BS, Sirati F, et al. Venous thromboembolism risk assessment, prophylaxis practices and interventions for its improvement (AVAIL-ME Extension Project, Iran). Thromb Res. 2014;133(4):567-73. http://dx.doi.org/10.1016/j.thromres.2014.01.006. PMid:24507872.
24. Sauer BC, Brookhart MA, Roy J, VanderWeele T. A review of covariate selection for non-experimental comparative effectiveness research. Pharmacoepidemiol Drug Saf. 2013;22(11):1139-45. http://dx.doi.org/10.1002/pds.3506. PMid:24006330.
25. Fuzinatto F, Wajner A, Waldemar FS, Hopf JLS, Schuh JF, Barreto SSM. Venous thromboembolism prophylaxis in a general hospital. J Bras Pneumol. 2011;37(2):160-7. http://dx.doi.org/10.1590/S1806-37132011000200005. PMid:21537651.
26. Deheinzelin D, Braga AL, Martins LC, Martins MA, Hernandez A, Yoshida WB, et al. Incorrect use of thromboprophylaxis for venous thromboembolism in medical and surgical patients: results of a multicentric, observational and cross-sectional study in Brazil. J Thromb Haemost. 2006;4(6):1266-70. http://dx.doi.org/10.1111/j.1538-7836.2006.01981.x. PMid:16706970.
27. Vazquez F, Watman R, Tabares A, Gumpel C, Baldessari E, Vilaseca AB, et al. Risk of venous thromboembolic disease and adequacy of prophylaxis in hospitalized patients in Argentina: a multicentric cross-sectional study. Thromb J. 2014;12(1):15. http://dx.doi.org/10.1186/1477-9560-12-15. PMid:25024645.
28. Bergmann J-F, Lloret-Linares C, Rami A, Cohen AT, Garay RP, Kakkar AK, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): results obtained in France. Presse Med. 1983;2011(40):e528-37.
29. Janus E, Bassi A, Jackson D, Nandurkar H, Yates M. Thromboprophylaxis use in medical and surgical inpatients and the impact of an electronic risk assessment tool as part of a multi-factorial intervention. A report on behalf of the elVis study investigators. J Thromb Thrombolysis.

2011;32(3):279-87. http://dx.doi.org/10.1007/s11239-011-0602-9. PMid:21643821.

30. Mitchell JD, Collen JF, Petteys S, Holley AB. A simple reminder system improves venous thromboembolism prophylaxis rates and reduces thrombotic events for hospitalized patients1. J Thromb Haemost. 2012;10(2):236-43. http://dx.doi.org/10.1111/j.1538-7836.2011.04599.x. PMid:22188121.
31. Piazza G, Rosenbaum EJ, Pendergast W, Jacobson JO, Pendleton RC, McLaren GD, et al. Physician alerts to prevent symptomatic venous thromboembolism in hospitalized patients. Circulation. 2009;119(16):2196-201. http://dx.doi.org/10.1161/CIRCULATIONAHA.108.841197. PMid:19364975.
32. Maynard G, Jenkins IH, Merli GJ. Venous thromboembolism prevention guidelines for medical inpatients: mind the (implementation) gap. J Hosp Med. 2013;8(10):582-8. http://dx.doi.org/10.1002/jhm.2071. PMid:23983041.
33. Brown C, Lilford R. Evaluating service delivery interventions to enhance patient safety. BMJ. 2008;337(1):a2764. http://dx.doi.org/10.1136/bmj.a2764. PMid:19091764.
34. Haas T, Fries D, Tanaka KA, Asmis L, Curry NS, Schöchl H. Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence? Br J Anaesth. 2015;114(2):217-24. http://dx.doi.org/10.1093/bja/aeu303. PMid:25204698.
35. Chee YL, Crawford JC, Watson HG, Greaves M. Guidelines on the assessment of bleeding risk prior to surgery or invasive procedures. Br J Haematol. 2008;140(5):496-504. http://dx.doi.org/10.1111/j.1365-2141.2007.06968.x. PMid:18275427.

J Bras Pneumol. 2020;46(4):e20180125
https://dx.doi.org/10.36416/1806-3756/e20180125

ORIGINAL ARTICLE

Early complications in flexible bronchoscopy at a university hospital

Marcia Jacomelli[1], Stephania Silva Margotto[1], Sergio Eduardo Demarzo[1], Paulo Rogério Scordamaglio[1], Paulo Francisco Guerreiro Cardoso[1], Addy Lidvina Mejia Palomino[1], Viviane Rossi Figueiredo[1]

1. Serviço de Endoscopia Respiratória, Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo – HCFMUSP – São Paulo (SP) Brasil.

Submitted: 16 May 2018.
Accepted: 29 May 2019.

Study carried out in the Serviço de Endoscopia Respiratória, Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo – HCFMUSP – São Paulo (SP) Brasil.

ABSTRACT

Objective: To analyze the complications related to flexible bronchoscopy (FB) and its collection procedures in outpatients and inpatients with various lung and airway diseases treated at a university hospital. **Methods:** This was a retrospective analysis of complications occurring during or within 2 h after FB performed between January of 2012 and December of 2013, as recorded in the database of the respiratory endoscopy department of a hospital complex in the city of São Paulo, Brazil. **Results:** We analyzed 3,473 FBs. Complications occurred in 185 procedures (5.3%): moderate to severe bleeding, in 2.2%; pneumothorax, in 0.7%; severe bronchospasm, in 0.8%; general complications (hypoxemia, psychomotor agitation, arrhythmias, vomiting, or hypotension), in 1.6%; and cardiopulmonary arrest, in 0.03%. There were no deaths related to the procedures. Specifically, among the 1,728 patients undergoing biopsy, bronchial brushing, or fine-needle aspiration biopsy, bleeding occurred in 75 (4.3%). Among the 1,191 patients undergoing transbronchial biopsy, severe pneumothorax (requiring chest tube drainage) occurred in 24 (2.0%). **Conclusions:** In our patient sample, FB proved to be a safe method with a low rate of complications. Appropriate continuing training of specialist doctors and nursing staff, as well as the development of standardized care protocols, are important for maintaining those standards.

Keywords: Bronchoscopy/adverse effects; Biopsy/adverse effects; Pneumothorax.

INTRODUCTION

Flexible bronchoscopy (FB) is a minimally invasive procedure that since its introduction in the 1960s has been widely used for direct visualization of the tracheobronchial tree in order to diagnose and treat lung and airway diseases. Although there have been reports of complications, the complication rate is low (ranging from 0.8% to 6.8%), confirming the safety of FB when preventive measures are employed, including adequate patient preparation, risk-benefit assessment, and the use of standardized protocols during the procedure.[1-3]

Complications are generally due to sedation and topical anesthesia,[4] but they can also be due to the following: introduction of the bronchoscope into the airway; sample collection procedures, such as BAL, endobronchial biopsy (EBB), transbronchial biopsy (TBB), and bronchial brushing (BB); and patient clinical status.[1,5] Most complications occur during or within 2 h after the procedure, and only a minority of patients require hospitalization.[4,6-8] Serious adverse effects requiring interruption of the procedure, including tension pneumothorax, heart/respiratory failure, and death, are rare and are generally related to the severity of underlying heart or lung disease, as well as to severe central airway obstruction.[2,7,9] The objective of the present study was to analyze early complications of FB in patients with various lung and airway diseases treated at a university hospital.

METHODS

We retrospectively analyzed complications occurring during or within 2 h after FB performed between January of 2012 and December of 2013, as recorded in the database of the Respiratory Endoscopy Department of the University of São Paulo School of Medicine *Hospital das Clínicas* Heart Institute, located in the city of São Paulo, Brazil. The present study was approved by the local research ethics committee (Protocol no. 4358/16/024).

All FBs were performed with patients receiving continuous monitoring (cardiac monitoring, noninvasive blood pressure monitoring, and oximetry) and supplemental oxygen via nasal cannula. Intravenous sedation was provided primarily with fentanyl and midazolam (with or without propofol), patients being maintained with mild or moderate sedation depending on the case.

We examined patient age, sex, and class (inpatient or outpatient), as well as indications for FB, sample collection methods, and potential complications.

Complications were divided into general complications and complications associated with collection procedures such as EBB, laryngeal biopsy, TBB, BB, and fine-needle

Correspondence to:
Márcia Jacomelli. Instituto do Coração, Setor de Endoscopia Respiratória, Rua Dr. Enéas Carvalho de Aguiar, 44, 7º andar, Cerqueira Cesar, CEP 05403-900, São Paulo, SP, Brasil.
Tel. 55 11 2661-5612. E-mail: jacomelli.marcia@yahoo.com.br
Financial support: None.

ISSN 1806-3713

aspiration biopsy (FNAB). General complications included persistent hypoxemia (an SpO_2 of < 90% throughout the procedure and in the postprocedural period, difficult to control despite raising the mandible and FiO_2), psychomotor agitation, arrhythmias, vomiting, bronchospasm, and cardiopulmonary failure. Specific complications included bleeding (during any sample collection procedure) and pneumothorax (during TBB only). Moderate to severe bleeding was defined as bleeding requiring interruption of the procedure or hemostatic measures such as wedging the flexible bronchoscope into the bleeding bronchial segment, using cold 0.9% saline, using an epinephrine solution (1:20,000), moving the patient to a lateral decubitus position with the bleeding side down, inserting a balloon catheter (bronchial blocker), and performing selective intubation to isolate the bleeding lung. A diagnosis of pneumothorax was made on the basis of clinical symptoms (pleuritic chest pain and dyspnea, with or without decreased SpO_2) and chest X-ray findings consistent with pneumothorax.

Before undergoing FB, all patients were informed of the risks of the procedure. They remained under observation until discharge by the medical and paramedical staff within 2 h after the procedure.

Statistical analysis

All statistical analyses were performed with the IBM SPSS Statistics software package, version 19.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were used in order to estimate the frequencies of the study variables. The only continuous variable, age, was summarized as a mean with standard deviation. The Student's t-test was used in order to analyze parametric data (age), and Pearson's correlation coefficient was used in order to correlate nonparametric data. The level of significance was set at 5% ($p < 0.05$).

RESULTS

We analyzed 3,473 FB procedures performed in outpatients, ward patients, ICU patients, ER patients, and operating room patients in our hospital. Endobronchial ultrasound, simple laryngoscopy, and therapeutic rigid bronchoscopy procedures were not included in the analysis.

The mean age of the patients was 52.58 ± 17.33 years, with a predominance of males (59.2%). In our patient sample, 2,061 (59.3%) were outpatients, 935 (27.0%) were ward patients, and 477 (13.7%) were ICU or ER patients (Table 1).

As can be seen in Table 1, reasons for undergoing FB included suspected infection, in 34.8%, suspected neoplasia, in 16.2%, post-lung transplant follow-up/surveillance, in 8.9%, esophageal cancer staging, in 7.6%, investigation/management of hemoptysis, in 5.4%, investigation of interstitial lung disease, in 4.6%, postoperative thoracic surgery, in 1.6%, and other reasons, in 20.9%.

A total of 3,701 sample collection procedures were performed; BAL was the most commonly performed procedure, followed by TBB and BB. Other procedures, including BB, FNAB, and laryngeal biopsy, were performed in 132 patients (3.6%). These results are shown in Table 2.

Complications occurred during or within 2 h after FB in 185 (5.3%) of the 3,473 procedures performed. Most of the complications occurred in patients undergoing sample collection procedures, particularly biopsy (n = 99; 53.5%).

General complications (hypoxemia, psychomotor agitation, arrhythmias, and vomiting) occurred in 56 patients (1.6%). Bronchospasm requiring interruption of the procedure occurred in 29 (0.8%). Cardiopulmonary arrest occurred in 1 (0.03%). There were no deaths related to the procedures. Bleeding occurred in 2.2% of the FBs, and pneumothorax occurred in 0.7%. Specifically, among the 1,728 patients undergoing a sample collection procedure (EBB, TBB, BB, or FNAB), moderate to severe bleeding occurred in 75 (4.3%). Among the 1,191 patients undergoing TBB, pneumothorax occurred in 24 (2.0%), all of whom required chest tube drainage. All complications are described in Table 2.

Complications were more common in patients > 50 years of age than in those ≤ 50 years of age (6.1% vs. 3.9%; $\rho = 0.002$). In addition, complications were most common in patients undergoing FB for the following reasons: investigation of interstitial lung disease, suspected neoplasia, suspected bronchopulmonary infection, postoperative thoracic surgery, investigation of hemoptysis, post-lung transplant follow-up/surveillance, and esophageal cancer staging. In patients undergoing FB for other reasons, including difficult airway management (difficult intubation or extubation), decannulation, burns, foreign body aspiration, and evaluation of airway malacia/fistula/stenosis, complications occurred in 2.8% (Table 1).

As can be seen in Table 1, there were no significant differences in the frequency of complications between outpatients and inpatients (including ward patients, ICU patients, and ER patients).

DISCUSSION

FB is a minimally invasive procedure that is used in various lung and airway diseases.[5,10,11] The reported overall complication rate varies, being higher when biopsy is performed.[5,12,13] To our knowledge, this is the first study in Brazil to report the overall complication rate of FB in a large number of patients, the reported rate (5.3%) being within the expected range.[5,12,13] These data are important because of the need to improve patient safety by preventing or reducing risks, especially in a teaching hospital setting. In addition, it is important to know the risks of the procedure in order to develop informed consent forms that clearly explain to patients and their families the expected complication rate.

Table 1. Characteristics of the study patients (N = 3,473), reasons for undergoing flexible bronchoscopy, and complications of the procedure.[a]

Characteristic	Complications		p
	No (n = 3,288)	Yes (n = 185)	
Age, years	52.36 ± 17.83	56.45 ± 15.75	0.002
Sex			
Male (n = 2,056)	1,965 (95.6)	91 (4.4)	0.004
Female (n = 1,417)	1,323 (93.4)	94 (6.6)	
Patient class			
Outpatient (n = 2,061)	1,939 (94.1)	122 (5.9)	
Ward patient (n = 935)	882 (94.3)	53 (5.7)	NS
ICU/ER patient (n = 477)	467 (98.0)	10 (2.0)	
Reason for undergoing flexible bronchoscopy			
Interstitial lung disease (n = 159)	142 (89.3)	17 (10.7)	
Neoplasia (n = 564)	508 (90.1)	56 (9.9)	
Infection (n = 1,207)	1,127 (93.4)	80 (6.7)	
Postoperative thoracic surgery (n = 57)	55 (96.5)	2 (3.5)	NS
Hemoptysis (n = 187)	183 (97.9)	4 (2.1)	
Lung transplantation (n = 308)	303 (98.4)	5 (1.6)	
Esophageal cancer staging (n = 264)	263 (99.6)	1 (0.4)	
Other (n = 727)[b]	707 (97.2)	20 (2.8)	

NS: not significant. [a]Values expressed as n (%) or mean ± SD. [b]Difficult intubation/extubation, evaluation of airway malacia/fistula/stenosis, atelectasis, decannulation, burns, and foreign body aspiration.

Table 2. Diagnostic procedures performed during flexible bronchoscopy and complications thereof.

	Procedure	n (%)
Diagnostic procedures (n = 3,701)	BAL	1,973 (53.3)
	Transbronchial biopsy	1,191 (32.2)
	Endobronchial biopsy	405 (10.9)
	Bronchial brushing	37 (1.0)
	Fine-needle aspiration biopsy	62 (1.7)
	Laryngeal biopsy	33 (0.9)
Complications (n = 185)	Bleeding[a]	75 (4.3)
	Pneumothorax[b]	24 (2.0)
	Bronchospasm[c]	29 (0.8)
	Other[d]	57 (1.63)

[a]Among the 1,728 patients undergoing biopsy. [b]Among the 1,191 patients undergoing transbronchial biopsy. [c]Among the 3,473 patients undergoing flexible bronchoscopy. [d]Hypoxemia, arrhythmias, cough, agitation, need for endotracheal intubation, and cardiopulmonary arrest.

In the present study, the most common complications were bleeding and pneumothorax. Other complications, such as bronchospasm, hypoxemia, hypotension, arrhythmias, and cardiopulmonary arrest, were less common, being related to respiratory and cardiovascular comorbidities, as well as to the passage of the bronchoscope through the airway and the drugs used for sedation and anesthesia.

We found no significant differences in the complication rates across patients, regardless of their origin or underlying respiratory disease. However, because this was a retrospective observational study, we used no severity scales or complication prediction scores; in addition, we did not analyze single comorbidities. Nevertheless, we found that patients with interstitial lung disease, cancer, or respiratory infection had a higher number of complications. Given these findings and the profile of our patients, we believe that hospitalization is required for patients with underlying hypoxemia and those at risk of hypoxemia or other types of decompensation during or after the procedure, including patients with COPD, severe asthma, and heart disease. The primary goal of this approach is to perform a clinical evaluation of patients before the procedure and minimize procedure cancellation rates.

The complication rate was low in our study because FB is performed in accordance with international standards at our institution. In addition, all FB procedures are performed by qualified professionals trained and with technical experience in performing FB and in diagnosing and managing complications, supervision being mandatory when a physician in training performs the procedure.[3] Physician training

in FB should also focus on the periods before and after the procedure.

Adequate patient preparation prior to FB is essential for identifying and preventing complications.[3] Careful history taking is required in order to identify clinical contraindications to FB, including signs of respiratory failure (including hypoxemia, tachypnea, and hypercapnia), bronchospasm during the procedure, decompensated arrhythmias, and recent hemodynamic instability or myocardial infarction (less than six weeks before the procedure).[4,5,10,11,14,15] All of these parameters should be interpreted within the clinical scenario of individual patients, the risks and benefits of the procedure being weighed.

Critically ill patients undergoing diagnostic FB require ventilatory support, multidisciplinary care, and full monitoring in order to minimize risk and facilitate early identification of complications, thus allowing timely management. In COPD or asthma patients experiencing bronchospasm, it is important to control the underlying disease before the procedure is performed.[4,15] In individuals at high risk of developing bronchospasm during or shortly after FB, a β_2 agonist and an intravenous corticosteroid can be administered before the procedure. If BAL is required, 0.9% saline at 37°C should be used in order to prevent bronchospasm.[16]

To prevent aspiration of gastric contents, patients undergoing FB at our institution are required to abstain from solid/semisolid foods for 8 h before the procedure; breast milk for 4 h before the procedure; and a clear or strained liquid diet for 2 h before the procedure. However, in intubated patients who are on mechanical ventilation and have a nasogastric feeding tube in place, fasting times can vary depending on how urgent the need for FB is and should be discussed on a case-by-case basis. In such patients, the following is recommended: better control of endotracheal tube cuff inflation pressure, fasting before the procedure, and nasogastric tube drainage.[4,15,17] In our study, there were no cases of bronchial aspiration during or after FB.

Before FB, it is essential to inquire about drug allergies, complications of previous surgeries or procedures, and the presence of cardiovascular diseases, endocrine disorders, and respiratory comorbidities, including the drugs and doses used.[1,12,15]

Because of the risk of bleeding, coagulation disorders and the use of anticoagulants should be carefully examined in patients requiring biopsy, BB, or FNAB during FB. Clinical history taking is important to identify signs of active bleeding. In addition, antiplatelet and anticoagulant drug use should be discontinued for as long as recommended, adjustments being required for patients with hepatic or renal failure. A platelet count > 50,000/mm^3 and a prothrombin time/international normalized ratio of < 1.5 are considered safe in patients undergoing biopsy. A platelet count of < 20,000/mm^3 is a contraindication to FB, even without biopsy.[4] Such patients should undergo platelet replacement therapy before undergoing FB.[4,9,14,18-21] Other laboratory data, such as urea and creatinine levels, should be assessed before biopsy.

In our study, all patients received supplemental oxygen (1-5 L/min, as needed) during and after FB. In intubated ICU patients, FiO_2 was set to 100% during the procedure, other ventilator settings being adjusted as needed.[4,15] Thus, the rate of oxygen saturation decrease was low in our study.

Sedatives and their doses should be chosen on a case-by-case basis. The sedatives used in our study included midazolam, fentanyl citrate, and, in some cases, propofol.[4] The medical staff should receive appropriate training in dosing and managing potential complications.

According to Brazilian Federal Medical Council Resolution no. 2,174/2017, a second physician should be present in the examination room, being responsible for administering sedation. In patients at risk of cardiovascular or respiratory decompensation, FB can be performed with endotracheal intubation in the ICU (if necessary).

It is also important to be familiar with benzodiazepine and opioid antagonists (flumazenil and naloxone, respectively). They can have adverse effects and should only be used in specific situations, in order to prevent complications such as convulsion, psychomotor agitation, and respiratory distress.[12] In addition, naloxone use can result in pain, especially in cancer patients receiving treatment with opioids.

With regard to the use of topical lidocaine for cough control during FB, the maximum total dose, including all doses of the three formulations (i.e., gel, 2%; spray, 10%; and liquid, 2%), should be 7-9 mg/kg.[5,12,15] Care must be taken when using lidocaine in elderly patients and patients with heart failure, as well as in those with upper/lower airway candidiasis, infection, or inflammation, because of the possibility of increased absorption and, consequently, toxicity. Major complications of excessive lidocaine include nausea, vomiting, metallic taste, mental confusion, cardiac arrhythmias, and seizures.

In patients undergoing biopsy, it is important to adopt measures to facilitate the management of bleeding complications and minimize the risk of pneumothorax. It is difficult to quantify bleeding risk in patients undergoing FB, and reports of bleeding during FB are very subjective. Hemostatic measures such as wedging the flexible bronchoscope into the bleeding bronchial segment, using cold 0.9% saline, using an epinephrine solution (1:20,000), moving the patient to a lateral decubitus position with the bleeding side down, and inserting a balloon catheter (in cases of bleeding that is massive or difficult to control with the aforementioned measures) are essential and possible to perform.[4] In our study, the first four measures were adopted during diagnostic FB. Future studies

should quantify bleeding risk in patients undergoing FB, correlating bleeding with bronchoscopic measures to manage it, as well as with clinical worsening after the procedure.

Whenever possible, fluoroscopy can be used in order to guide biopsy of lung nodules and infiltrates, improving safety in patients with pulmonary emphysema and at increased risk of pneumothorax.[4] However, there is a lack of consistent data regarding other patient groups. Given that fluoroscopy is not available for all FB procedures performed at our institution, we did not analyze the role of fluoroscopy in guiding bronchoscopic sample collection. Nevertheless, the rate of pneumothorax in the present study (2%) is consistent with that in the literature (1-6%).[1,3,22,23]

For bronchoscopists, appropriate continuing training is essential to improve knowledge and practice, including management of complications.[1,12,13,15,24] Training is also essential for paramedical and nonmedical staff. Resuscitation equipment and adequate physical space are also important.

With regard to postprocedure care, patients should be monitored in the recovery room until regaining full consciousness.[24] At discharge, patients and their companions should be alerted to the possibility of accidental falls, fever, bleeding, and symptoms suggestive of pneumothorax.[4] Minor bleeding can occur 2-3 days after the procedure, rest therefore being important. In cases of persistent bleeding, patients are advised to return for further evaluation. It should be noted that pneumothorax can go unnoticed on examination at discharge. Patients experiencing chest pain or dyspnea should return for medical evaluation and, if necessary, a chest X-ray.

Imaging tests are reserved for patients with clinical symptoms suggestive of pneumothorax.[4,6-8,10] Although it has been reported that only a minority of cases require intervention,[1] nearly all cases of pneumothorax in our study required chest tube drainage.

In order to develop best-care practices that prioritize patient safety and health care efficiency, it is essential to know the complication rates at a given medical institution. Our study showed low rates of early FB complications. However, it has limitations inherent to its retrospective nature, including the use of database records, written reports of FB procedures, and complication notes, all of which are subject to problems such as missing or incorrectly recorded data. Therefore, the complication rates might have been underestimated. Prospective studies are needed in order to address this issue.

REFERENCES

1. Pue CA, Pacht ER. Complications of fiberoptic bronchoscopy at a university hospital. Chest. 1995;107(2):430-432. https://doi.org/10.1378/chest.107.2.430
2. Jin F, Mu D, Chu D, Fu E, Xie Y, Liu T. Severe complications of bronchoscopy. Respiration. 2008;76(4):429-433. https://doi.org/10.1159/000151656
3. Facciolongo N, Patelli M, Gasparini S, Lazzari Agli L, Salio M, Simonassi C, et al. Incidence of complications in bronchoscopy. Multicentre prospective study of 20,986 bronchoscopies. Monaldi Arch Chest Dis. 2009;71(1):8-14. https://doi.org/10.4081/monaldi.2009.370
4. Du Rand IA, Blaikley J, Booton R, Chaudhuri N, Gupta V, Khalidet S, et al. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. Thorax. 2013;68 Suppl 1:i1-i44. https://doi.org/10.1136/thoraxjnl-2013-203618
5. Geraci G, Pisello F, Sciumè C, Li Volsi F, Romeo M, Modica G. Complication of flexible fiberoptic bronchoscopy. Literature review [Article in Italian]. Ann Ital Chir. 2007;78(3):183-192.
6. Frazier WD, Pope TL Jr, Findley LJ. Pneumothorax following transbronchial biopsy. Low diagnostic yield with routine chest roentgenograms. Chest. 1990;97(3):539-540. https://doi.org/10.1378/chest.97.3.539
7. Tukey MH, Wiener RS. Population-based estimates of transbronchial lung biopsy utilization and complications. Respir Med. 2012;106(11):1559-1565. https://doi.org/10.1016/j.rmed.2012.08.008
8. Hernández Blasco L, Sánchez Hernández IM, Villena Garrido V, de Miguel Poch E, Nuñez Delgado M, Alfaro Abreu J. Safety of the transbronchial biopsy in outpatients. Chest. 1991;99(3):562-565. https://doi.org/10.1378/chest.99.3.562
9. Carr IM, Koegelenberg CF, von Groote-Bidlingmaier F, Mowlana A, Silos K, Haverman T, et al. Blood loss during flexible bronchoscopy: a prospective observational study. Respiration. 2012;84(4):312-318. https://doi.org/10.1159/000339507
10. Alzeer AH, Al-Otair HA, Al-Hajjaj MS. Yield and complications of flexible fiberoptic bronchoscopy in a teaching hospital. Saudi Med J. 2008;29(1):55-59.
11. Joos L, Patuto N, Chhajed PN, Tamm M. Diagnostic yield of flexible bronchoscopy in current clinical practice. Swiss Med Wkly. 2006;136(9-10):155-159.
12. Kaparianos A, Argyropoulou E, Sampsonas F, Zania A, Efremidis G, Tsiamita M, et al. Indications, results and complications of flexible fiberoptic bronchoscopy: a 5-year experience in a referral population in Greece. Eur Rev Med Pharmacol Sci. 2008;12(6):355-363.
13. Ibrahim AS, Allangawi MH, Sattar HA, Mobyed HS, Almohammed AA. Indications, diagnostic yields and complications of transbronchial biopsy over 5 years in the State of Qatar. Saudi Med J. 2005;26(4):641-645.
14. Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. Blood. 2012;120(15):2954-2962. https://doi.org/10.1182/blood-2012-06-415943
15. de Blic J, Marchac V, Scheinmann P. Complications of flexible bronchoscopy in children: prospective study of 1,328 procedures. Eur Respir J. 2002;20(5):1271-1276. https://doi.org/10.1183/09031936.02.02072001
16. Technical recommendations and guidelines for bronchoalveolar lavage (BAL). Report of the European Society of Pneumology Task Group. Eur Respir J. 1989;2(6):561-585.
17. Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures: An Updated Report by the American Society of Anesthesiologists Task Force on Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration. Anesthesiology. 2017;126(3):376-393. https://doi.org/10.1097/ALN.0000000000001452
18. Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet. 2010;49(4):259-268. https://doi.org/10.2165/11318170-000000000-00000
19. van Ryn J, Stangier J, Haertter S, Liesenfeld K, Wienen W, Feuring M, et al. Dabigatran etexilate–a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost. 2010;103(6):1116-1127.

https://doi.org/10.1160/TH09-11-0758

20. Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. Circulation. 2011;123(13):1436-1450. https://doi.org/10.1161/CIRCULATIONAHA.110.004424
21. Ernst A, Eberhardt R, Wahidi M, Becker HD, Herth FJ. Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. Chest. 2006;129(3):734-737. https://doi.org/10.1378/chest.129.3.734
22. Colt HG, Matsuo T. Hospital charges attributable to bronchoscopy-related complications in outpatients. Respiration. 2001;68(1):67-72. https://doi.org/10.1159/000050465
23. Milman N, Faurschou P, Munch EP, Grode G. Transbronchial lung biopsy through the fibre optic bronchoscope. Results and complications in 452 examinations. Respir Med. 1994;88(10):749-753. https://doi.org/10.1016/S0954-6111(05)80197-0
24. Alamoudi OS, Attar SM, Ghabrah TM, Kassimi MA. Bronchoscopy, indications, safety and complications. Saudi Med J. 2000;21(11):1043-1047.

J Bras Pneumol. 2020;46(4):e20180255
https://dx.doi.org/10.36416/1806-3756/e20180255

ORIGINAL ARTICLE

Distinct models to assess the cost-effectiveness of EGFR-tyrosine kinase inhibitors for the treatment of metastatic non-small cell lung cancer in the context of the Brazilian Unified Health Care System

Pedro Aguiar Jr[1], Felipe Roitberg[2], Gilberto Lopes Jr[3], Auro del Giglio[4]

1. Faculdade de Medicina do ABC, Santo André (SP) Brasil.
2. Instituto do Câncer de São Paulo Octavio Frias de Oliveira, São Paulo (SP) Brasil.
3. Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA.
4. Centro de Estudos e Pesquisa de Hematologia e Oncologia, Faculdade de Medicina do ABC, Santo André (SP) Brasil.

Submitted: 6 September 2017.
Accepted: November 6 2019.

Study carried out at the Centro de Estudos e Pesquisa de Hematologia e Oncologia, Faculdade de Medicina do ABC, Santo André, Brasil.

ABSTRACT

Objective: Lung cancer is an important health problem due to its high incidence and mortality. The treatment of metastatic disease improved after the molecular pathways of cancer came to be known. However, targeted therapy is unavailable to many patients treated within the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System). Our objective was to assess the cost-effectiveness of erlotinib, gefitinib, and afatinib versus that of chemotherapy for the treatment of non-small cell lung cancer in the context of the SUS. **Methods:** Different analytical models were developed based on data in the literature. The outcomes were presented in quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs) per QALY gained. All costs related to treatment and supportive therapies were included in the models. **Results:** In one model, data from retrospective studies showed 2.01 life-years saved and a mean QALY gain of 1.169. The ICER per QALY gained ranged from R$48,451.29 (for gefitinib) to R$85,559.22 (for erlotinib). In another model, data from a meta-analysis showed −0.01 life-years saved and a mean QALY gain of 0.178. The ICER per QALY gained ranged from R$27,028.30 (for gefitinib) to R$75,203.26 (for erlotinib). **Conclusions:** There is no ideal analytical model for the SUS. However, targeted therapy with EGFR-tyrosine kinase inhibitors has been shown to be cost-effective in various scenarios. The adoption of drug price discounts will improve the cost-effectiveness of treatment.

Keywords: Health policy; Molecular targeted therapy; Economics, pharmaceutical; Brazil.

INTRODUCTION

Lung cancer is the most common cancer worldwide, with more than 1.8 million new cases diagnosed in 2012.[1] In Brazil, despite the potential underestimation of data, 28,220 new cases of and more than 22,000 deaths from lung cancer were expected to occur in 2017.[2]

Most cases of lung cancer (70%) are detected at an advanced stage, when prognosis is poor and 5-year survival is approximately 4%.[3] The standard treatment for advanced lung cancer at all facilities within the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System) continues to be platinum-based chemotherapy, after which median overall survival does not exceed 12 months.[4,5]

At the beginning of the 21st century, knowledge of molecular pathways led to the development of specific therapies and an improvement in outcomes. The therapies most widely studied in non-small cell lung cancer (NSCLC) are those based on EGFR, which is a transmembrane receptor involved in signaling to regulate cell proliferation, angiogenesis, and cell survival.[6] Treatment with tyrosine kinase inhibitors (TKIs) targeting the EGFR pathway has led to a tumor response rate greater than 50% and an increase in median progression-free survival of nearly 100%.[7-9]

Despite its significant benefits, targeted therapy (with EGFR-TKIs) is not yet widely available within the SUS because of its high cost compared with that of chemotherapy. The reimbursement from the SUS, in Brazilian reals (R$), is currently R$1,100.00 for each month of treatment for metastatic lung cancer, whereas the mean monthly cost of therapies with first- and second-generation EGFR-TKIs ranges from R$2,700.00 to R$5,600.00. The manager of each facility within the SUS is charged with identifying solutions for incorporating targeted therapy. The main options are to include in the facility budget the difference between the cost of targeted therapy and the amount reimbursed by the SUS or negotiate with manufacturers for a price that is consistent with the amount reimbursed by the SUS.

Given all of the above, our hypothesis was that molecular targeted therapy may be cost-effective for the treatment of NSCLC in Brazil. In addition, strategies that lead to a reduction in the cost of EGFR-TKIs may

Correspondence to:
Pedro Aguiar Jr. Américas Centro de Oncologia Integrado, Rua Martiniano de Carvalho, 741, CEP 01321-001, São Paulo, SP, Brasil.
Tel.: 55 11 3016-1000. E-mail: pnajpg@hotmail.com
Financial support: None.

ISSN 1806-3713

further improve the cost-effectiveness of targeted therapy compared with that of chemotherapy and increase the availability of targeted therapy to patients treated within the SUS.

Data from randomized clinical trials differ from those describing the current context of the SUS.[7-9] The first difference relative to the current practice within the SUS is that, in those studies, all patients were tested for *EGFR* mutations and only *EGFR* mutation-positive patients were included.[7,8] In addition, all such trials have shown a high degree of overlap (approximately 70%) between the study arms; that is, most patients received first- or second-line molecular targeted therapy and therefore no gain in overall survival was observed.[7-9] In order to provide a view complementary to that of randomized clinical trials,[7-9] we developed distinct models based on data from the literature that are closest to the current reality in Brazil.

The primary objective of the present study was to calculate the incremental cost-effectiveness ratio (ICER) for targeted therapy (with EGFR-TKIs) versus chemotherapy in distinct models, in order to understand the cost-effectiveness of EGFR-TKIs for the treatment of advanced NSCLC. The secondary objectives were to identify which variables most influence the cost-effectiveness of targeted therapy and to identify which model is closest to the ideal for the current context of the SUS.

METHODS

We developed two analytical decision models. Each model considered a different strategy based on distinct data from the literature. In all models, deterministic sensitivity analyses were performed to confirm the robustness of the findings

The study considered the current reality of the SUS, including the costs of *EGFR* mutation testing (Sanger DNA sequencing), the purchase of drugs for first- and second-line treatments, monitoring, treatment of adverse events, and supportive therapies.

Structure of the models

In all models, patients were classified into three mutually exclusive health status groups: progression-free survival; post-progression survival; and death.

The first model considered two distinct retrospective studies, both of which involved Asian populations.[10,11] In one study,[10] patients with *EGFR* mutations were treated with first-line EGFR-TKIs, whereas in the other study,[11] *EGFR* mutation testing was not performed and all patients were treated with conventional chemotherapy. In this model, two strategies were compared: testing all patients for *EGFR* mutations and treating *EGFR* mutation-positive patients with first-line EGFR-TKIs and second-line chemotherapy; and not performing *EGFR* mutation testing and treating all patients with chemotherapy in all lines of treatment.

The second model considered data from an individual meta-analysis including the major randomized clinical trials comparing chemotherapy versus EGFR-TKIs in first-line treatment.[12] However, most (74%) of the patients who were randomized to chemotherapy received EGFR-TKIs in second-line treatment. Therefore, in this model, two strategies were compared: testing patients for *EGFR* mutations and treating *EGFR* mutation-positive patients with first-line EGFR-TKIs and second-line chemotherapy; and testing patients for *EGFR* mutations and treating *EGFR* mutation-positive patients with first-line chemotherapy and second-line EGFR-TKIs. The two models are summarized in Figure 1.

Clinical effectiveness and quality of life

Effectiveness data were obtained by comparing the areas under the progression-free and overall survival curves reported in each study used in the distinct models.[10-12] The minimum follow-up time was set at 5 years.

Data on afatinib effectiveness were based on the results of a study that compared afatinib with gefitinib and demonstrated that both had similar efficacy, with a small benefit in terms of progression-free survival for afatinib.[13]

Quality-adjusted life-years (QALYs) for each health status group were calculated from the utility values published in the literature, adjusted for the adverse events provoked by each treatment.[14,15]

Costs

The costs of erlotinib, gefitinib, and afatinib were based on the maximum prices set for their sale to the Brazilian government, which are available on the website of the Brazilian Chamber of Drug Market Regulation.[16]

The cost of chemotherapy, regardless of the agent used or the line of treatment considered, was fixed at the amount paid by the SUS for the treatment of advanced NSCLC (R$1,100.00 per month). The duration of treatment for each pharmacological regimen was linked to progression-free survival for first-line treatments and to post-progression survival for second-line treatments.

We considered the costs of *EGFR* mutation testing (Sanger sequencing) for all patients (considering that for each test with a positive result, three tests with a negative result will also be paid for). The costs of treatment of adverse events and supportive therapies were calculated from values available in the Brazilian literature.[17,18]

Deterministic sensitivity analyses

We performed univariate deterministic sensitivity analysis (DSA) in all models. We used 95% CIs or plausible ranges (when the 95% CI was unavailable). Table 1 summarizes the variables considered in the DAS.

RESULTS

Retrospective study model

Compared with the strategy of not testing for EGFR mutations and treating all patients with chemotherapy, that of testing for *EGFR* mutations and administering targeted therapy to *EGFR* mutation-positive patients saved 2.01 life-years.

In the base case, erlotinib lead to a QALY gain of 1.169 at a mean incremental cost per patient of R$100,000.67, which resulted in an ICER per QALY gained of R$85,559.22 and an incremental cost per life-year saved of R$49,730.96. Gefitinib led to a QALY gain of 1.173 at an incremental cost per patient of R$56,839.28, resulting in an ICER per QALY gained of R$48,451.29 and an incremental cost per life-year saved of R$28,266.53. Afatinib led to a QALY gain of 1.165 and increased the cost per patient by R$58,756.87. The ICER per QALY gained was R$ 50,444.25, and the incremental cost per life-year saved was R$29,220.16. Figure 2 presents the results of the DSA for the retrospective study model.

Meta-analysis model

In the meta-analysis model, overall survival was virtually identical for the two strategies. In the arm that received EGFR-TKIs as the first-line treatment, −0.01 life-years were saved in comparison with the

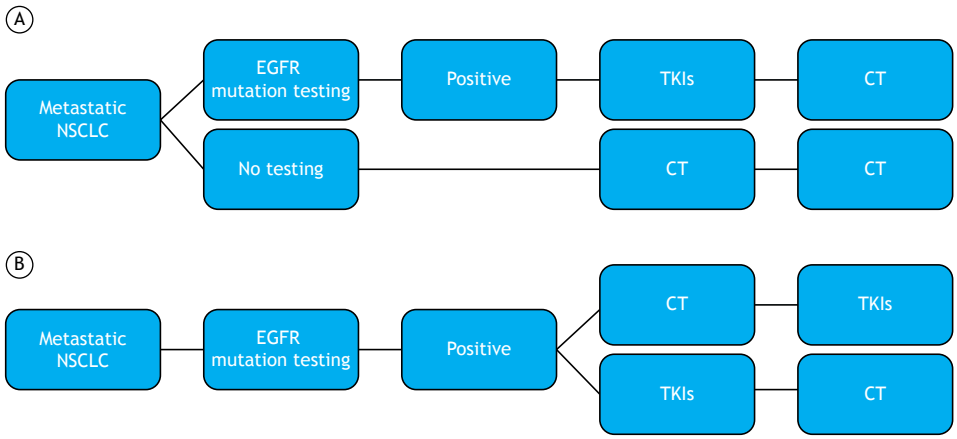


Figure 1. Analytical decision models. In A, retrospective study model. In B, meta-analysis model. NSCLC: non-small cell lung cancer; TKIs: tyrosine kinase inhibitors; and CT: chemotherapy.

Table 1. Deterministic sensitivity analysis parameters.

Parameter	Value considered	Minimum	Maximum
Overall			
Discount on the cost of TKIs	10%	NA	NA
	20%	NA	NA
Gefitinib at a fixed cost	R$1,000	NA	NA
Costs			
Erlotinib	R$5,581.55	NA	NA
Gefitinib	R$2,701.94	NA	NA
Afatinib	R$2,824.43	NA	NA
Monitoring (per cycle)	R$448.72	R$358.98	R$538.46
Supportive therapy (per month)	R$1,034.31	R$827.45	R$1,241.17
Outcomes			
Utility of PFS for TKIs	0.6393	0.6193	0.6593
Utility of PFS for CT	0.6107	0.5907	0.6307
Utility of post-progression survival	0.4734	0.4334	0.5134
Survival			
CI for mPFS for TKIs (retrospective studies)	12.1 months	10.2 months	13.5 months
CI for mOS for TKIs (retrospective studies)	30.9 months	28.2 months	35.7 months
CI for mPFS for CT (retrospective studies)	3.1 months	2.8 months	3.9 months
CI for mOS for CT (retrospective studies)	11.9 months	10.2 months	13.6 months
HR for PFS (meta-analysis)	0.37	0.32	0.42
HR for OS (meta-analysis)	1.01	0.88	1.17

TKIs: tyrosine kinase inhibitors; R$: Brazilian reals; NA: not assessed; PFS: progression-free survival; CT: chemotherapy; CI: confidence interval; mPFS: median progression-free survival; mOS: median overall survival; HR: hazard ratio; and OS: overall survival.

arm that received chemotherapy as the first-line treatment.

Erlotinib led to a QALY gain of 0.193 at a mean incremental cost per patient of R$14,517.13, which resulted in an ICER per QALY gained of R$75,203.26. Gefitinib led to a QALY gain of 0.175 at a mean incremental cost per patient of R$4,741.93, resulting in an ICER per QALY gained of R$27,028.30. Afatinib led to a QALY gain of 0.167 and increased the mean cost per patient by R$5,239.37. The ICER per QALY gained was R$31,352.97. Figure 3 presents the results of the DSA for the meta-analysis model.

DSA

The 95% CI for overall survival (0.009-1.396) was the variable with the greatest influence on QALY. The 95% CI for progression-free survival (30-50%) was the variable with the greatest influence on costs.

Negotiating discounts for the purchase of the target drug or fixing the cost of EGFR-TKIs at a monthly amount of R$1,000.00 resulted in an important improvement in the cost-effectiveness of treatment.

DISCUSSION

The cost of cancer treatment is a growing concern worldwide.[19] The American Society of Clinical Oncology has recently published a framework to assess the value of cancer treatment options on the basis efficacy, adverse events, and cost.[20] Although such initiatives are important and practical, traditional cost-effectiveness models remain essential for estimating the economic implications of cancer treatment options in Brazil. However, in order for cost-effectiveness studies to be considered before health policy decisions are made, such studies should follow some important methodological rules. The most important rule is all relevant costs and benefits to be considered in the study should be identified, assessed, and described in a transparent manner.[21] In addition, it is important to define the clinical context that was considered in the cost-effectiveness study in order to obtain the costs and benefits of treatments and to determine whether that context matches the reality of the locale at which the study will be implemented.[21]

Market movements, government regulations, and tax legislation influence drug costs. Differences in health care systems worldwide make it difficult to translate the results of an economic study into a context different from the one in which that study was developed. Therefore, pharmacoeconomic assessments are relatively specific to the health care system in which they are performed.[21]

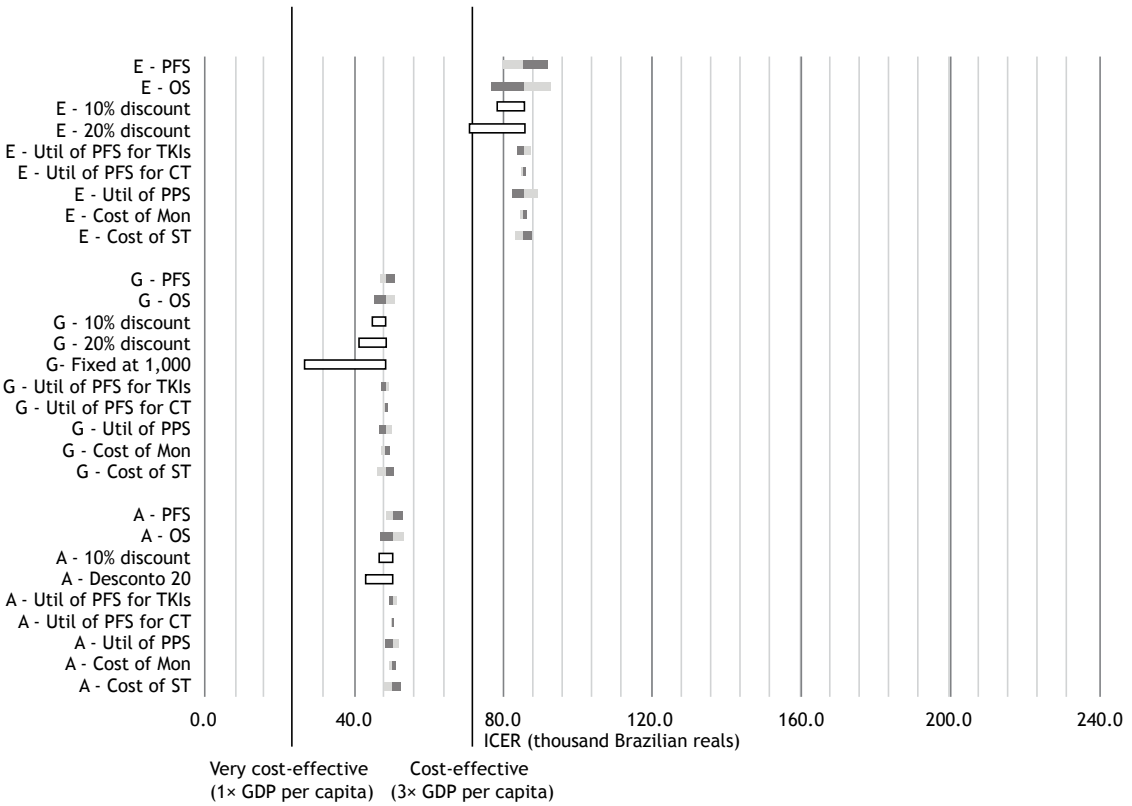


Figure 2. Tornado diagrams for tyrosine kinase inhibitors versus chemotherapy (retrospective studies). E: erlotinib; PFS: progression-free survival; OS: overall survival; Util: utility; TKIs: tyrosine kinase inhibitors; CT: chemotherapy; PPS: post-progression survival; Mon: monitoring; ST: supportive therapy; G: gefitinib; A: afatinib; ICER: incremental cost-effectiveness ratio; and GDP: gross domestic product.

In this light, the major limitation of the present study was the literature used in each model developed. The ideal would be to conduct a randomized prospective study in Brazil comparing EGFR-TKI treatment for *EGFR* mutation-positive patients versus chemotherapy for patients who did not undergo molecular testing. However, a study with such a design would not be approved by a research ethics committee, given that the benefits of molecular targeted therapy are well established.

In our study, each model developed has strong and weak points. In the retrospective study model, the strong points are the overall and progression-free survival values consistent with the literature and the design that is closest to the ideal for the context of the SUS. However, that model was based on two retrospective studies that included two completely distinct populations. Data from the Brazilian population, even retrospective data, could allow an analysis with fewer limitations. Regarding *EGFR* mutation testing, we considered the costs of testing by Sanger sequencing, which has a lower cost than does Next-Gen Sequencing, which is the currently preferred method. In addition, we are aware of the difficulty in making *EGFR* mutation testing available at all SUS facilities throughout Brazil. Centralization of testing facilities can reduce costs and increase the reliability of test results, whereas regionalized training makes it possible to expedite test results, although at a higher cost and with the challenges of implementing testing at various locations.

In the meta-analysis model, the strong points were the robust data obtained from multiple randomized clinical trials, showing overall and progression-free survival values consistent with those in the literature. However, this model does not reflect the context of the SUS, given that all patients were tested for *EGFR* mutations and approximately 70% of the patients received EGFR-TKIs after chemotherapy failure.

Considering the limitations of each model, we believe that the combination of all findings provides an overview close to the ideal for the context of the SUS. Other studies conducted in Brazil have assessed the cost-effectiveness of using EGFR-TKIs for the treatment of advanced NSCLC. One such study, developed by the Brazilian National Commission for the Incorporation of Technologies into the SUS, discussed the lack of benefit in terms of overall survival and pointed out limitations in performing and funding molecular testing.[22] However, that analysis had severe methodological limitations. Only data from randomized clinical trials were considered, which does not represent the current reality of the SUS,

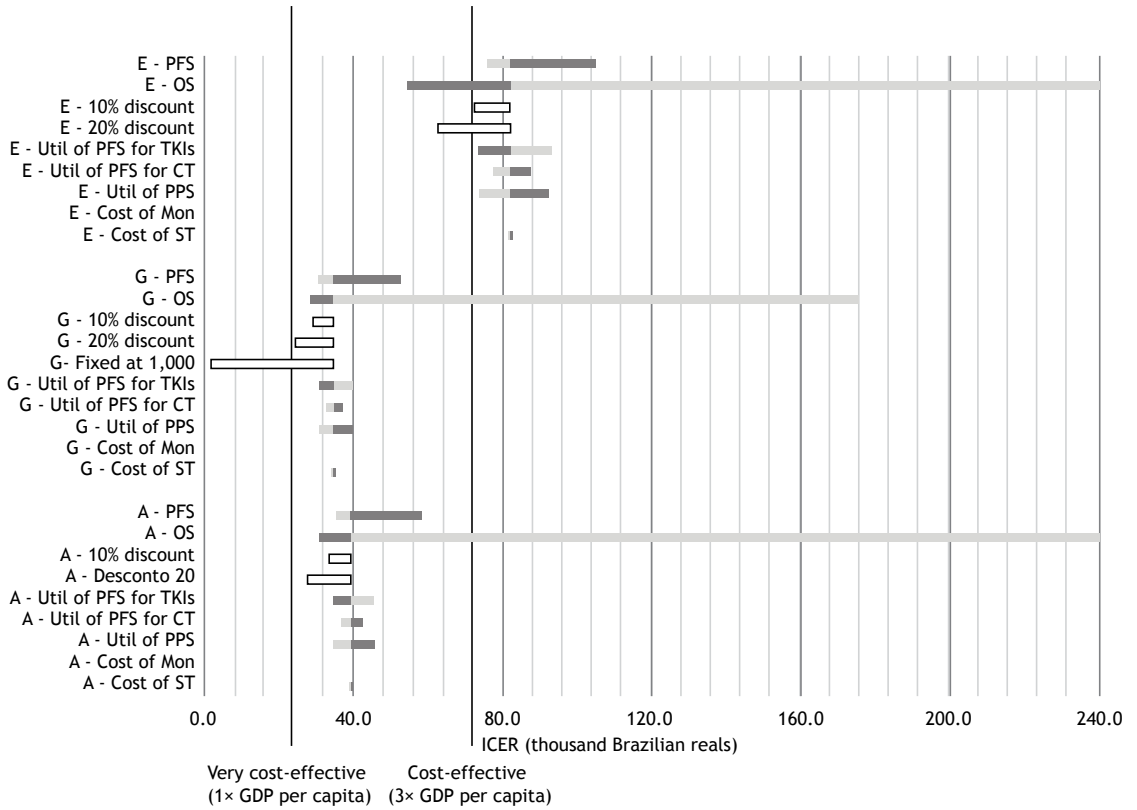


Figure 3. Tornado diagrams for tyrosine kinase inhibitors versus chemotherapy (meta-analysis). E: erlotinib; PFS: progression-free survival; OS: overall survival; Util: utility; TKIs: tyrosine kinase inhibitors; CT: chemotherapy; PPS: post-progression survival; Monit: monitoring; ST: supportive therapy; G: gefitinib; A: afatinib; ICER: incremental cost-effectiveness ratio (ICER); and GDP: gross domestic product.

given that, within the SUS, tumors are not routinely tested and there is no possibility of patients receiving EGFR-TKIs after chemotherapy failure.

Piha et al.[18] also considered data from randomized clinical trials for assessing efficacy, although information on costs was obtained from the Brazilian Chamber of Drug Market Regulation, causing the costs of platinum-based chemotherapy to be higher than the costs of gefitinib. Therefore, gefitinib surpassed chemotherapy because it had greater efficacy at a lower cost. However, as in the private health care network, the reimbursement for health care services is not based on the cost of treatment within the SUS, although it is fixed at a monthly value of R$1,100.00, a value that was used in our study as the cost of chemotherapy. The exact cost of drugs is not known because each hospital conducts its own negotiations with drug manufacturers so that the cost of treatment is at or below the amount paid by the SUS.

Subsequently, Geib[17] conducted a study of the cost-effectiveness of gefitinib that evaluated not testing for *EGFR* mutations and treating all patients with chemotherapy versus treating *EGFR* mutation-positive patients with gefitinib. Although the design was ideal for the context of the SUS, the author assessed the efficacy of chemotherapy on the basis of retrospective data from his own facility, whereas data on the efficacy of gefitinib were extracted from randomized clinical trials.[17] In addition to the fact that two completely distinct populations were compared, survival is known to be often overestimated in retrospective studies relative to prospective randomized studies. As a consequence, no significant clinical benefit was found, and gefitinib was not considered cost-effective.

Finally, we believe there is no ideal model to address the issue in question within the SUS. However, considering the different scenarios, we can conclude that EGFR-TKIs are cost-effective (EGFR-TKIs have a 64% probability of being cost-effective with an incremental investment of up to three times the GDP per capita of Brazil per patient). Negotiating discounts or fixing costs at an amount lower than that currently paid by the SUS can increase the likelihood of cost-effectiveness to up to 100%. Once such negotiated discounts or fixed costs have been incorporated into clinical practice, another need is molecular testing to inform decisions regarding treatment, which underscores the importance of investing in pathology services within the SUS.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-E386. https://doi.org/10.1002/ijc.29210
2. Brasil. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA) [homepage on the Internet]. Rio de Janeiro: INCA; [cited 2017 Jan 8]. Estimativa 2016: Incidência de Câncer no Brasil; 2015. Available from: http://inca.gov.br
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7-30. https://doi.org/10.3322/caac.21332
4. Sandler AB, Nemunaitis J, Denham C, von Pawel J, Cormier Y, Gatzemeier U, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol. 2000;18(1):122-130. https://doi.org/10.1200/JCO.2000.18.1.122
5. Wozniak AJ, Crowley JJ, Balcerzak SP, Weiss GR, Spiridonidis CH, Baker LH, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study. J Clin Oncol. 1998;16(7):2459-2465. https://doi.org/10.1200/JCO.1998.16.7.2459
6. DeVita VT Jr, Lawrence TS, Rosenberg SA. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology (Cancer Principles and Practice of Oncology). 10th ed. Philadelphia (PA): Wolters Kluwer Health; 2014. 2280 p.
7. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13(3):239-246. https://doi.org/10.1016/S1470-2045(11)70393-X
8. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3327-3334. https://doi.org/10.1200/JCO.2012.44.2806
9. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947-957. https://doi.org/10.1056/NEJMoa0810699
10. Lin JJ, Cardarella S, Lydon CA, Dahlberg SE, Jackman DM, Jänne PA, et al. Five-Year Survival in EGFR-Mutant Metastatic Lung Adenocarcinoma Treated with EGFR-TKIs. J Thorac Oncol. 2016;11(4):556-565. https://doi.org/10.1016/j.jtho.2015.12.103
11. Ozkaya S, Findik S, Dirican A, Atici AG. Long-term survival rates of patients with stage IIIB and IV non-small cell lung cancer treated with cisplatin plus vinorelbine or gemcitabine. Exp Ther Med. 2012;4(6):1035-1038. https://doi.org/10.3892/etm.2012.714
12. Lee CK, Davies L, Wu YL, Mitsudomi T, Inoue A, Rosell R, et al. Gefitinib or Erlotinib vs Chemotherapy for EGFR Mutation-Positive Lung Cancer: Individual Patient Data Meta-Analysis of Overall Survival. J Natl Cancer Inst. 2017;109(6):10.1093/jnci/djw279. https://doi.org/10.1093/jnci/djw279
13. Park K, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol. 2016;17(5):577-589. https://doi.org/10.1016/S1470-2045(16)30033-X
14. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008;6:84. https://doi.org/10.1186/1477-7525-6-84
15. Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer. 2008;62(3):374-380. https://doi.org/10.1016/j.lungcan.2008.03.019
16. Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária [homepage on the Internet]. Brasília: Ministério da Saúde; c2017 [cited 2017 Jan 8]. Listas de preços de medicamentos. Available from: http://portal.anvisa.gov.br/listas-de-precos
17. Geib G. Avaliação da custo-efetividade do tratamento do adenocarcinoma de pulmão avançado direcionado pela avaliação molecular do EGFR [dissertation]. Porto Alegre: Universidade Federal do Rio Grande do Sul; 2012.
18. Piha T, Marques M, Paladini L, Teich V. Cost-effectiveness analysis of gefitinib versus chemotherapy protocols in the first line treatment of non small-cell EGFR positive lung cancer [Article in Portuguese]. J Bras Econ Saude. 2011;3(3):269-277.
19. Saltz LB. Perspectives on Cost and Value in Cancer Care. JAMA Oncol. 2016;2(1):19-21. https://doi.org/10.1001/jamaoncol.2015.4191

20. Schnipper LE, Davidson NE, Wollins DS, Tyne C, Blayney DW, Blum D, et al. American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options. J Clin Oncol. 2015;33(23):2563-2577. https://doi.org/10.1200/JCO.2015.61.6706
21. Earle CC, Coyle D, Evans WK. Cost-effectiveness analysis in oncology. Ann Oncol. 1998;9(5):475-482. https://doi.org/10.1023/A:1008292128615
22. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Gestão e Incorporação de Tecnologias em Saúde. Comissão Nacional de Incorporação de Tecnologias no SUS. Brasília: Ministério da Saúde; [updated 2013 Nov; cited 2017 Jan 8]. Gefitinibe para câncer de pulmão de células não pequenas em primeira linha. [Adobe Acrobat document, 41p.]. Available from: http://conitec.gov.br/images/Incorporados/Gefitinibe-final.pdf

J Bras Pneumol. 2020;46(4):e20180366
http://dx.doi.org/10.36416/1806-3756/e20180366

ORIGINAL ARTICLE

Brazilian Versions of the Physical Function ICU Test-scored and de Morton Mobility Index: translation, cross-cultural adaptation, and clinimetric properties

Vinicius Zacarias Maldaner da Silva[1,2], Amanda Sanches Lima[1], Hilana Nadiele[1], Ruy Pires-Neto[3], Linda Denehy[4], Selina M. Parry[4]

1. Programa de Pós-Grauação em Ciencias da Saúde, Escola Superior de Ciências da Saúde, Brasília (DF) Brasil.
2. Instituto Hospital de Base do Distrito Federal, Brasília (DF) Brasil.
3. Departamento de Fisioterapia, Universidade de São Paulo, São Paulo (SP) Brasil.
4. Department of Physiotherapy, School of Health Sciences, The University of Melbourne, Melbourne (Vic) Australia.

Submitted: 21 December 2018.
Accepted: 12 July 2019.

Study carried out in the Instituto Hospital de Base do Distrito Federal and Escola Superior de Ciências da Saúde, Brasília (DF) Brasil.

ABSTRACT

Objective: The present study aimed to translate and cross-culturally adapt the Physical Function in ICU Test-scored (PFIT-s) and the De Morton Mobility Index (DEMMI) to Brazilian Portuguese. **Methods:** This study consisted of the translation, synthesis, and back-translation of the original versions of the PFIT-s and DEMMI, including revision by the Translation Group and pretesting of the translated version, assessed by an Expert Committee. The Brazilian versions of these instruments were applied to 60 cooperative patients with at least 48 h of mechanical ventilation at ICU discharge. The interrater reliability of both scales was tested using the Intraclass Correlation Coefficient (ICC). **Results:** The authors of both original scales have approved the cross-culturally validated versions. Translation and back-translation attained consensus, and no item was changed. Both scales showed good interrater reliability (ICC>0.80) and internal consistency (α>0.80). **Conclusion:** The versions of the PFIT-s and DEMMI adapted to Brazilian Portuguese proved to be easy to understand and apply clinically in the ICU environment.

Keywords: Physical therapy; Questionnaires; Translation; Intensive care unit.

INTRODUCTION

Impairments in physical functioning and muscle weakness are evident in the intensive care unit (ICU) setting, and can persist long after hospital discharge, impacting on activities of daily living and participation in societal and work roles.[1,2]

Physical functioning assessment is critical to understanding the trajectories of recovery and treatment efficacy in response to interventions such as rehabilitation.[3] In recent years, a number of assessment tools have been developed specifically for the ICU setting or adapted from other patient populations, e.g., geriatric and neurological patients, to assist with the physical functioning evaluation in critically ill patients.[4] When selecting the most appropriate measure to evaluate efficacy and change over time, clinicians and researchers should consider whether the clinimetric properties of the measure of interest have been established.[5]

Among these measures, clinicians may utilize the Physical Function in ICU Test-scored (PFIT-s) and De Morton Mobility Index (DEMMI). The PFIT-s is a four-component outcome measure: Assistance (sit-to-stand level of assistance: 0, 1, or 2 people needed), Cadence (maximal marching on the spot duration and number of steps), Shoulder (flexion strength), and Knee (extension strength), with the last two items based on the greatest of left and right using the Oxford grading system.[6] The PFIT-s is a robust measurement tool with demonstrated reliability, validity and responsiveness, and a minimal clinically important difference (MCID) >1.5 points using a 0-10 interval scale range.[4,6,7] The DEMMI is a one-dimensional measure of mobility originally developed for the geriatric population.[8,9] It has recently been assessed in a study within the ICU setting, showing excellent reliability and low floor and ceiling effects during and after ICU discharge[10].

Most tools utilized by health professionals to evaluate functional outcomes in ICU (including PFIT-s and DEMMI) were originally developed in English. In order to be used in Brazil, they must be translated, cross-culturally adapted, and tested for their measurement properties within the local setting. In addition, this procedure facilitates comparison of the results from the same outcome measure in different countries and cultures.[11] Some tools, such as the Functional Status Score for the ICU, ICU Mobility Scale, and Perme Intensive Care Unit Mobility Score have already been translated into Brazilian Portuguese.[12,13] To date, neither the PFIT-s nor the DEMMI has been appropriately translated and validated for use in Brazil taking into account the language and cultural differences. Thus, the aims of this study were 1) to translate and cross-culturally adapt the DEMMI and PFIT-s instruments to Brazilian Portuguese and 2) to evaluate their clinimetric properties (content validity, reliability, floor and ceiling effects). The Strengthening the Reporting of Observational

Correspondence to:
Vinicius Zacarias Maldaner da Silva. Instituto Hospital de Base do Distrito Federal, SQSW 105, Bloco F, Ap. 413, CEP 70670-426, Brasília, DF, Brasil.
Tel.: +55 61 33151297. E-mail: viniciusmaldaner@gmail.com
Financial support: None.

Studies in Epidemiology (STROBE)[14] and COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) guidelines[15,16] were followed in the conduct and reporting of this study.

METHODS

This process was authorized by one of the authors of the original version, Professor Linda Denehy, the University of Melbourne, Melbourne, Australia. This study approved by the Ethics Committee of the Health Sciences Teaching and Research Foundation (FEPECS- Brasilia-Brazil) under process no. 1.338.188.

Translation and cross-cultural adaptation

The translation and cross-cultural adaptation of the aforementioned instruments was conducted according to the guidelines proposed by Beaton et al.[11] which included the following steps: translation, synthesis of the translation, back-translation, review by the expert committee, and pretesting of the pre-final version. This expert committee included an author of the original tool, three physical therapists with over three years of experience specifically in intensive care unit (ICU), and four Portuguese-English accredited translators.

The questionnaire and instructions were translated into Portuguese by two bilingual (Portuguese and English) translators whose native language was Brazilian Portuguese. Translator 1 had experience in occupational health and knowledge of the concepts of the instrument, whereas Translator 2 had no experience in health care and was not familiar with the assessment tools. Both were accredited translators for Portuguese. Once the independent translated versions (T1 and T2) were completed, the teams met with the expert committee (which included the project and translation coordinators) to compare the versions and reach a consensus on any discrepancy, which resulted in a common translated pilot version (T12). Next, the single version was back-translated into the original language by two other independent bilingual translators, native speakers of English and fluent in Brazilian Portuguese, who had no knowledge on the instrument (the so-called naive translators). This step resulted in two back-translations.

The expert committee evaluated all translations and back-translations thoroughly. Rather than focusing on indices of agreement, the translation board attempted to make the best use of the language expertise of its members. The next step consisted of the back-translation of the T12, which was performed by two independent translators fluent in both languages. The back-translated versions (BT1 and BT2) were also compared and a consensus back-translated version (BT12) was attained. The BT12 was submitted to the evaluation of one of the authors of the scales. After this process, the expert committee produced a pre-final version of the DEMMI and PFIT-s instruments for use in Brazil. The professional background of the participants is described in Table 1.

Pretesting was performed to verify whether this version was equivalent to the original scale and whether the target group could understand it properly. The objective of this stage was to identify interpretative problems regarding the experiential, conceptual, semantic and idiomatic equivalence of the items with the aim of enhancing the inventory as well as reviewing and modifying problematic issues.

For the pretesting, a sample of thirty (30) physical therapists (PTs) from public and private hospitals in Brazil were selected and invited by e-mail to participate in the study. To this end, the following selection criteria were used: having degree in physical therapy and at least one year of clinical work experience in ICU.

The PTs were asked to read the scale, fully explain their answers, and report any issues. None of the PTs reported difficulty in understanding or interpreting the questions.

Application of the translated scales in a Brazilian setting

Study design and setting

This is a single-center prospective study conducted in the surgical and trauma ICUs of the *Hospital de Base do Distrito Federal*. All participants provided written informed consent.

Participants

Inclusion criteria were as follows: 1) adults, aged ≥18 years; 2) mechanically ventilated for more than 48 h; 3) able to ambulate independently for at least 10 m prior to ICU admission (with or without a gait aid); 4) expected to remain in ICU for longer than four days. Additionally, due to the volitional (patient effort dependence) nature of the physical measures, the participants were required to be cooperative with assessments to be included in the study. The ability to comprehend and follow commands was determined using the De Jonghe comprehension criteria (open and

Table 1. Characteristics of the Expert Committee members.

Professional	Occupation	Academic Degree	Professional Experience
Translator 1	Language Professional	M.Sc.	11 years
Translator 2	Physical Therapist	Ph.D.	6 years
Back-translator 1	Physical Therapist	M.Sc.	15 years
Back-translator 2	Language Professional	Ph.D.	21 years
Project Coordinator	Physical Therapist	M.Sc.	15 years
Translation Coordinator	Bachelor of Arts	Ph.D.	24 years

close your eyes; look at me; open your mouth and put out your tongue; nod your head; raise your eyebrows when I have counted up to five).[17] Participants should score at least 3 out of 5 on two consecutive occasions within a six-hour period.[17] Participants were excluded from the study if they presented pre-existing cognitive impairment prior to hospitalization or were admitted with a new neurological condition, such as stroke or spinal cord injury.

Outcome measures

The final Brazilian Portuguese version (available in the online Supplementary Material) was tested by two qualified physical therapists who had received a minimum of 8 hours of training from a senior physical therapist with five years of experience in ICU and who had received specific training in the performance of both assessment tools. The training session included didactic lectures and practical training using simulated ICU patients. After this training session, the assessors evaluated consecutive eligible ICU patients using the PFIT-s and DEMMI instruments. The assessors performed their tests independently and were blinded to the scores obtained by the other therapist. The two scales and the raters were randomized per balanced incomplete blocks using sealed envelopes. All assessments were performed within a 12-hour period, which enabled adequate rest in between assessments to minimize patient fatigue.

Description of the Physical Function ICU Test-scored (PFIT-s) and de Morton Mobility Index (DEMMI)

The PFIT-s was developed for the ICU setting, and examines four activities: 1) Assistance (sit-to-stand level of assistance: 0, 1, or 2 people needed), 2) Cadence (maximal marching on the spot duration and number of steps), 3) Shoulder (flexion strength), and 4) Knee (extension strength), with the last two items based on the greatest of left and right using the Oxford grading system, ranging from 0 – no visible or palpable muscle contraction through to 5 – normal strength. In individuals with greater than movement against gravity (Oxford grade 3), strength was assessed isometrically (at one point in range). The isometric technique was used because this is the preferred method for manual muscle strength testing in ICU.[18] Both interval and ordinal scoring is available. The PFIT-s score ranges from 0 (unable to perform activities) to 10 (high physical functioning).[6]

The DEMMI is composed of 15 items. Eleven items are dichotomous (scored 0 or 1) and four items are scored as 0, 1, or 2. There are 15 hierarchical mobility activities (three are bed based, three chair based, four involve static balance, two are walking-related, and three involve dynamic balance).[8] Patients are rated on their ability as either able/unable or able/partial/unable to perform the tasks.[8] The total score is converted with Rasch Analysis to an interval score range from 0 to 100, where 0 represents poor mobility and 100 indicates high levels of independent mobility.[9]

Assessments were performed only at ICU discharge. Baseline demographics were recorded, including age, gender, body mass index (BMI), admission diagnosis, comorbidities, severity of illness (Acute Physiological and Chronic Health Evaluation - APACHE II) within the first 24 h of ICU admission). Additionally, ICU and hospital length of stay (LOS) and mechanical ventilation (MV) duration (in days) were recorded.

Peripheral muscle strength

Knee extension and handgrip strength were assessed using a digital dynamometer - Manual Muscle Tester (Microfet®, Hoogan Scientific, UTAH, USA). Peripheral muscle strength assessments were conducted with patients in sitting position. Three trials were performed for both limbs according to published protocols, and the highest value of the three trials of both limbs was used as the score.[19,20] Peripheral muscle strength values were reported in kilograms (Kg), with higher values indicating greater muscle strength.

Functional Status Score for Intensive Care Unit (FSS- ICU)

The FSS-ICU is an outcome measure of physical function assessment specially designed for ICU patients, and involves five functional tasks (rolling, supine to sit transfer, sit to stand transfer, sitting on the edge of bed, and walking). Each task is evaluated using an 8-point ordinal scale ranging from 0 (unable to attend or complete task due to weakness) to 7 (complete independence). The FSS-ICU total score is the sum of the scores of all five items, ranging 0-35. The higher scores indicate better functional status. This scale was translated and cross-culturally adapted to Brazilian Portuguese.[12]

Statistical analysis

The study sample comprised 60 patients. Aiming to enhance the generalizability of findings, sample sizes ≥50 participants are recommended for studies assessing clinimetric properties of measurements.[21] The one-sample Kolmogorov-Smirnov test was used to verify the normality of the data. Parametric data are presented as mean and standard deviation, whereas non-parametric data are presented as median and interquartile range. The Intraclass Correlation Coefficient (ICC) using the method of absolute agreement was calculated to evaluate the reliability between the two evaluators (interrater reliability). An ICC greater than 0.75 indicates good-to-excellent reliability.[22] The data measured by one rater across two trials for both scales (DEMMI and PFIT-s) were used to assess the intra-rater reliability, whereas the data measured by two raters for the same group of individuals were used to assess the interrater reliability.

Concurrent construct validity was evaluated using the Spearman's correlation coefficients between both the DEMMI and PFIT-s scores and other variables. To evaluate the convergent validity, a correlation between the DEMMI and PFIT-s with handgrip, knee extension

strength, and the FSS-ICU score were calculated. To assess the divergent validity, correlations with body mass index (BMI) and the APACHE II were calculated.

The proportion of patients who had a minimum (floor) and maximum (ceiling) score was calculated for ICU discharge to determine the presence of a floor or ceiling effect at this time. Floor or ceiling effects are considered to be present if >15% of respondents achieved the lowest or highest possible score, respectively.[23]

RESULTS

Sixty patients were enrolled in this study. Table 2 displays their demographic characteristics.

In the analysis of conceptual equivalence, the DEMMI and PFIT-s scales were understood by the professionals responsible for the translation and back-translation, and the instruments were considered adequate for translation into Brazilian Portuguese. In the meeting held to reach a consensus translation version for both scales, four discrepancies were observed and resolved. The proposed solutions are described in Table 3.

In the back-translation, a couple of differences were identified in the comparison with the original versions. In the PFIT-s, the term *cadence* in the original version was back-translated as *rhythm*. In the DEMMI, the term *sit to stand without using arms* was back-translated as *sit to stand with no arms*. In the pretesting stage, the physical therapists did not report any uncertainties or problems with interpretation affecting their performance; therefore, no additional adjustments were done in the Brazilian Portuguese version. The final electronic versions of the DEMMI and PFIT-s Brazil can be found in the Supplementary Material.

Table 2. Baseline characteristics of the patients enrolled in this study.

Patient characteristics	
Age (years)	42 ±17
Gender (male) n (%)	24 (60%)
APACHE II mean ±SD	19 ± 4
Admission category, n (%)	
• Surgical	17 (43%)
• Trauma	23 (54%)
FCI score	2 [1-4]
BMI (kg/m^2), median [IQR]	25 [23-32]
ICU-AW diagnosis, n (%)	24 (60%)
Time to awakening (days)	5 [4-9]
MV duration (days)	7 [4-11]
ICU LOS (days)	10 [5-16]
Hospital LOS (days)	15 [7-16]
PFIT-s at ICU discharge (0-10 range) mean ±SD	6.55 ±2.06
DEMMI at ICU discharge (0-100 range) mean ±SD	42.6 ±23.80
FSS-ICU at ICU discharge (0-35 range) mean ±SD	26 ±6
Knee extension strength (kg), mean ±SD	18 ±6

ADL: activities of daily living; APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: Body Mass Index; DEMMI: De Morton Mobility Index; FCI: Functional Comorbidity Index; ICU: intensive care unit; ICU-AW: intensive care unit acquired weakness; kg: kilograms; LOS: length of stay; MV: mechanical ventilation; FSS: Functional Status Score for the ICU; n: number; PFIT-s: Physical Function in ICU Test-scored. The values are expressed as n (%), mean ± standard deviation or median [interquartile range].

Table 3. Discrepancies observed by the Expert Committee between the translation versions (T1 and T2) of the de Morton Mobility Index (DEMMI) and the Physical Function in ICU Test-scored (PFIT-s) – Brazilian Version, and the proposed solutions (T12).

Modified Item	T1 and T2	T12 – Proposed Solutions
Assistance (PFIT-s)	T1 - Assistência T2 - Auxílio	Assistência
Sit to Stand (PFIT-s and DEMMI)	Sentar e Levantar Sentado para em pé	Sentar e levantar
Walk 4 steps backwards	T1- Caminhar 4 passos para trás T2- Andar 4 passos para trás	Andar 4 passos para trás
Roll onto side	T1- Rolar para os lados T2 Virar-se para o lado	Rolar para os lados

T1: Translator 1; T2: Translator 2; T12: consensus-based translation; DEMMI: De Morton Mobility Index; PFIT-s: Physical Function ICU Test-scored.

Table 4. Interrater agreement and internal consistency between the Physical Function ICU Test-scored (PFIT-s) and the de Morton Mobility Index (DEMMI).

Instrument	*Assessor 1 Median [min-max]*	*Assessor 2 Median [min-max]*	*Reproducibility ICC (95% CI)*
PFIT-s			
Sit-to-stand Assistance	2 [0-3]	2 [0-3]	0.87 (0.81-0-92)
Marching on the spot	2 [0-3]	2 [0-3]	0.81 (0.79-0.84)
Shoulder Flexion Strength	2 [1-3]	2 [1-3]	0.96 (0.94-1.00)
Knee Extension Strength	2 [0-3]	2 [0-3]	0.97 (0.95-1.00)
PFIT-s Total	6 [0-12]	6 [0-12]	0.91 (0.87-0.93)
DEMMI			
Bed-based Activities	3 [0-4]	3[0-4]	0.90 (0.87-0.93)
Chair	2 [0-4]	2 [0-4]	0.92 (0.89-0.95)
Static Balance	2 [0-4]	2 [0-4]	0.95 (0.93-0.98)
Walking	2 [0-4]	2 [0-4]	0.95 (0.93-0.98)
Dynamic Balance	1 [0-3]	1 [0-3]	0.91 (0.87 -0.94)
Total Score	31 [0-100]	33 [0-100]	0.90 (0.87-0.94)

ICC: Intraclass correlation coefficient; PFIT-s: Physical Function ICU Test-scored; DEMMI: de Morton Mobility Index.

Table 5. Cross-sectional relationship between the de Morton Mobility Index (DEMMI) and the Physical Function ICU Test-scored (PFIT-s) – Brazilian Version according to outcome measures and baseline characteristics.

	DEMMI score	PFIT-s score
Convergent Validity		
Knee extension strength	0.79 (p<0.05)	0.83 (p<0.05)
FSS-ICU	0.91 (p<0.05)	0.93 (p< 0.05)
Divergent Validity		
BMI	-0.09 (p>0.05)	-0.13 (p>0.05)
APACHE II	-0.21 9 p>0.05)	-0.17 (p>0.05)

BMI: Body Mass index; APACHE II: Acute Physiology and Chronic Health Evaluation II; FSS: Functional Status Score for the ICU.

Table 4 shows the interrater agreement and reliability for each domain of the DEMMI and PFIT-s. Good interrater agreement and reliability was observed for all items of in both scales.

Moderate to large criterion validity was found between the DEMMI and PFIT-s instruments and the two functional outcomes (Table 5). Both scales showed negligible correlations with body mass index and APACHE II.

There were minimal floor and ceiling effects to the PFIT-s (1 and 3%, respectively) and the DEMMI (3 and 6%, respectively) assessed at ICU discharge.

DISCUSSION

This study describes the translation and cultural adaptation to Brazilian-Portuguese of the DEMMI and PFIT-s scales for use in critically ill patients. The cross-cultural adaptation process is an approach that can be applied to many instruments developed in other cultural and linguistic settings. For Brazil, it may assist with filling the data gap on the functional evaluation of critically ill patients.

An important reason to adapt an existing assessment tool is that it is more efficient than developing a new one. There is substantial work involved in developing and validating an outcome measure or questionnaire.[24] Because this process is not simple and involves costs, it is necessary to consider whether the instrument is relevant to research and clinical practice, and whether its characteristics are adequate for the purpose, population, and context in which it is intended to be used.[25]

The ICU is a challenging environment to conduct research due to patient heterogeneity and severity of illness. In order to improve the ability to compare findings between research studies, there is now a large body of literature that validates outcomes and indeed much work engaged in finding a standardized core set of outcome measures.[5] Cross-cultural validation, such as the one conducted in this study, is an important aspect of this body of work.

The clinimetric properties found for the DEMMI and PFIT-s instruments are similar to those reported in previous studies. Sommers et al.[10] found a reliability of 0.93 and low ceiling and floor effects at ICU discharge (2.6%), closely corroborating the results of this study results. Similarly to the results of the present study, Parry et al.[4] observed strong correlation between the PFIT-s and muscle strength, but high ceiling effects

(10.3% *vs.* 3%, respectively). These differences can be explained by the difference in the ICU populations investigated - the sample of this study was composed of younger surgical and trauma patients. New studies addressing whether different populations influence functional outcomes should be conducted for better understanding.

The PFIT-s is recommended for the evaluation of critically ill patients,[6,10] whereas the DEMMI has received relatively little attention within the ICU setting.[26] Sommers et al.[10] have demonstrated that the DEMMI is valid and reliable for critically ill patients. Interrater reliability of the Dutch and German translations of the DEMMI was considered excellent (ICC≥0.90), which confirms the reliability results of the DEMMI for Brazil obtained in the present study.[27,28] Denehy et al.[6] demonstrated that the PFIT-s is safe, valid, responsive to change, and predictive of key outcomes, and recommended its adoption to test physical function in ICU. Additionally, Skinner et al.[29] reported the reliability of the PFIT-s for critically ill patients, corroborating the findings of this study, which showed that the PFIT-s presents excellent reproducibility (ICC>0.90).

Recent studies have used the PFIT-s as a key functional outcome to examine early rehabilitation within the ICU setting. Parry et al.[30] demonstrated that functional electrical stimulation cycling in critically ill patients may improve physical function evaluated by the PFIT-s. Nordon-Craft et al.[7] reported that the PFIT-s is feasible and safe to evaluate physical function in ICU patients who are alert and able to follow commands. More recently, this scale has been recommended as one of the four key physical functioning measurement tools for evaluation of physical functioning within the ICU setting[3,31]. The DEMMI still requires further use and evaluation in the ICU environment. Thus, the cross-cultural adaptation of these scales will assist Brazilian physical therapists with obtaining valid and reliable physical function assessments in this population.

It is worth noting that this study was conducted at a single center. However, the findings in this sample are consistent with those obtained in previously published research from Australia, the USA, and the Netherlands,[6,10] lending support to the results of this study.

The versions of the DEMMI and PFIT-s adapted to Brazilian Portuguese proved to be valid, easy to understand, and able to be feasibly implemented in the ICU clinical setting. It is expected that, by providing a consistent and reliable assessment tool, this study will contribute to improvement of the functional assessment of individuals with critical illness in both research and clinical practice in Brazil.

REFERENCES

1. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014;371(3):287-8. http://dx.doi.org/10.1056/NEJMc1406274. PMid:25014703.
2. Parry SM, Puthucheary ZA. The impact of extended bed rest on the musculoskeletal system in the critical care environment. Extrem Physiol Med. 2015;4(1):16. http://dx.doi.org/10.1186/s13728-015-0036-7. PMid:26457181.
3. Parry SM, Nydahl P, Needham DM. Implementing early physical rehabilitation and mobilisation in the ICU: institutional, clinician, and patient considerations. Intensive Care Med. 2017 PMid:28842731.
4. Parry SM, Denehy L, Beach LJ, Berney S, Williamson HC, Granger CL. Functional outcomes in ICU: what should we be using? An observational study. Crit Care. 2015;19(1):127. http://dx.doi.org/10.1186/s13054-015-0829-5. PMid:25888469.
5. Parry SM, Granger CL, Berney S, Jones J, Beach L, El-Ansary D, et al. Assessment of impairment and activity limitations in the critically ill: a systematic review of measurement instruments and their clinimetric properties. Intensive Care Med. 2015;41(5):744-62. http://dx.doi.org/10.1007/s00134-015-3672-x. PMid:25652888.
6. Denehy L, de Morton NA, Skinner EH, Edbrooke L, Haines K, Warrillow S, et al. A physical function test for use in the intensive care unit: validity, responsiveness, and predictive utility of the physical function ICU test (scored). Phys Ther. 2013;93(12):1636-45. http://dx.doi.org/10.2522/ptj.20120310. PMid:23886842.
7. Nordon-Craft A, Schenkman M, Edbrooke L, Malone DJ, Moss M, Denehy L. The physical function intensive care test: implementation in survivors of critical illness. Phys Ther. 2014;94(10):1499-507. http://dx.doi.org/10.2522/ptj.20130451. PMid:24810863.
8. de Morton NA, Davidson M, Keating JL. Validity, responsiveness and the minimal clinically important difference for the de Morton Mobility Index (DEMMI) in an older acute medical population. BMC Geriatr. 2010;10(1):72. http://dx.doi.org/10.1186/1471-2318-10-72. PMid:20920285.
9. Morton NA, Davidson M, Keating JL. The de Morton Mobility Index (DEMMI): an essential health index for an ageing world. Health Qual Life Outcomes. 2008;6(1):63. http://dx.doi.org/10.1186/1477-7525-6-63. PMid:18713451.
10. Sommers J, Vredeveld T, Lindeboom R, Nollet F, Engelbert RH, Van der Schaaf M. de Morton mobility index is feasible, reliable, and valid in patients with critical illness. Phys Ther. 2016;96(10):1658-66. http://dx.doi.org/10.2522/ptj.20150339. PMid:27081202.
11. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine. 2000;25(24):3186-91. http://dx.doi.org/10.1097/00007632-200012150-00014. PMid:11124735.
12. Silva V, Araujo JAN, Cipriano G Jr, Pinedo M, Needham DM, Zanni JM, et al. Brazilian version of the Functional Status Score for the ICU: translation and cross-cultural adaptation. Rev Bras Ter Intensiva. 2017;29(1):34-8. http://dx.doi.org/10.5935/0103-507X.20170006. PMid:28444070.
13. Kawaguchi YM, Nawa RK, Figueiredo TB, Martins L, Pires-Neto RC. Perme intensive care unit mobility score and ICU mobility scale: translation into portuguese and cross-cultural adaptation for use in Brazil. J Bras Pneumol. 2016;42(6):429-34. http://dx.doi.org/10.1590/s1806-37562015000000301. PMid:28117473.
14. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014;12(12):1500-24. http://dx.doi.org/10.1016/j.ijsu.2014.07.014. PMid:25046751.
15. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford P, Knol DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international delphi study. Qual Life Res. 2010;19(4):539-49. http://dx.doi.org/10.1007/s11136-010-9606-8. PMid:20169472.
16. Mokkink L, Terwee C, Knol D, Stratford P, Alonso J, Patrick D, et al. The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: a clarification of its content. BMC Med Res Methodol. 2010;10(22):22. http://dx.doi.org/10.1186/1471-2288-10-22. PMid:20298572.

17. De Jonghe B, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA. 2002;288(22):2859-67. http://dx.doi.org/10.1001/jama.288.22.2859. PMid:12472328.
18. Parry SM, Berney S, Granger CL, Dunlop DL, Murphy L, El-Ansary D, et al. A new two-tier strength assessment approach to the diagnosis of weakness in intensive care: an observational study. Crit Care. 2015;19(1):52. http://dx.doi.org/10.1186/s13054-015-0780-5. PMid:25882719.
19. Bohannon RW. Reference values for extremity muscle strength obtained by hand-held dynamometry from adults aged 20 to 79 years. Arch Phys Med Rehabil. 1997;78(1):26-32. http://dx.doi.org/10.1016/S0003-9993(97)90005-8. PMid:9014953.
20. Baldwin CE, Paratz JD, Bersten AD. Muscle strength assessment in critically ill patients with handheld dynamometry: an investigation of reliability, minimal detectable change, and time to peak force generation. J Crit Care. 2013;28(1):77-86. http://dx.doi.org/10.1016/j.jcrc.2012.03.001. PMid:22520490.
21. Terwee CB, Mokkink LB, Van Poppel MN, Chinapaw MJ, Van Mechelen W, Vet HC. Qualitative attributes and measurement properties of physical activity questionnaires: a checklist. Sports Med. 2010;40(7):525-37. http://dx.doi.org/10.2165/11531370-000000000-00000. PMid:20545379.
22. Sarwal A, Parry SM, Berry MJ, Hsu FC, Lewis MT, Justus NW, et al. Interobserver reliability of quantitative muscle sonographic analysis in the critically Ill population. J Ultrasound Med. 2015;34(7):1191-200. http://dx.doi.org/10.7863/ultra.34.7.1191. PMid:26112621.
23. Terwee CB, Bot SD, Boer MR, Van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007;60(1):34-42. http://dx.doi.org/10.1016/j.jclinepi.2006.03.012. PMid:17161752.
24. Costa FA, Duggan C, Bates I. A systematic approach to cross-cultural adaptation of survey tools. Pharm Pract. 2007;5(3):115-24. http://dx.doi.org/10.4321/S1886-36552007000300004. PMid:25214927.
25. Epstein J, Santo RM, Guillemin F. A review of guidelines for cross-cultural adaptation of questionnaires could not bring out a consensus. J Clin Epidemiol. 2015;68(4):435-41. http://dx.doi.org/10.1016/j.jclinepi.2014.11.021. PMid:25698408.
26. Parry SM, Huang M, Needham DM. Evaluating physical functioning in critical care: considerations for clinical practice and research. Crit Care. 2017;21(1):249. http://dx.doi.org/10.1186/s13054-017-1827-6. PMid:28978333.
27. Jans MP, Slootweg VC, Boot CR, de Morton NA, van der Sluis G, van Meeteren NL. Reproducibility and validity of the Dutch translation of the de Morton Mobility Index (DEMMI) used by physiotherapists in older patients with knee or hip osteoarthritis. Arch Phys Med Rehabil. 2011;92(11):1892-9. http://dx.doi.org/10.1016/j.apmr.2011.05.011. PMid:22032224.
28. Braun T, Schulz RJ, Reinke J, van Meeteren NL, de Morton NA, Davidson M, et al. Reliability and validity of the German translation of the de Morton Mobility Index (DEMMI) performed by physiotherapists in patients admitted to a sub-acute inpatient geriatric rehabilitation hospital. BMC Geriatr. 2015;15(1):58. http://dx.doi.org/10.1186/s12877-015-0035-y. PMid:25935559.
29. Skinner EH, Berney S, Warrillow S, Denehy L. Development of a physical function outcome measure (PFIT) and a pilot exercise training protocol for use in intensive care. Crit Care Resusc. 2009;11(2):110-5. PMid:19485874.
30. Parry SM, Berney S, Warrillow S, El-Ansary D, Bryant AL, Hart N, et al. Functional electrical stimulation with cycling in the critically ill: a pilot case-matched control study. Crit Care. 2014;29(4):695.e1-7. http://dx.doi.org/10.1016/j.jcrc.2014.03.017.
31. Selina Mary Parry P, Huang M, Needham DM. Evaluating physical functioning in critical care: considerations for clinical practice and research. Crit Care. 2017;21:249. http://dx.doi.org/10.1186/s13054-017-1827-6.

SUPPLEMENTARY MATERIAL

Supplementary material accompanies this paper.

Teste de Função Física em Unidades de Terapia Intensiva (PFIT-s): PFIT-s Brasil.

This material is available as part of the online article at http://jornaldepneumologia.com.br/detalhe_anexo.asp?id=82

J Bras Pneumol. 2020;46(4):e20190420
https://dx.doi.org/10.36416/1806-3756/e20190420

ORIGINAL ARTICLE

Role that anorexia and weight loss play in patients with stage IV lung cancer

Juliana Pereira Franceschini[1], Sergio Jamnik[1], Ilka Lopes Santoro[1]

1. Disciplina de Pneumologia, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil.

Submitted: 18 December 2019.
Accepted: 15 March 2020.

Study carried out in the Disciplina de Pneumologia, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil.

ABSTRACT

Objective: To evaluate the prevalence of anorexia and weight loss at diagnosis (pre-treatment), to identify the factors associated with pre-treatment weight loss, and to determine the prognostic role of anorexia and weight loss in the overall survival of patients with stage IV lung cancer. **Methods:** This was a retrospective observational cohort study. The patients were stratified by the presence/absence of anorexia and of pre-treatment weight loss, which generated a measure composed of four categories, which were the independent variables. **Results:** Among the 552 patients included in the study, anorexia and pre-treatment weight loss were present in 39.1% and 70.1%, respectively. After adjusting for age, male gender, and Karnofsky performance status, we found that anorexia and tumor size were significantly associated with pre-treatment weight loss. In a Cox multivariate analysis, adjusted for age, male gender and low Karnofsky performance status were found to be independent predictors of worse survival, as was concomitance of anorexia and weight loss. **Conclusions:** Anorexia and pre-treatment weight loss appear to be relevant problems in the follow-up of patients with advanced (stage IV) lung cancer Specific interventions are of crucial importance in individualized treatment plans, even within the context of palliative care.

Keywords: Lung neoplasms; Anorexia; Weight loss; Neoplasms/mortality.

INTRODUCTION

Anorexia, defined as a loss of appetite, is a common symptom in patients with lung cancer, especially in those with advanced disease. Caused by the adverse effects of treatment or by comorbidities related to the evolution of the disease, anorexia is seen in 30-40% of cancer patients, leading to reduced food intake or reduced nutrient absorption and, consequently, to a worsening of quality of life, as well as to increased morbidity and mortality.[1-3]

Unintentional pre-treatment weight loss, which can be a consequence of anorexia,[4-7] is also associated with a worsening of functional capacity and tolerance to treatment.[8-10] Previous studies have reported that 60% of patients with advanced lung cancer present this sign,[11] which makes them more prone to fatigue and pain, as well as worsening their overall quality of life.[12,13]

The combination of anorexia and weight loss can be present in more than two-thirds of patients with advanced lung cancer. This combination has been linked to decreased effectiveness of treatment modalities, especially chemotherapy, and to an increase in the frequency of side effects of such treatment, including fatigue.[14]

Despite the growing number of studies showing the impacts of anorexia and weight loss on the quality of life and survival of patients with lung cancer, these conditions are underdiagnosed and undertreated in clinical practice because of the scarcity of protocols for diagnosis and effective treatment.[6,15] In addition, predictive factors for unintentional weight loss in the period preceding the diagnosis of lung cancer are not well described in the literature, nor is the importance of the role that anorexia and weight loss play in the prognosis of lung cancer in Brazil. Therefore, the objectives of the present study were to determine the prevalence of anorexia and pre-treatment weight loss, to identify the factors associated with unintentional pre-treatment weight loss, and to define the role that anorexia and pre-treatment weight loss play in the overall survival of patients with stage IV lung cancer.

METHODS

This was a retrospective, observational nested cohort study involving patients diagnosed with stage IV lung cancer, selected from a structured database of patients with lung cancer within the electronic records of a tertiary referral outpatient clinic in the city of São Paulo, Brazil. The study was approved by the local research ethics committee, and all patients had previously given written informed consent.

The starting date for inclusion of patients in this study was 2 January 2000, and the ending date was 1 October 2017. For the purposes of data analysis, patients were followed until 30 December 2017. Included in the study were patients diagnosed with stage IV lung cancer,

Correspondence to:
Ilka Lopes Santoro. Disciplina de Pneumologia, Universidade Federal de São Paulo, Rua Botucatu, 740, CEP 04023-062, São Paulo, SP, Brasil.
Tel./Fax: 55 11 97143-4396. E-mail: ilkasantoro@gmail.com
Financial support: None.

ISSN 1806-3713

confirmed by histological or cytological analysis or by complete clinical evaluation.

At diagnosis, we assessed the following demographic and clinical variables: age; gender; functional performance, expressed as the Karnofsky performance status; smoking status (never smoker vs. current or former smoker); current weight (measured in kg); pre-cancer weight; and presence of anorexia. We also assessed variables related to the tumor, including the histological type (e.g., adenocarcinoma, squamous cell carcinoma, and small cell carcinoma) and the presence of metastases, based on the 7th edition of the tumor-node-metastasis staging of lung cancer, categorized as intrathoracic metastases (stage M1A) or extrathoracic metastasis (stage M1B).

The instrument used in order to evaluate anorexia and weight loss consisted of the following questions: "Are you eating less because of decreased appetite?"; "What is your usual weight?"; "Have you lost weight recently without trying to do so?"; and, if so, "How much weight have you lost?"

Anorexia was defined above as a loss of appetite or a state of reduced calorie intake, whereas pre-treatment weight loss was defined as the involuntary loss of more than 2.4 kg[11] and estimated by the formula *pre-cancer weight* minus *weight at diagnosis*.

The patients were stratified by the presence/absence of anorexia and of pre-treatment weight loss. The stratification resulted in a four-category variable: no anorexia and no weight loss (the reference category); weight loss and no anorexia; anorexia and no weight loss; and anorexia plus weight loss.

Survival was defined as the time from the histological diagnosis to the final event. The final event was defined as all-cause mortality (date of death) or was censored if the patient was alive at the end of the study (30 December 2017) or at the date of the last contact, for patients who were lost to follow-up.

The *post hoc* calculation was performed to assess the power of the study by means of one-way ANOVA, with the program G*Power, version 3.1 (Heinrich Heine University, Düsseldorf, Germany). Considering the four categories of anorexia and weight loss as independent variables, an effect size of 0.29, and an alpha error of 5%, we obtained a power of 99% (with an estimated variation of 7.043 and an error of variance of 84.098) for identifying differences in survival among the categories with a sample of 552 patients.

Categorical variables are expressed as absolute and relative frequencies, evaluated by either the chi-square test or Fisher's exact test. Continuous variables are expressed as means ± standard deviations or as medians (interquartile ranges) and were analyzed by one-way ANOVA or the Kruskal-Wallis test and the Jonckheere-Terpstra test (for trend analysis). We performed univariate and multivariate analyses, using logistic regression to explore the associations between pre-treatment weight loss and the following (continuous, dichotomous, and categorical) variables: age; male gender (reference, female); current or former smoker (reference, never smoker); Karnofsky performance status (as a continuous variable); tumor size (as a continuous variable); the presence of anorexia (reference, no anorexia); stage M1B (reference, stage M1A), and histological type (adenocarcinoma, squamous cell, or small cell—reference, all other types). The univariate and multivariate analyses of independent risk factors for survival were assessed by Cox proportional hazards regression with stepwise selection. The final model was derived from the variables with $p < 0.10$ in the univariate analysis or of clinical relevance for the analysis of survival (age). Survival was analyzed with Kaplan-Meier curves, and the curves were compared by using the log-rank test. The statistical analysis was performed with the IBM SPSS Statistics program, version 19.0 (IBM Corporation, Armonk, NY, USA). For all statistical tests, the level of significance was set at 5%.

Table 1. Characteristics of patients with stage IV lung cancer (N = 552).[a]

Characteristics	Results
Age, years	65 [56-71.5]
Karnofsky performance status	80 [70-90]
Size of tumor, cm	5 [3.5-7.0]
Anorexia	216 (39.1)
Pre-treatment weight loss, kg	6.7 [0.0-13.1]
Gender	
Male	324 (58.7)
Female	228 (41.3)
Smoking history	
Never smoker	115 (20.8)
Current smoker	116 (21.0)
Former smoker	321 (58.2)
Histological type	
Adenocarcinoma	277 (50.2)
Squamous cell	168 (30.4)
Small cell	44 (8.0)
Other	63 (11.4)
Metastatic stage	
M1A	263 (47.6)
Lungs	143 (25.9)
Pleura	118 (21.4)
Pericardium	2 (0.4)
M1B	289 (52.4)
Adrenal	50 (9.1)
Brain	80 (14.5)
Liver	53 (9.6)
Bones	89 (16.1)
Other	17 (3.5)
Death	304 (55.1)
Overall survival, months	6.8 [2.8-13.1]

M1A: intrathoracic metastases; and M1B: extrathoracic metastases. [a]Values expressed as n (%) or median [interquartile range].

RESULTS

The prevalence of anorexia and unintentional pre-treatment weight loss in 552 patients with stage IV lung cancer was 39.1% and 70.1%, respectively. The median pre-treatment weight loss was 6.7 kg (interquartile range, 0.0-13.1 kg). Although we identified an association between anorexia and pre-treatment weight loss, the correlation coefficient can be considered low (0.305). Table 1 describes this and other variables related to the patients and tumors.

The variables related to the patients, the tumors, and overall survival were compared among the four categories (Table 2). It is of note that the proportion of patients with squamous cell carcinoma was more pronounced in the categories including the presence of pre-treatment weight loss. In addition, survival was shorter in patients with presence of anorexia and pre-treatment weight loss.

The logistic regression analysis of factors associated with pre-treatment weight loss is presented in Table 3. In the univariate analysis, age, male gender, Karnofsky performance status, tumor size, anorexia, and histological type were significant predictors of pre-treatment weight loss. After adjustments for age, male gender, Karnofsky performance status, and histological type, the presence of anorexia and the size of the tumor were significantly associated with pre-treatment weight loss.

Figure 1 shows the Kaplan-Meier survival curves as functions of the concomitant presence of anorexia and pre-treatment weight loss; the presence or absence of anorexia; and the presence or absence of pre-treatment weight loss.

In the univariate analysis of survival, the significant predictors of survival were male gender (p = 0.034), Karnofsky performance status (p < 0.001), and the concomitant presence of anorexia and weight loss (p <

Table 2. Characteristics of patients with stage IV lung cancer according to the combinations (categories) of anorexia and pre-treatment weight loss (N = 552).

Characteristics	Category				
	AN−/WL− n = 138 (25%)	AN−/WL+ n = 198 (36%)	AN+/WL− n = 27 (5%)	AN+/WL+ n = 189 (34%)	p
Age, years	62 [51-72]	65 [58-72]	65 [60-70]	64 [55-72]	ns*
Karnofsky performance status	80 [70-90]	80 [70-90]	70 [70-90]	70 [60-80]	< 0.001†§
Size of tumor, cm	4.5 [2.9-6.4]	5.2 [4.1-7.0]	4.0 [3.0-8.2]	4.2 [3.0-7.0]	ns†
Gender					
Male	73 (53)	118 (60)	14 (52)	119 (63)	ns‡
Female	65 (47)	80 (40)	13 (48)	70 (37)	
Smoking history					
Never smoker	30 (22)	38 (19)	7 (26)	40 (21)	
Current smoker	24 (21)	47 (41)	8 (30)	37 (20)	ns‡
Former smoker	84 (57)	113 (40)	12 (44)	112 (59)	
Histological type					
Adenocarcinoma	79 (57)	91 (46)	7 (26)	65 (34)	
Squamous	26 (19)	70 (35)	17 (56)	92 (49)	0,044‡ ??
Small cells	18 (13)	13 (7)	2 (7)	11 (6)	
Other	15 (11)	24 (12)	3 (11)	21 (11)	
Metastases					
M1A					ns‡
Lungs	40 (62)	45 (52)	8 (62)	50 (51)	
Pleura	25 (38)	42 (48)	5 (38)	46 (47)	
Pericardium	-	-	-	2 (2)	
M1B					ns‡
Adrenal	9 (12)	17 (15)	5 (36)	19 (21)	
Brain	26 (36)	33 (30)	-	21 (23)	
Liver	12 (16)	21 (19)	3 (21)	17 (19)	
Bones	19 (26)	35 (32)	6 (43)	29 (32)	
Other	7 (10)	5 (4)	-	5 (5)	
Mortality	80 (58)	96 (48)	13 (48)	115 (61)	ns‡
Overall survival, months	14.4 [12.4-16.4]	9.4 [7.1-11.7]	12.4 [5.5-19.4]	7.6 [5.9-9.2]	< 0.001†§

AN−: no anorexia; WL−: no weight loss; WL+: weight loss; AN+: anorexia; ns: not significant; M1A: intrathoracic metastases; and M1B: extrathoracic metastases. [a]Values expressed as n (%) or median [interquartile range]. *Univariate ANOVA. †Kruskal-Wallis test. ‡Chi-square test. §Jonckheere-Terpstra Test.

0.001). In the multivariate analysis, after adjustments for age, male gender, the concomitant presence of anorexia and pre-treatment weight loss, and low Karnofsky performance status were independent predictors of shorter survival (Table 4).

DISCUSSION

The present study investigated the prevalence of anorexia and pre-treatment weight loss, as well as their impact on prognosis, in patients with advanced lung cancer. We found that anorexia and weight loss at diagnosis were both highly prevalent among patients with stage IV lung cancer. The presence of anorexia and the size of the tumor were considered factors associated with pre-treatment weight loss, whereas being male, presenting concomitant anorexia and weight loss, and presenting a low Karnofsky performance status were independent predictors of mortality. In addition, the

Table 3. Unadjusted and adjusted logistic regression analysis of factors associated with pre-treatment weight loss in patients with stage IV lung cancer.*

Variables	Univariate analysis		Multivariate analysis	
	Unadjusted OR	p	Adjusted OR	p
Age, years	1.02	0.046	1.02	0.357
Male gender	1.42	0.063	0.95	0.873
Current or former smoker	1.15	0.548	-	-
Karnofsky performance status	0.97	< 0.001	0.98	0.167
Size of tumor, cm	1.12	0.077	1.14	0.049
Anorexia	4.88	< 0.001	6.09	0.001
M1B	0.91	0.980	-	-
Histological type		< 0.001		
Other	Ref.		Ref.	
Adenocarcinoma	0.78	0.414	0.51	0.285
Squamous cell	1.64	0.147	0.63	0.494
Small cell	0.48	0.075	0.36	0.222

Ref.: reference variable; and M1B: extrathoracic metastases. *−2 log likelihood of 197,380; overall accuracy of the model = 71.2%.

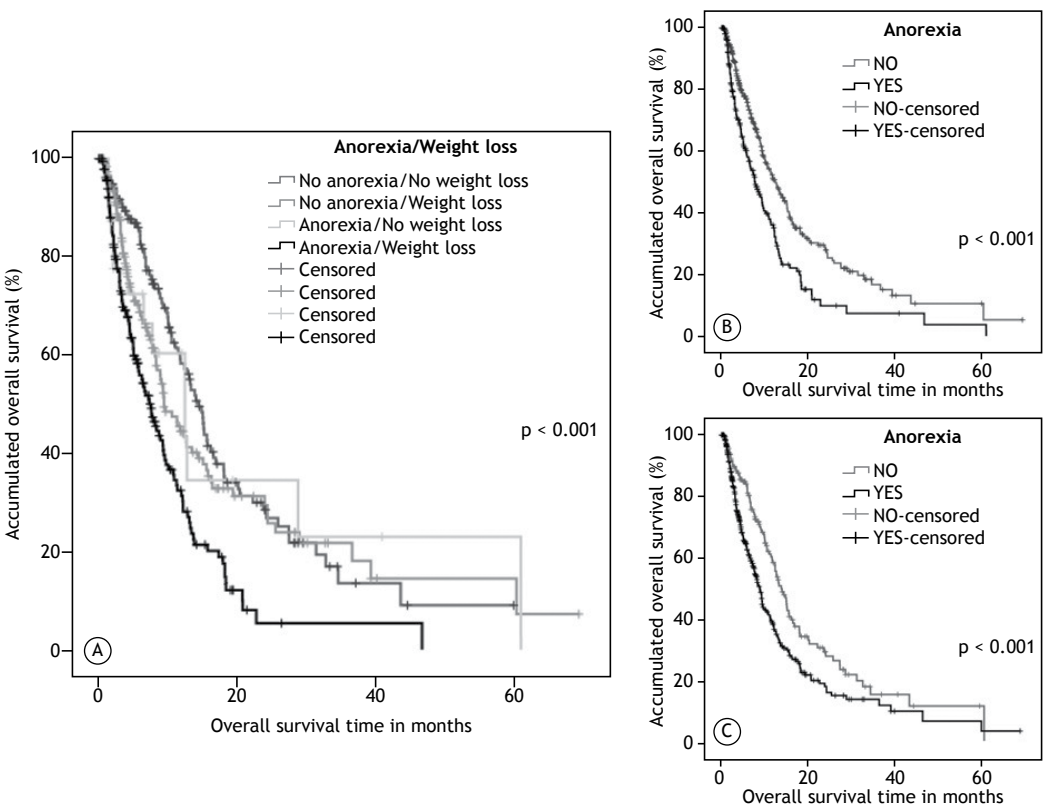


Figure 1. Overall survival in patients with stage IV lung cancer by category of anorexia and weight loss in concomitance (in A), presence or absence of pre-treatment anorexia (in B), and presence/absence of pre-treatment weight loss (in C).

Table 4. Unadjusted and adjusted Cox proportional hazards regression analysis of overall mortality in patients with stage IV lung cancer.*

Variables	Univariate analysis		Multivariate analysis	
	Unadjusted HR	p	Adjusted HR	p
Age, years	1.00	0.990	0.99	0.288
Male	1.28	0.034	1.31	0.021
Karnofsky performance status	0.97	< 0.001	0.97	< 0.001
Size of tumor, cm	0.99	0.743	-	-
Anorexia/weight loss		< 0.001		
AN−/WL−	Ref.		Ref.	
AN−/WL+	1.22	0.185	1.11	0.510
AN+/WL−	1.09	0.767	1.12	0.700
AN+/WL+	2.08	< 0.001	1.90	< 0.001
M1B	1.09	0.460	-	-
Histological type		0.380		
Other	Ref.		-	-
Adenocarcinoma	0.20	0.250	-	-
Squamous cell	0.00	0.980	-	-
Small cell	1.18	0.905	-	-

HR: hazard ratio; AN−: no anorexia; WL−: no weight loss; WL+: weight loss; AN+: anorexia; Ref.: reference variable; and M1B: extrathoracic metastases. *−2 log likelihood of 3148.004.

presence of anorexia and pre-treatment weight loss were both strongly associated with shorter survival.

In our sample, the prevalence of anorexia at diagnosis was approximately 40%. Other studies have shown that anorexia is a common symptom in the scenario of advanced disease and is often accompanied by weight loss.[5,16] However, in our study, pre-treatment weight loss was present in nearly two times as many patients than was anorexia.

Two different factors contribute to explaining the weight loss and decreased appetite in patients with advanced lung cancer. First, the shock of receiving the diagnosis of lung cancer, especially if the cancer has metastasized, can reduce the desire for food. Second, the inflammatory response caused by the tumor can lead to changes in hypothalamic function, with an impact on appetite.[17-19] Even though the correlation between anorexia and weight loss in our study was low, anorexia and the size of the tumor were found to be major determinants of the intensity of pre-treatment weight loss.

The presence of anorexia or weight loss in patients with advanced lung cancer is not a new finding.[12,20-22] However, we have demonstrated that the concomitance of these conditions is an important predictor of shorter survival. Other studies have shown that the presence of these symptoms may result in complications, including reduced tolerance to chemotherapy, as well as decreased mobility and functionality, leading to a worse quality of life and a consequent reduction of survival.[23,24] Therefore, the appropriate management of this clinical condition is probably the key to holistic care in this context.

It is noteworthy that the size of the tumor did not influence mortality in our sample of patients. Therefore, we can speculate that death can be associated not only with the size of the tumor but also, more particularly, with the interactions between the primary tumor and the adjacent vital structures, as well as with distant metastases.[25]

Our study has some limitations. Because of the retrospective and observational nature of the analysis, some data to supplement or explain the results were not available, such as those related to the measurement of inflammatory markers, immunological markers, metabolic markers, and muscle mass. It is recognized that the measurement of weight does not differentiate between lean and fat mass; therefore, patients with sarcopenic obesity might have been overlooked.[2,10,12,13] Finally, we recognize that the pre-cancer weight was self-reported, which could have introduced a memory bias.

In conclusion, the present study demonstrated that anorexia and pre-treatment weight loss are relevant factors in the follow-up of patients with advanced (stage IV) lung cancer, and that this combination was associated with higher mortality. Specific interventions are of crucial importance in individualized treatment plans, even within the context of palliative care.

REFERENCES

1. Kimura M, Naito T, Kenmotsu H, Taira T, Wakuda K, Oyakawa T, et al. Prognostic impact of cancer cachexia in patients with advanced non-small cell lung cancer. Support Care Cancer. 2015;23(6):1699-1708. https://doi.org/10.1007/s00520-014-2534-3
2. Aapro M, Arends J, Bozzetti F, Fearon K, Grunberg SM, Herrstedt J, et al. Early recognition of malnutrition and cachexia in the cancer

patient: a position paper of a European School of Oncology Task Force. Ann Oncol. 2014;25(8):1492-1499. https://doi.org/10.1093/annonc/mdu085

3. Dans M, Smith T, Back A, Baker JN, Bauman JR, Beck AC, et al. NCCN Guidelines Insights: Palliative Care, Version 2.2017. J Natl Compr Canc Netw. 2017;15(8):989-997. https://doi.org/10.6004/jnccn.2017.0132
4. Muscaritoli M, Lucia S, Farcomeni A, Lorusso V, Saracino V, Barone C, et al. Prevalence of malnutrition in patients at first medical oncology visit: the PreMiO study. Oncotarget. 2017;8(45):79884-79896. https://doi.org/10.18632/oncotarget.20168
5. Zhu R, Liu Z, Jiao R, Zhang C, Yu Q, Han S, et al. Updates on the pathogenesis of advanced lung cancer-induced cachexia. Thorac Cancer. 2019;10(1):8-16. https://doi.org/10.1111/1759-7714.12910
6. Morel H, Raynard B, d'Arlhac M, Hauss PA, Lecuyer E, Oliviero G, et al. Prediagnosis weight loss, a stronger factor than BMI, to predict survival in patients with lung cancer. Lung Cancer. 2018;126:55-63. https://doi.org/10.1016/j.lungcan.2018.07.005
7. LeBlanc TW, Samsa GP, Wolf SP, Locke SC, Cella DF, Abernethy AP. Validation and real-world assessment of the Functional Assessment of Anorexia-Cachexia Therapy (FAACT) scale in patients with advanced non-small cell lung cancer and the cancer anorexia-cachexia syndrome (CACS). Support Care Cancer. 2015;23(8):2341-2347. https://doi.org/10.1007/s00520-015-2606-z
8. Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss [published correction appears in J Clin Oncol. 2015 Mar 1;33(7):814]. J Clin Oncol. 2015;33(1):90-99. https://doi.org/10.1200/JCO.2014.56.1894
9. Mohan A, Singh P, Kumar S, Mohan C, Pathak AK, Pandey RM, et al. Effect of change in symptoms, respiratory status, nutritional profile and quality of life on response to treatment for advanced non-small cell lung cancer. Asian Pac J Cancer Prev. 2008;9(4):557-562. https://doi.org/10.1378/chest.132.4_MeetingAbstracts.589
10. Sánchez-Lara K, Turcott JG, Juárez E, Guevara P, Núñez-Valencia C, Oñate-Ocaña LF, et al. Association of nutrition parameters including bioelectrical impedance and systemic inflammatory response with quality of life and prognosis in patients with advanced non-small-cell lung cancer: a prospective study. Nutr Cancer. 2012;64(4):526-534. https://doi.org/10.1080/01635581.2012.668744
11. Wong CJ. Involuntary weight loss. Med Clin North Am. 2014;98(3):625-643. https://doi.org/10.1016/j.mcna.2014.01.012
12. Bye A, Sjoblom B, Wentzel-Larsen T, Gronberg BH, Baracos VE, Hjermstad MJ, et al. Muscle mass and association to quality of life in non-small cell lung cancer patients. J Cachexia Sarcopenia Muscle. 2017;8(5):759-767. https://doi.org/10.1002/jcsm.12206
13. Scott HR, McMillan DC, Brown DJ, Forrest LM, McArdle CS, Milroy R. A prospective study of the impact of weight loss and the systemic inflammatory response on quality of life in patients with inoperable non-small cell lung cancer. Lung Cancer. 2003;40(3):295-299. https://doi.org/10.1016/S0169-5002(03)00077-1
14. O'Donoghue N, Shrotriya S, Aktas A, Hullihen B, Ayvaz S, Estfan B, et al. Clinical significance of weight changes at diagnosis in solid tumours. Support Care Cancer. 2019;27(7):2725-2733. https://doi.org/10.1007/s00520-018-4551-0
15. LeBlanc TW, Nipp RD, Rushing CN, Samsa GP, Locke SC, Kamal AH, et al. Correlation between the international consensus definition of the Cancer Anorexia-Cachexia Syndrome (CACS) and patient-centered outcomes in advanced non-small cell lung cancer. J Pain Symptom Manage. 2015;49(4):680-689. https://doi.org/10.1016/j.jpainsymman.2014.09.008
16. Patel JD, Pereira JR, Chen J, Liu J, Guba SC, John WJ, et al. Relationship between efficacy outcomes and weight gain during treatment of advanced, non-squamous, non-small-cell lung cancer patients. Ann Oncol. 2016;27(8):1612-1619. https://doi.org/10.1093/annonc/mdw211
17. Blauwhoff-Buskermolen S, Ruijgrok C, Ostelo RW, de Vet HCW, Verheul HMW, de van der Schueren MAE, et al. The assessment of anorexia in patients with cancer: cut-off values for the FAACT-A/CS and the VAS for appetite. Support Care Cancer. 2016;24(2):661-666. https://doi.org/10.1007/s00520-015-2826-2
18. Laviano A, Meguid MM, Rossi-Fanelli F. Cancer anorexia: clinical implications, pathogenesis, and therapeutic strategies. Lancet Oncol. 2003;4(11):686-694. https://doi.org/10.1016/S1470-2045(03)01247-6
19. Argilés JM, Busquets S, Toledo M, López-Soriano FJ. The role of cytokines in cancer cachexia. Curr Opin Support Palliat Care. 2009;3(4):263-268. https://doi.org/10.1097/SPC.0b013e3283311d09
20. Masel EK, Berghoff AS, Füreder LM, Heicappell P, Schlieter F, Widhalm G, et al. Decreased body mass index is associated with impaired survival in lung cancer patients with brain metastases: A retrospective analysis of 624 patients. Eur J Cancer Care (Engl). 2017;26(6):10.1111/ecc.12707. https://doi.org/10.1111/ecc.12707
21. Watte G, Nunes CHA, Sidney-Filho LA, Zanon M, Altmayer SPL, Pacini GS, et al. Proportional weight loss in six months as a risk factor for mortality in stage IV non-small cell lung cancer. J Bras Pneumol. 2018;44(6):505-509. https://doi.org/10.1590/s1806-37562018000000023
22. Bowden JCS, Williams LJ, Simms A, Price A, Campbell S, Fallon MT, et al. Prediction of 90 Day and Overall Survival after Chemoradiotherapy for Lung Cancer: Role of Performance Status and Body Composition. Clin Oncol (R Coll Radiol). 2017;29(9):576-584.
23. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Cancer: disease and nutrition are key determinants of patients' quality of life. Support Care Cancer. 2004;12(4):246-252. https://doi.org/10.1007/s00520-003-0568-z
24. Teunissen SC, Wesker W, Kruitwagen C, de Haes HC, Voest EE, de Graeff A. Symptom prevalence in patients with incurable cancer: a systematic review. J Pain Symptom Manage. 2007;34(1):94-104. https://doi.org/10.1016/j.jpainsymman.2006.10.015
25. Nichols L, Saunders R, Knollmann FD. Causes of death of patients with lung cancer. Arch Pathol Lab Med. 2012;136(12):1552-1557. https://doi.org/10.5858/arpa.2011-0521-OA

J Bras Pneumol. 2020;46(4):e20180294
https://dx.doi.org/10.36416/1806-3756/e20180294

ORIGINAL ARTICLE

Effectiveness of a multistep *Pseudomonas aeruginosa* eradication treatment protocol in children with cystic fibrosis in Brazil

Barbara Riquena[1], Luiz Vicente Ribeiro Ferreira da Silva Filho[1,2], Cleyde Myriam Aversa Nakaie[1], Marina Buarque de Almeida[1], Joaquim Carlos Rodrigues[1], Fabíola Villac Adde[1]

1. Unidade de Pneumologia, Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Unidade de Pneumologia, Hospital Israelita Albert Einstein, São Paulo (SP) Brasil.

Submitted: 23 September 2018.
Accepted: 21 June 2019.

Study carried out in the Unidade de Pneumologia, Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: Although various strategies have been proposed for eradicating *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF), only a few employ multistep treatment in children colonized by that pathogen for the first time. The aim of this study was to describe the effectiveness of a three-phase eradication protocol, initiated after the first isolation of *P. aeruginosa*, in children with CF in Brazil. **Methods:** This was a retrospective real-life study in which we reviewed the medical records of pediatric CF patients in whom the eradication protocol was applied between June of 2004 and December of 2012. The three-phase protocol was guided by positive cultures for *P. aeruginosa* in airway secretions, and the treatment consisted of inhaled colistimethate and oral ciprofloxacin. Success rates were assessed after each phase, as well as cumulatively. **Results:** During the study period, 47 episodes of *P. aeruginosa* colonization, in 29 patients, were eligible for eradication. Among the 29 patients, the median age was 2.7 years, 17 (59%) were male, and 19 (65%) had at least one *F508del* allele. All 29 patients completed the first phase of the protocol, whereas only 12 and 6 completed the second and third phases, respectively. Success rates for eradication in the three treatment phases were 58.6% (95% CI: 40.7-74.5), 50.0% (95% CI: 25.4-74.6), and 66.7% (95% CI: 30.0-90.3), respectively. The cumulative success rate was 93.1% (95% CI: 78.0-98.1). Treatment failure in all three phases occurred in only 2 patients. **Conclusions:** In this sample of patients, the multistep eradication protocol was effective and had a high success rate.

Keywords: Cystic fibrosis/therapy; Cystic fibrosis/prevention & control; Pseudomonas aeruginosa; Treatment outcome.

INTRODUCTION

Chronic pulmonary infection with *Pseudomonas aeruginosa* is associated with high morbidity and mortality in patients with cystic fibrosis (CF).[1] *P. aeruginosa* is the most prevalent pathogen causing severe lung disease in patients with CF.[2] *P. aeruginosa* infection can occur very early in life,[1,3-5] the risk of death being 2.6 times higher in CF patients infected with *P. aeruginosa* in the first 5 years of life.[6] Once chronic infection is established, *P. aeruginosa* is virtually impossible to eradicate; therefore, early intervention is mandatory.[1,7]

Several antibiotic strategies for *P. aeruginosa* eradication have been proposed in recent years.[8] Most include inhaled antibiotic therapy in isolation or in combination with systemic antibiotic therapy, and multistep eradication approaches are rarely used. In addition, despite evidence that early eradication of *P. aeruginosa* is beneficial, there are few reports of CF patients receiving eradication treatment upon first isolation of *P. aeruginosa*. Most studies include CF patients with a prior positive airway culture for *P. aeruginosa*.[8] It should be noted that there is currently no standard eradication treatment or evidence that a particular treatment is superior to other treatments.[7]

In 2004, the CF center of the University of São Paulo School of Medicine Hospital das Clínicas Institute for Children, located in the city of São Paulo, Brazil, adopted a multistep *P. aeruginosa* eradication protocol guided by positive cultures for *P. aeruginosa* in airway secretions routinely collected from patients (Figure 1). It is expected that the use of systematic treatment protocols can eradicate initial colonization of the respiratory tract by *P. aeruginosa* in CF patients. A multistep approach is used in order to increase the chance of eradication in cases of new *P. aeruginosa* colonization, through long-term treatment for persistent or early recurrent infection. The objective of the present study was to describe the effectiveness of the multistep eradication protocol used in our institution.

METHODS

Study design

This was a real-life retrospective cohort study with prospective outcome assessment. Data were collected from the medical records of pediatric patients (under 18 years of age) followed at the CF Outpatient Clinic of the University of São Paulo School of Medicine *Hospital das*

Correspondence to:
Barbara Riquena. Unidade de Pneumologia, ICr-HC-FMUSP, Avenida Dr. Enéas de Carvalho Aguiar, 647, Cerqueira César, CEP 05403-000, São Paulo, SP, Brasil.
Tel.: 55 11 2661-8500. E-mail: barbara.riquena@gmail.com
Financial support: None.

ISSN 1806-3713

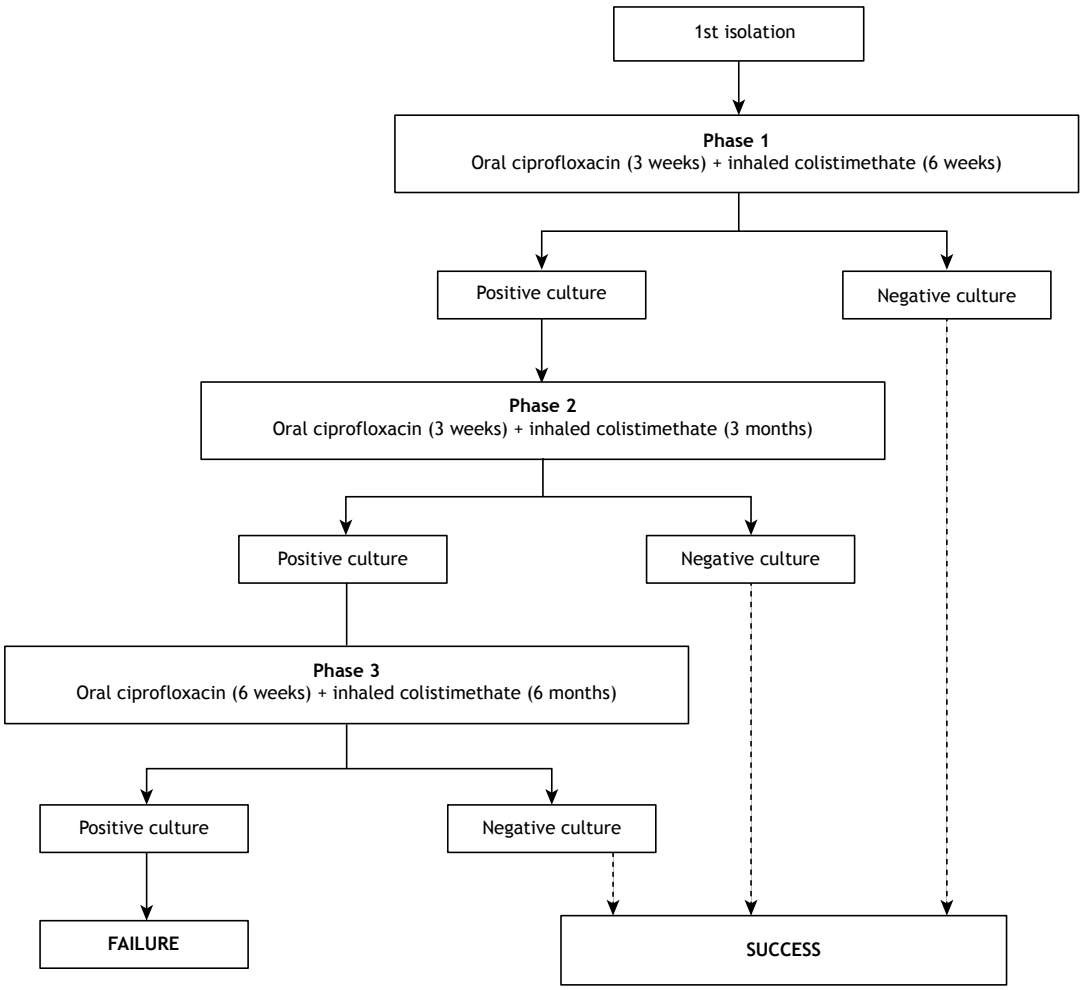


Figure 1. Multistep *Pseudomonas aeruginosa* eradication protocol. Oral ciprofloxacin (25-50 mg/kg/day up to a maximum of 1,500 mg/day, 12/12 h). Inhaled colistimethate (1,000,000 IU, 12/12 h). Patients with pulmonary exacerbations requiring hospitalization received intravenous systemic antibiotics (ceftazidime, 150 mg/kg/day up to a maximum of 9 g/day, 8/8 h, and amikacin, 20 mg/kg/day, 24/24 h), without changes in the inhaled antibiotic regimen.

Clínicas Institute for Children between June of 2004 and December of 2012. The inclusion criteria were as follows: having undergone at least four cultures of airway secretions (oropharyngeal secretions, sputum, or bronchoalveolar lavage fluid) over a 12-month period; having acquired *P. aeruginosa* for the first time; and having undergone our multistep eradication protocol (Figure 2). The study was approved by the Research Ethics Committee of the University of São Paulo School of Medicine *Hospital das Clínicas* (Ruling no. 1175/24/2014).

Multistep eradication protocol

Figure 1 shows a flow chart of our multistep *P. aeruginosa* eradication protocol. Patients with first *P. aeruginosa* isolation were eligible for eradication treatment. Patients were instructed to undergo culture of airway secretions 1-2 weeks after each treatment phase. Patients with a positive culture for *P. aeruginosa* moved on to the second phase of treatment. Those with a positive culture for *P. aeruginosa* after the second phase of treatment moved on to the third. Cases of patients with a negative culture for *P. aeruginosa* after the third phase of treatment were considered to be cases of successful eradication, whereas those of those with a positive culture were considered to be cases of eradication failure.

Variables and outcomes

The efficacy of the eradication protocol was evaluated on the basis of culture results after each phase of treatment, a negative culture for *P. aeruginosa* indicating treatment success and a positive culture for *P. aeruginosa* indicating treatment failure.

Clinical and epidemiological data were collected from medical records during routine patient visits. The body mass index was calculated and converted to a z-score by the WHO Anthro Survey Analyser (World Health Organization, Geneva, Switzerland) for children ≤ 5 years of age or by the WHO AnthroPlus software for those > 5 years of age.[9] The Shwachman-Kulczycki score[10] assesses disease severity by scores for physical

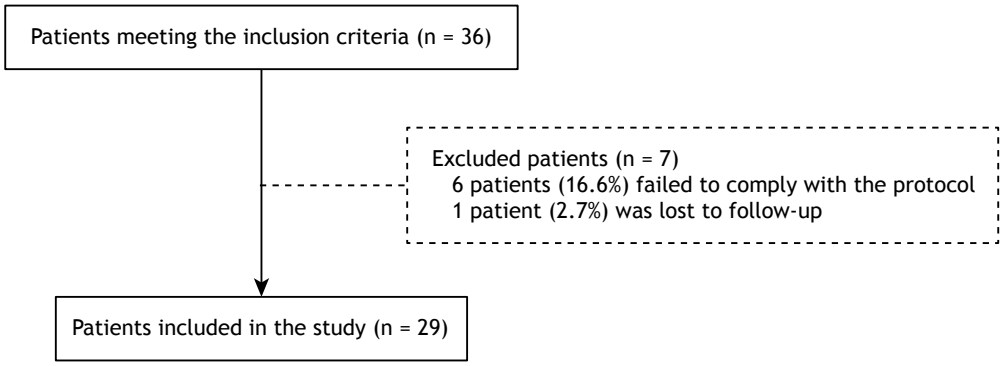


Figure 2. Flow chart of the sample selection process. Pa: *Pseudomonas aeruginosa*.

activity, changes in pulmonary propedeutics, nutritional status, and chest X-ray findings, being measured annually in accordance with the institutional protocol.

Statistical analysis

Success rates were assessed after each phase, as well as cumulatively, by dividing the number of negative cultures by the number of patients treated in each phase. Descriptive statistics were calculated, including measures of central tendency, measures of dispersion (interquartile range—IQR—and 95% CI), and proportions.

RESULTS

Twenty-nine patients were included in the study. Their clinical and epidemiological characteristics are described in Table 1. It is noteworthy that the first colonization by *P. aeruginosa* occurred in preschoolers, most being male.

During the 8.5-year study period, 47 episodes of *P. aeruginosa* colonization, in 29 patients, were eligible for eradication. Of those 47 episodes, 13 (27.7%) were accompanied by pulmonary exacerbations, with hospitalization and intravenous antibiotics being required in only 5.

Of the 47 episodes of *P. aeruginosa* isolation eligible for eradication, 87.2% were episodes of colonization with nonmucoid strains. The mean number of cultures of airway secretions over the course of 12 months was 7 ± 2, and most (75%) of the cultures were cultures of oropharyngeal secretions. The median time elapsed between the end of eradication treatment phase 1 and culture of airway secretions was 16 days (IQR: 6-28 days). The median time elapsed between the end of eradication treatment phase 2 and culture of airway secretions was 35 days (IQR: 14-43 days). The median time elapsed between the end of eradication treatment phase 3 and culture of airway secretions was 43 days (IQR: 31-63 days).

All of the patients included in the present study completed the first phase of the eradication protocol. Eradication was successful in 17, whereas 12 moved on to the second phase of treatment because of a positive culture for *P. aeruginosa* after the first phase. Of those 12 patients, 6 achieved eradication and 6 moved on to the third phase of treatment. Of those 6 patients, 4 achieved eradication and 2 did not (Figure 3). Success rates for eradication in the three treatment phases were 58.6% (95% CI: 40.7-74.5), 50.0% (95% CI: 25.4-74.6), and 66.7% (95% CI: 30.0-90.3), respectively. The cumulative success rate was 93.1% (95% CI: 78.0-98.1).

DISCUSSION

To our knowledge, ours is the first study to evaluate a *P. aeruginosa* eradication protocol in pediatric CF patients in Brazil. Our multistep eradication protocol in pediatric CF patients in Brazil. Our multistep eradication protocol was found to be effective in a real-life setting, with a high (93%) success rate. This finding shows that a multistep approach is a therapeutic strategy that can increase the success rate of eradication. However, the success rate after the first phase of treatment was approximately 60%, which is lower than that recently reported in the literature.[4,5,11] The reason for this is unknown.

In contrast to most eradication protocols, ours was initiated after the first isolation of *P. aeruginosa*. Other studies have included pediatric CF patients previously infected with *P. aeruginosa* and generally older than those in our sample.[1,3,6,7,10-12] A minority received intravenous antibiotic therapy for pulmonary exacerbation at the time of *P. aeruginosa* eradication. We believe that this had no impact on treatment efficacy, given that there is no evidence in the literature that parenteral treatment increases the success of *P. aeruginosa* eradication.[7] The patients included in our study were younger than those in other studies; their median age was 2.7 years, whereas, in other studies, mean ages were 5.5 years[11] and 9 years.[4] This might explain the high success rate in our study, given that structural airway disease is less severe in younger populations. This shows the need for early therapeutic intervention to maximize the chance of success.

Although eradication of *P. aeruginosa* is a well-established treatment, there is insufficient evidence regarding the best approach.[13] There are few studies evaluating the effectiveness of multistep eradication

Table 1. Clinical and laboratory characteristics of patients in each treatment phase.[a]

Parameter	Phase 1 (n = 29)	Phase 2 (n = 12)	Phase 3 (n = 6)
Female sex	12 (41.4)	8 (66.7)	4 (66.7)
Age, years	2.7 (0.9-5.3)	3.6 (1.9-5.8)	3.8 (2.6-4.5)
BMI, z-score	−0.4 (−1.0 to −0.7)	−0.4 (−0.8 to −0.9)	−1.2 (−1.6 to −1.1)
Genotype, %			
Heterozygous *F508del*	13 (44.8)	4 (33.3)	2 (33.3)
Homozygous *F508del*	6 (20.7)	4 (33.3)	1 (16.7)
Other mutations	10 (34.5)	4 (33.3)	3 (50.0)
Shwachman-Kulczycki score	85.0 (85.0-90.0)	77.5 (72.5-90.0)	72.5 (60.0-82.5)
Pulmonary exacerbation of CF	9 (31.0)	4 (33.3)	1 (16.7)
Coinfection			
Staphylococcus aureus	8 (27.6)	5 (41.7)	2 (33.3)
MRSA	1 (3.4)	1 (8.3)	0 (0.0)
Burkholderia cepacia complex	1 (3.4)	2 (16.7)	0 (0.0)
Pancreatic status			
Pancreatic insufficiency	26 (86.2)	11 (91.7)	5 (83.3)
Use of inhaled medications			
3% NaCl	1 (3.4)	0 (0.0)	0 (0.0)
Dornase alfa	3 (10.3)	1 (8.3)	0 (0.0)
Short-acting β_2 agonist	4 (13.8)	1 (8.3)	1 (16.7)

BMI: body mass index; CF: cystic fibrosis; and MRSA: methicillin-resistant *Staphylococcus aureus*. [a]Values expressed as n (%) or median (interquartile range).

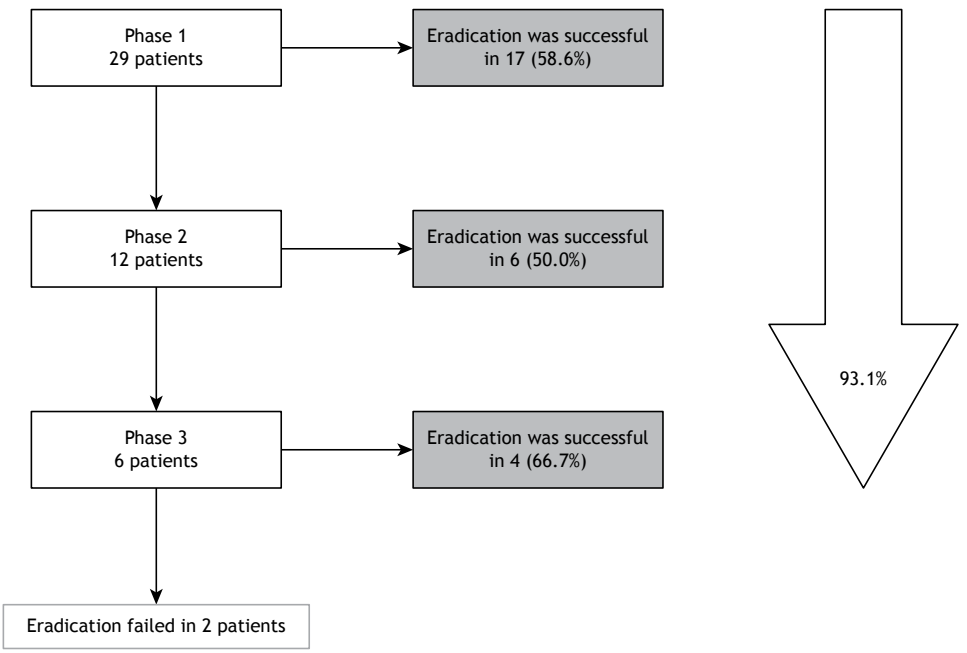


Figure 3. Description of the effectiveness of the eradication protocol (cumulative success rate, 93.1%; 95% CI: 78.0-98.1).

approaches. A CF center in Denmark was the first to publish the results of implementing a multistep protocol for early treatment of *P. aeruginosa* colonization. Patients were treated with nebulized colistimethate and oral ciprofloxacin; drug dose and treatment duration varied across treatment phases, with a maximum duration of 3 months, resulting in a success rate of 78% and improved lung function in the treated patients.[6] In a study conducted in Italy,[14] 173 patients received a multistep eradication treatment with nebulized colistimethate and oral ciprofloxacin for 3 weeks in the first phase. In the second phase, patients received double the dose of colistimethate, which was used for 3 months in those who moved on to the third phase of treatment. The success rate was 81%, with a median time of 18 months between eradication and new *P. aeruginosa* acquisition.[14] In a recently published study conducted at a CF center in

Canada, the effectiveness of a multistep eradication treatment protocol was evaluated.[4] The protocol was based on culture results and the presence of symptoms, with up to three phases of treatment with nebulized tobramycin for 28 days, with or without an intravenous antibiotic. The cumulative success rate was 88%.[4] These results, as well as those of the present study, show that a multistep eradication protocol for *P. aeruginosa* has a high success rate.

Although nebulized colistimethate is commonly used in combination with oral ciprofloxacin for *P. aeruginosa* eradication,[10] the role that nebulized antibiotic alone plays in eradicating *P. aeruginosa* has recently been highlighted, and there is a trend toward reducing the duration of eradication therapy.[7] A large, four-arm randomized clinical trial conducted in the USA was published in 2011,[11] involving 304 CF patients (mean age, 5.5 years) and lasting 18 months. Patients were divided into two groups: one group received cycled therapy every 3 months, regardless of follow-up culture results, and the other received culture-based therapy. The two groups of patients received eradication therapy with nebulized tobramycin for 28 days, with oral ciprofloxacin or oral placebo for 14 days. No difference in the rate of exacerbation or prevalence of *P. aeruginosa* positivity was detected between the two groups. According to the authors, the addition of oral ciprofloxacin produced no benefits and therapy should be guided by culture results.[11] In a study comparing the efficacy and safety of 28 days and 56 days of nebulized tobramycin for the treatment of early onset *P. aeruginosa* infection in CF patients,[5] it was shown that 93% and 92% of the patients were free of *P. aeruginosa* infection 1 month after the end of treatment for 28 days and 56 days, respectively, and that the median time to recurrence of *P. aeruginosa* was similar between the two groups (6-9 months vs. 9-12 months). The authors found that treatment with nebulized tobramycin for 56 days was not superior to treatment with nebulized tobramycin for 28 days.[5] These findings support the use of inhaled antibiotics for 28 days and suggest that the use of an inhaled antibiotic in combination with ciprofloxacin be considered on a case-by-case basis (e.g., in patients with pulmonary exacerbations and first-ever isolation of *P. aeruginosa*).

In European countries, colistimethate is the most commonly used inhaled antibiotic therapy for *P. aeruginosa* eradication,[6,7,13,15] whereas, in North America, tobramycin is.[4,5,11] In a multicenter randomized controlled clinical trial conducted at a CF center in Belgium and including more than 200 patients, eradication therapy with nebulized tobramycin + oral ciprofloxacin was compared with eradication therapy with nebulized colistimethate + oral ciprofloxacin for 28 days, treatment success rates being similar between the two strategies (63% and 65%, respectively).[3] In a study including 105 CF patients and comparing nebulized tobramycin for 28 days with nebulized colistimethate + oral ciprofloxacin for 3 months, the two eradication regimens were shown to be equivalent (eradication rate, 80% vs. 90%).[1] The Brazilian guidelines for the diagnosis and treatment of CF recommend the use of inhaled tobramycin for 28 days as the treatment of first choice, inhaled colistimethate with oral ciprofloxacin for 2-3 weeks being recommended as an alternative treatment option.[16] Therefore, the two inhaled antibiotic therapies are effective in eradicating *P. aeruginosa*, with the choice being based on drug availability and patient tolerance.

The limitations of our study include the retrospective design based on medical record review, which precludes the analysis of data on treatment adherence and correct medication use. However, this probably had little impact on our results, because the eradication rate was high. Another limitation is that lung function was not assessed given the young age of the study population, although it would have shown interesting data. Despite this limitation, the study included patients with first *P. aeruginosa* isolation, thus producing a sample that was more homogeneous and providing important real-life information.

The criterion for successful eradication in the present study was a negative culture for *P. aeruginosa* after the end of each treatment phase. It is known that the primary goal of eradication treatment is to achieve a sustained response (i.e., at least 6 months without *P. aeruginosa* isolation). However, this was not evaluated in our study, meaning that the eradication success rate might have been overestimated.

In conclusion, our multistep *P. aeruginosa* eradication protocol appears to be effective in very young CF patients with first *P. aeruginosa* isolation, with a success rate of 93%. Although many studies have described one-step eradication protocols, the present study demonstrated in a real-life setting that a multistep eradication protocol is effective and sometimes necessary. Larger, long-term multicenter studies with comparator arms evaluating first *P. aeruginosa* colonization are needed in order to identify the best treatment regimen for *P. aeruginosa* eradication and the best intervention in cases of failure.

ACKNOWLEDGMENTS

We would like to thank Dr. Claudio Leone for his invaluable aid in evaluating the study results; Dr. Luísa Nunes for providing patient genetic data; and the staff in the Department of Medical Archives of the University of São Paulo School of Medicine *Hospital das Clínicas* Institute for Children, whose help was essential to complete this study.

REFERENCES

1. Taccetti G, Bianchini E, Cariani L, Buzzetti R, Costantini D, Trevisan F, et al. Early antibiotic treatment for Pseudomonas aeruginosa eradication in patients with cystic fibrosis: a randomised multicentre study comparing two different protocols. Thorax. 2012;67(10):853-

859. https://doi.org/10.1136/thoraxjnl-2011-200832

2. Li Z, Kosorok MR, Farrell PM, Laxova A, West SE, Green CG, et al. Longitudinal development of mucoid Pseudomonas aeruginosa infection and lung disease progression in children with cystic fibrosis. JAMA. 2005;293(5):581-588. https://doi.org/10.1001/jama.293.5.581
3. Proesmans M, Vermeulen F, Boulanger L, Verhaegen J, De Boeck K. Comparison of two treatment regimens for eradication of Pseudomonas aeruginosa infection in children with cystic fibrosis. J Cyst Fibros. 2013;12(1):29-34. https://doi.org/10.1016/j.jcf.2012.06.001
4. Blanchard AC, Horton E, Stanojevic S, Taylor L, Waters V, Ratjen F. Effectiveness of a stepwise Pseudomonas aeruginosa eradication protocol in children with cystic fibrosis. J Cyst Fibros. 2017;16(3):395-400. https://doi.org/10.1016/j.jcf.2017.01.007
5. Ratjen F, Munck A, Kho P, Angyalosi G; ELITE Study Group. Treatment of early Pseudomonas aeruginosa infection in patients with cystic fibrosis: the ELITE trial. Thorax. 2010;65(4):286-291. https://doi.org/10.1136/thx.2009.121657
6. Frederiksen B, Koch C, Høiby N. Antibiotic treatment of initial colonization with Pseudomonas aeruginosa postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. Pediatr Pulmonol. 1997;23(5):330-335. https://doi.org/10.1002/(SICI)1099-0496(199705)23:5<330::AID-PPUL4>3.0.CO;2-O
7. Langton Hewer SC, Smyth AR. Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis. Cochrane Database Syst Rev. 2017;4(4):CD004197. https://doi.org/10.1002/14651858.CD004197.pub5
8. Schelstraete P, Haerynck F, Van daele S, Deseyne S, De Baets F. Eradication therapy for Pseudomonas aeruginosa colonization episodes in cystic fibrosis patients not chronically colonized by P. aeruginosa. J Cyst Fibros. 2013;12(1):1-8. https://doi.org/10.1016/j.jcf.2012.07.008
9. World Health Organization [homepage on the Internet]. Geneve: World Health Organization; [cited 2019 May 6]. WHO Anthro Survey Analyser and other tools [about 2 screens]. Available from: https://www.who.int/childgrowth/software/en/
10. SHWACHMAN H, KULCZYCKI LL. Long-term study of one hundred five patients with cystic fibrosis; studies made over a five- to fourteen-year period. AMA J Dis Child. 1958;96(1):6-15. https://doi.org/10.1001/archpedi.1958.02060060008002
11. Treggiari MM, Retsch-Bogart G, Mayer-Hamblett N, Khan U, Kulich M, Kronmal R, et al. Comparative efficacy and safety of 4 randomized regimens to treat early Pseudomonas aeruginosa infection in children with cystic fibrosis. Arch Pediatr Adolesc Med. 2011;165(9):847-856. https://doi.org/10.1001/archpediatrics.2011.136
12. Mayer-Hamblett N, Kloster M, Rosenfeld M, Gibson RL, Retsch-Bogart GZ, Emerson J, et al. Impact of Sustained Eradication of New Pseudomonas aeruginosa Infection on Long-term Outcomes in Cystic Fibrosis. Clin Infect Dis. 2015;61(5):707-715. https://doi.org/10.1093/cid/civ377
13. Littlewood JM, Miller MG, Ghoneim AT, Ramsden CH. Nebulised colomycin for early pseudomonas colonisation in cystic fibrosis. Lancet. 1985;1(8433):865. https://doi.org/10.1016/S0140-6736(85)92222-6
14. Taccetti G, Campana S, Festini F, Mascherini M, Döring G. Early eradication therapy against Pseudomonas aeruginosa in cystic fibrosis patients. Eur Respir J. 2005;26(3):458-461. https://doi.org/10.1183/09031936.05.00009605
15. Valerius NH, Koch C, Høiby N. Prevention of chronic Pseudomonas aeruginosa colonisation in cystic fibrosis by early treatment. Lancet. 1991;338(8769):725-726. https://doi.org/10.1016/0140-6736(91)91446-2
16. Athanazio RA, Silva Filho LVRF, Vergara AA, Ribeiro AF, Riedi CA, Procianoy EFA, et al. Brazilian guidelines for the diagnosis and treatment of cystic fibrosis. J Bras Pneumol. 2017;43(3):219-245. https://doi.org/10.1590/s1806-37562017000000065

J Bras Pneumol. 2020;46(4):e20190005
https://dx.doi.org/10.36416/1806-3756/e20190005

ORIGINAL ARTICLE

Mechanical ventilation weaning practices in neonatal and pediatric ICUs in Brazil: the Weaning Survey-Brazil

Suzi Laine Longo dos Santos Bacci[1], Cíntia Johnston[2], Wallisen Tadashi Hattori[3], Janser Moura Pereira[4], Vívian Mara Gonçalves de Oliveira Azevedo[1,5]

1. Programa de Pós-Graduação em Ciências da Saúde, Faculdade de Medicina, Universidade Federal de Uberlândia, Uberlândia (MG) Brasil.
2. Departamento de Pediatria, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
3. Departamento de Saúde Coletiva, Faculdade de Medicina, Universidade Federal de Uberlândia, Uberlândia (MG) Brasil.
4. Faculdade de Matemática, Universidade Federal de Uberlândia, Uberlândia (MG) Brasil.
5. Faculdade de Educação Física e Fisioterapia, Universidade Federal de Uberlândia, Uberlândia (MG) Brasil.

Submitted: 14 January 2019.
Accepted: 14 May 2019.

Study carried out in the Programa de Pós-Graduação em Ciências da Saúde, Faculdade de Medicina, Universidade Federal de Uberlândia, Uberlândia (MG) Brasil, with the assistance of the Research Committee of the Associação de Medicina Intensiva Brasileira (AMIB/AMIBnet, Brazilian Association of Intensivists).

ABSTRACT

Objective: The aim of this study was to describe practices for weaning from mechanical ventilation (MV), in terms of the use of protocols, methods, and criteria, in pediatric ICUs (PICUs), neonatal ICUs (NICUs), and mixed neonatal/pediatric ICUs (NPICUs) in Brazil. **Methods:** This was a cross-sectional survey carried out by sending an electronic questionnaire to a total of 298 NICUs, PICUs, and NPICUs throughout Brazil. **Results:** Completed questionnaires were assessed for 146 hospitals, NICUs accounting for 49.3% of the questionnaires received, whereas PICUs and NPICUs accounted for 35.6% and 15.1%, respectively. Weaning protocols were applied in 57.5% of the units. In the NICUs and NPICUs that used weaning protocols, the method of MV weaning most commonly employed (in 60.5% and 50.0%, respectively) was standardized gradual withdrawal from ventilatory support, whereas that employed in most (53.0%) of the PICUs was spontaneous breathing trial (SBT). During the SBTs, the most common ventilation mode, in all ICUs, was pressure-support ventilation (10.03 ± 3.15 cmH_2O) with positive end-expiratory pressure. The mean SBT duration was 35.76 ± 29.03 min in the NICUs, compared with 76.42 ± 41.09 min in the PICUs. The SBT parameters, weaning ventilation modes, and time frame considered for extubation failure were not found to be dependent on the age profile of the ICU population. The findings of the clinical evaluation and arterial blood gas analysis are frequently used as criteria to assess readiness for extubation, regardless of the age group served by the ICU. **Conclusions:** In Brazil, the clinical practices for weaning from MV and extubation appear to vary depending on the age group served by the ICU. It seems that weaning protocols and SBTs are used mainly in PICUs, whereas gradual withdrawal from ventilatory support is more widely used in NICUs and NPICUs.

Keywords: Ventilator weaning/methods; Respiration, artificial; Airway extubation/methods; Intensive care units, pediatric/standards; Intensive care units, neonatal/standards.

INTRODUCTION

Determining the optimal timing of weaning from mechanical ventilation (MV) and of extubation continues to be a challenge in ICUs.[1,2] In pediatrics and neonatology, there is no strong evidence of an effective and standardized method for MV weaning; nor are there any validated tests or criteria that are considered reliable means of determining patient readiness for extubation.[3-7]

A variety of strategies and criteria for weaning and extubation have been described in the literature, including evaluation of ventilatory parameters, clinical/biochemical criteria, and predictive indices of extubation that can be followed by or combined with spontaneous breathing trials (SBTs) or gradual withdrawal from ventilatory support.[3,4,6-9] It is important to standardize the criteria and methods of evaluating these variables, to identify accurate, reproducible predictors of weaning from MV and extubation.[1,2] Few studies have evaluated the weaning and extubation practices in pediatric and neonatal ICUs (PICUs and NICUs, respectively).[4,8-13]

To our knowledge, there have been no comprehensive studies characterizing the clinical practices for weaning and extubation in NICUs and PICUs. Therefore, this survey aims to describe the characteristics related to the application of protocols, methods, and criteria used in the process of MV weaning and extubation in such ICUs in Brazil.

METHODS

Study design and population

This was a cross-sectional analytical survey, designated the Weaning Survey-Brazil, involving a nationwide sample of 693 ICUs identified from the National Registry of

Correspondence to:
Suzi Laine Longo dos Santos Bacci. UTI Pediátrica, Hospital das Clínicas, Universidade Federal de Uberlândia, Avenida Pará, 1720, CEP 38405-320, Uberlândia, MG, Brasil.
Tel.: 55 34 3218-2552. E-mail: santosbacci@gmail.com
Financial support: None.

ISSN 1806-3713

Health Care Facilities of the Brazilian National Ministry of Health.[14] Of those 693 facilities, 337 are NICUs, 323 are PICUs, and 33 are mixed neonatal/pediatric units (NPICUs).

To define our study sample, the number of ICUs was calculated[15] so that the survey would represent all of Brazil. The sample size calculation considered a significance of $\alpha = 0.05$ and a statistical power of $1 - \beta = 0.95$, with a minimum recommended sample in each state/region according to the sample of ICUs registered with the National Registry of Health Care Facilities, resulting in a minimum sample size of 82 ICUs.

We obtained e-mail addresses or telephone numbers for professionals to contact at 298 ICUs by consulting the membership list of the Brazilian Association of Intensive Care Medicine and by making telephone calls to the hospitals whose ICUs were registered with the National Registry of Health Care Facilities (Figure 1). The ICU professionals contacted were the coordinator or intensivist in charge of each ICU (physical therapist/respiratory therapist, physician, or nurse).

Development of the survey

The survey was developed by the main researchers, who were experts in intensive care, and was based on a review of relevant literature and other surveys.[1,4,11,12] A pilot study was conducted with 10 practitioners representing each ICU type (NICUs, PICUs, and NPICUs) and from each profession, to allow correction for potential confounding factors in the items on the questionnaire. Using Google Forms, a web-based survey tool, we developed a survey questionnaire containing 23 questions, divided into 11 subscales, with mandatory responses.

We collected data on the MV weaning and extubation processes in the neonatal and pediatric age groups. The issues addressed were aspects of ICU practice regarding the application of weaning protocols; weaning/

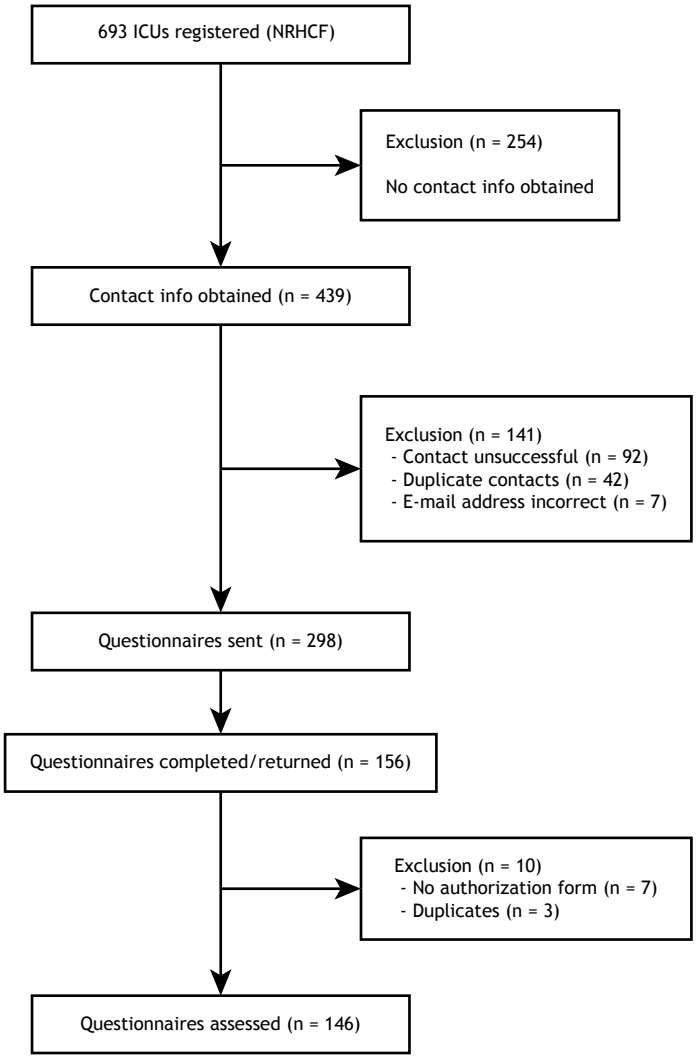


Figure 1. Flow chart of ICU selection process. NRHCF: (Brazilian National Ministry of Health) National Registry of Health Care Facilities.

extubation methods and strategies; application of SBTs; weaning ventilation modes; weaning/extubation readiness criteria; and the clinical indicators recorded. We also evaluated aspects related to weaning/extubation failure in each type of ICU (NICU, PICU, and NPICU).

The initial contact with eligible respondents was made through a personalized e-mail containing a link to the electronic survey, as well as an invitation to take part in the survey, and the authorization form was sent to the coordinator or intensivist in charge of each ICU (physical therapist/respiratory therapist, physician, or nurse). Only one of those was a representative of the ICU. After the initial invitation, reminders were sent and phone calls were made until the minimum sample size was reached for each state/region.

Ethical considerations

This study was approved by the Research Ethics Committee of the Federal University of Uberlandia (Reference no. 1.301.015). Participation was voluntary, and the survey included those ICUs for which the authorization form was signed by and received from the coordinator or intensivist in charge.

Statistical analysis

Multiple-response categorical variables were compared by using chi-square tests.[16] Continuous variables were evaluated for normality with the Kolmogorov-Smirnov test and were compared by using the Kruskal-Wallis test followed by the Games-Howell post hoc test. The results are expressed as absolute and relative frequencies or as medians and interquartile ranges (IQRs). Multiple comparisons of proportions were performed in the program R (R Development Core Team, 2017).[17] For all analyses, values of $p < 0.05$ were considered significant.

RESULTS

Of the 298 questionnaires sent, 156 were completed and returned, corresponding to a response rate of 52.3%. However, 10 questionnaires were excluded, either because of duplication (two questionnaires received from the same ICU) or because the authorization form was not received (Figure 1). Therefore, the final sample comprised 146 questionnaires: 72 (49.3%) received from NICUs; 52 (35.6%) received from PICUs; and 22 (15.1%) received from NPICUs. Our survey included ICUs in all 26 states and in the Federal District, across all regions of the country, the response rates ranging from 13.0% to 100.0% for each state and from 16.0% to 36.3% for each region.

Of the 146 respondents, 84 (57.5%) reported that weaning protocols were employed in their ICUs. Among those 84 ICUs, the most commonly applied method of MV weaning was standardized gradual withdrawal from ventilatory support, in 39 (46.4%), followed by SBT, in 34 (40.5%). Among the 61 ICUs (41.8%) for which the use of weaning protocols was not reported, the main weaning strategy, in 33 (54.1%), was gradual withdrawal from ventilatory support based on clinical judgment (Table 1).

Of the 145 ICUs for which data regarding the use of SBTs were available, 60 (41.3%) reported using them, although information regarding the ventilation modes used during SBT and the average pressure values applied were available for only 54: continuous positive airway pressure (CPAP) of 5 cmH_2O, in 7 (13.0%); pressure-support ventilation (PSV) at a median of 10.0 cmH_2O (IQR, 8.0-12.0 cmH_2O) together with positive end-expiratory pressure (PEEP) at a median of 5.0 cmH_2O (5.0-5.5 cmH_2O), in 43 (79.6%); and a T-piece connected to an oxygen source with an FiO_2 of 0.4, in 4 (7.4%). Regarding the median SBT duration, there was a significant difference among the ICU profiles ($p = 0.004$), as well as significant differences between them: 30.0 min (IQR, 20.0-60.0 min) in the NICUs vs. 67.5 min (IQR, 30.0-120.0 min) in the PICUs ($p = 0.001$); and 45.0 min (IQR, 30.0-60.0 min) in the NPICUs ($p > 0.050$ vs. the NICUs and PICUs). However, the median SBT duration did not differ significantly among the three ventilation modes ($p = 0.053$): 15.0 min (IQR, 10.0-30.0 min) for CPAP vs. 60.0 min (IQR, 30.0-120.0 min) for PSV+PEEP vs. 60.0 min (IQR, 20.0-75.0 min) for the T-piece trial. The time frame considered for extubation failure and other variables collected are presented in Table 2. The ventilation modes used during weaning are shown in Figure 2. The ventilation mode most often employed during the weaning of pediatric patients from MV (in PICUs and NPICUs) was the combination of synchronized intermittent mandatory ventilation (SIMV) and PSV, shifted to PSV alone before extubation. For neonatal patients, there was no one mode that was predominant, in the NICUs or the NPICUs.

Among the NICUs, the main causes of extubation failure reported were apnea, in 68.1%, respiratory distress, in 54.2%, and clinical hemodynamic, infectious, or neurological worsening, in 34.7%. Among the NPICUs, the main causes of extubation failure reported for the neonatal patients were respiratory distress, in 59.1%, clinical worsening, in 59.1%, and apnea, in 50.0%. Among the PICUs, the main causes of extubation failure reported were upper airway obstruction, in 59.6%, neurological or neuromuscular disease, in 51.9%, and respiratory distress, in 44.2%. Among the pediatric patients admitted to the NPICUs, the most common cause of extubation failure was respiratory distress, in 59.1%, followed by upper airway obstruction, in 45.5%, and prolonged sedation time, in 36.4%.

The three types of ICU were compared in terms of the strategies employed in protocolized and non-protocolized MV weaning, as well as the SBT ventilation modes and other variables (Table 3). The proportion of ICUs using weaning protocols was comparable between the NICUs and NPICUs (52.8% and 57.1%, respectively), whereas it was higher (65.4%) among the PICUs. Regarding the methods of liberation from MV, 60.5% of the NICUs and 50.0% of the NPICUs reported using standardized gradual withdrawal from ventilatory

Table 1. Practices related to weaning from mechanical ventilation and spontaneous breathing trials in neonatal and pediatric ICUs in Brazil.

Practice	n (%)
Use of a weaning protocol (N = 146)	
Yes	84 (57.5)
No	61 (41.8)
Unknown	1 (0.7)
Weaning protocol employed (n = 84)[a]	
Standardized gradual withdrawal from ventilatory support	39 (46.4)
SBT with or without daily interruption of sedation	34 (40.5)
Other	11 (13.1)
Non-protocolized weaning strategies (n = 61)[a]	
Gradual withdrawal from ventilatory support based on clinical judgment	33 (54.1)
SBT after parameter reduction	26 (42.6)
Others	2 (3.3)
Ventilation modes during SBT (n = 54)[a]	
PSV+PEEP	43 (79.6)
CPAP	7 (13)
T-piece	4 (7.4)
Parameters monitored during SBT (n = 54)[a]	
Respiratory effort	53 (98.1)[b]
SpO_2	51 (94.4)[b]
Vital signs	47 (87)[b]
Conscious level	32 (59.3)[b]
Tidal volume	27 (50)[b]
Cough reflex	19 (35.2)[b]
PaO_2/FiO_2 ratio	12 (22.2)[b]
SpO_2/FiO_2 ratio	7 (13)[b]
Exhaled CO_2	6 (11.1)[b]

SBT: spontaneous breathing trial; PSV: pressure-support ventilation; PEEP: positive end-expiratory pressure; and CPAP: continuous positive airway pressure. [a]Number of respondents differed from the total. [b]Total may be greater than 100% because the respondents could choose more than one response.

support, whereas SBT was the most common method used in most (53.0%) of the PICUs and in 41.7% of the NPICUs, compared with 29.0% of the NICUs. Among the ICUs which did not report using weaning protocols, a gradual withdrawal from ventilatory support based on clinical judgment was employed in 67.6% of the NICUs and 77.8% of the NPICUs, compared with only 16.7% of the PICUs. The proportion of ICUs using the SBT strategy after withdrawal from ventilatory support was highest (83.3%) among the PICUs (Table 3).

Table 4 shows a comparison between the ICUs with protocolized weaning and those without, in terms of weaning and extubation criteria, as well as extubation failure and its characteristics. Some significant differences were identified.

DISCUSSION

To our knowledge, the Weaning Survey-Brazil is the first study to evaluate MV weaning practices in the pediatric and neonatal age groups in Brazil. We found that the clinical practice for weaning from MV and extubation varies according to the age group served by the ICU.

Our results indicate that most of the participating ICUs (57.5%) employ weaning and extubation protocols, and that such protocols are employed most often in the PICUs. Overall, the most common method of weaning from MV was found to be gradual withdrawal from ventilatory support, which was employed in 49.7% of the ICUs surveyed, especially in the NICUs and NPICUs, although most of the PICUs employed the SBT method.

Protocols are useful for conducting safe, efficient MV weaning, reducing unnecessary or harmful variations in the process.[18] However, we found that the MV weaning protocols employed differed from one ICU to another, demonstrating that there are no standardized protocols in the fields of pediatrics and neonatology. Although such protocols should be used as a complement to clinical judgment,[18] gradual withdrawal from ventilatory support, based on clinical judgment, is the weaning approach more frequently applied in neonatal and pediatric patients, extubation being performed after the minimal ventilation parameters have been reached or the patient has undergone a successful SBT.[3] There is no consensus on which MV weaning method is the best,[19] and it is possible that not all patients require gradual weaning.[3]

Table 2. Criteria for weaning from mechanical ventilation and extubation in neonatal and pediatric ICUs in Brazil.

Criteria and other variables	n (%)
Weaning and extubation readiness criteria (N = 146)	
Clinical criteria	11 (7.5)
Clinical and biochemical criteria	101 (69.2)
Clinical criteria, biochemical criteria, and predictive indices	33 (22.6)
Clinical criteria and predictive indices	1 (0.7)
Biochemical criteria (n = 134)[a]	
Arterial blood gas analysis	129 (96.3)[b]
Other	80 (59.7)[b]
Predictive indices (n = 33)[a]	
RSBI	14 (42.4)[b]
MV parameters	11 (33.3)[b]
MIP, MEP, or both	6 (18.2)[b]
SBT	4 (12.1)[b]
PaO_2/FiO_2 ratio	4 (12.1)[b]
Other	15 (45.4)[b]
Time frame considered for extubation failure (N = 146)	
24 h	39 (26.7)
48 h	68 (46.6)
72 h	14 (9.6)
Undefined	25 (17.1)
Number of extubation attempts (N = 146)	
Most patients are successfully extubated on the first attempt	130 (89)
Most patients require up to 3 attempts	13 (8.9)
Most patients require more than 3 attempts	0 (0.0)
Could not inform	3 (2.1)
Use of a weaning protocol after extubation failure on the first attempt (N = 146)	
No	94 (64.4)
Yes	41 (28.1)
In some cases	11 (7.5)
Registration of clinical indicators (N = 146)	
Time on MV	139 (95.2)[b]
Cause of extubation failure	88 (60.3)[b]
Weaning time	40 (27.4)[b]

RSBI: rapid shallow breathing index; MV: mechanical ventilation; and SBT: spontaneous breathing trial. [a]Number of respondents differed from the total. [b]Total may be greater than 100% because the respondents could choose more than one response.

Two previous studies carried out in PICUs in Europe showed that weaning protocols were either available in few (22%) of the PICUs[20] or were seldom used, being employed in only 9%.[10] Regarding the weaning methods, those same studies indicated that the weaning methods adopted varied according to clinical preferences[10] and that SBTs were applied in 44%.[20] A prospective cohort[9] evaluating PICUs in the United States found that most (62%) use SBT as a method of weaning from MV, similar to the 83.3% found in the present study. However, the proportion of NICUs using weaning protocols has varied across surveys carried out in different countries,[11,12] where an SBT was either not part of the weaning practice[12] or was rarely used.[11]

In general, SBTs are applied as an early means of determining whether a patient is capable of spontaneous autonomous breathing and is ready to be extubated.[7] Studies involving pediatric patients[21-24] and neonatal patients[6,25,26] suggest that SBTs are applicable in those age groups, showing that the trials have high sensitivity for predicting successful extubation. In the present study, we found that the SBT ventilation mode most often employed was CPAP in the NICUs, whereas it was PSV+PEEP in the PICUs. Ventilatory support and SBT duration varied regardless of the method chosen, as has been described in previous studies conducted in other countries.[4,9-11] When PSV+PEEP is employed, the PSV is typically ≤ 10 cmH_2O.[21,22,24,27-29] In keeping with our findings, most neonatology studies of SBT have used the CPAP ventilation mode, with rates of 3-5 cmH_2O and a duration of 3-120 min.[6,11,25,26,30] In the present survey, we found that the parameters usually monitored during SBT are respiratory effort, SpO_2, and vital signs, as shown in previous studies of pediatric patients[21-23,28,29] and neonatal patients.[6,25,26,30]

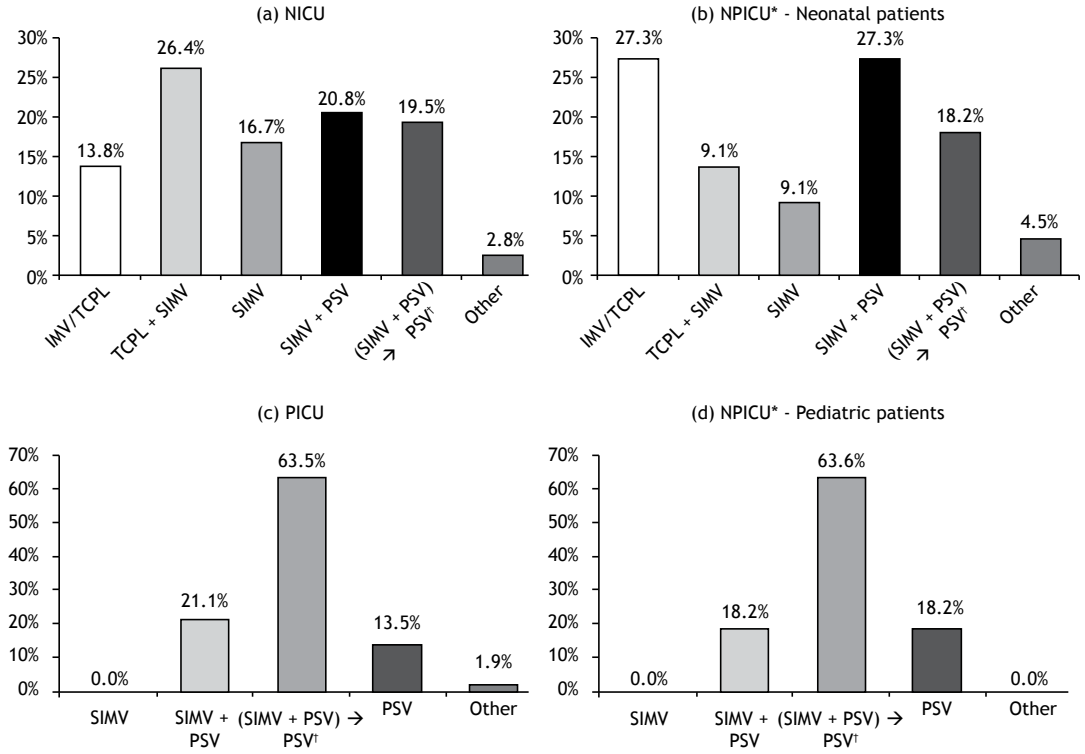


Figure 2. Ventilation modes during weaning in neonatal ICUs (NICUs, n = 72), pediatric ICUs (PICUs, n = 52), and mixed neonatal/pediatric ICUs (NPICUs, n = 22). IMV: intermittent mandatory ventilation; TCPL: time-cycled pressure-limited (ventilation); SIMV: synchronized intermittent mandatory ventilation; and PSV: pressure-support ventilation. *NPICUs answered questions related to ventilation modes during weaning separately for neonatal and pediatric patients. †Shifted from SIMV+PSV to PSV alone before extubation.

The impact of applying MV weaning protocols is typically evaluated by clinical indicators such as the time on MV, weaning time, and extubation failure rate.[5,19,22,27,31] In the present survey, the time on MV was an indicator recorded in all ICUs, although weaning time was not commonly recorded. In one systematic review,[5] it was suggested that weaning protocols decrease the time on MV in children. However, there is still insufficient evidence to support that suggestion, especially as it applies to neonates.[19]

In the present survey, we found that the majority of patients were successfully extubated on the first attempt, regardless of whether the ICU employed protocolized weaning or not. We also found that ICU teams that did not apply weaning protocols also did not apply protocols after extubation failure. Extubation failure is defined as the need for reintubation within the first 24-72 h after extubation.[3,6,22,29,30,32] Many of the ICUs evaluated in the present survey defined extubation failure as a need for reintubation within the first 48 h after extubation. That definition was more often used in the PICUs than in the NICUs and NPICUs.

The causes of extubation failure were more often recorded in the PICUs and in the ICUs that employed weaning protocols. Obstruction of the upper airways was the most common cause of extubation failure, as has been reported in previous studies involving pediatric patients.[8,21,23,27] Among the neonates, apnea was the most commonly reported cause of extubation failure, as has also been reported previously.[26,30,32,33]

The use of a combination of subjective and objective criteria might have greater predictive accuracy in assessing fitness for liberation from ventilatory support and has provided major insights into the mechanisms of weaning failure.[18,34] Clinical and laboratory criteria, as well as the application of predictive indexes[2] can assist in assessing readiness for extubation.[3,35] In our survey, we observed that 69.2% of the ICUs evaluated were using clinical and laboratory criteria, mainly the arterial blood gas data, to evaluate patient readiness for weaning and extubation. The predictive index most often employed was the rapid shallow breathing index. However, when asked about the predictive indices employed, 33.3% of the respondents reported using the MV parameters and 45.4% reported using other criteria, which shows that there is a lack of knowledge regarding the correct terms related to the predictive indices.

Corroborating our findings, previous surveys conducted in other countries have found that the criteria most often evaluated to determine extubation readiness were clinical criteria in PICUs,[4] whereas the criteria most often evaluated in NICUs were ventilation parameters (in 98%), blood gas analyses (in 92%), and clinical

Table 3. Comparison among ICUs serving different age groups, in terms of ventilator weaning and extubation practices, in Brazil.

Practice	NICU (n = 75)	PICU (n = 52)	NPICU (n = 22)
Use of a weaning protocol, %			
Yes	52.8^{aA}	65.4^{aA}	57.1^{aA}
No	47.2^{aA}	34.6^{bA}	42.9^{aA}
Weaning protocol employed, %			
Standardized gradual withdrawal from ventilatory support	60.5^{aA}	29.4^{abB}	50.0^{aAB}
SBT with or without daily interruption of sedation	29.0^{bA}	53.0^{aA}	41.7^{aA}
Other	10.5^{bA}	17.6^{bA}	8.3^{aA}
Non-protocolized weaning strategies, %			
Gradual withdrawal from ventilatory support based on clinical judgment	67.6^{aA}	16.7^{bB}	77.8^{aA}
SBT after parameter reduction	26.5^{bB}	83.3^{aA}	22.2^{bB}
Other	5.9^{b}	---	---
Ventilation modes during SBT, %			
CPAP	27.8^{bA}	6.7^{bB}	---
PSV+PEEP	66.7^{aA}	86.7^{aA}	83.3^{aA}
T-piece	5.5^{bA}	6.7^{bA}	16.7^{bA}
Weaning and extubation readiness criteria, %			
Clinical criteria	4.1^{bA}	13.7^{bA}	4.5^{bA}
Clinical and biochemical criteria	73.6^{aA}	58.9^{aA}	81.8^{aA}
Clinical criteria, biochemical criteria, and predictive indices	22.3^{bA}	27.4^{bA}	13.7^{bA}
Clinical criteria and predictive indices	---	---	---
Time frame considered for extubation failure, %			
24 h	27.8^{aA}	23.1^{bA}	31.8^{abA}
48 h	36.1^{aB}	59.6^{aA}	50.0^{aAB}
72 h	12.5^{bA}	5.8^{bA}	9.1^{bA}
Undefined	23.6^{aA}	11.5^{bA}	9.1^{bA}
Use of a weaning protocol after extubation failure on the first attempt, %			
Yes	26.4^{bA}	26.9^{bA}	36.4^{abA}
No	65.3^{aA}	65.4^{aA}	59.1^{aA}
In some cases	8.3^{bA}	7.7^{bA}	4.5^{bA}
Time on MV recorded, %			
Yes	94.4^{aA}	96.2^{aA}	95.5^{aA}
No	5.6^{bA}	3.8^{bA}	4.5^{bA}
Weaning time recorded, %			
Yes	25.0^{bA}	32.7^{bA}	22.7^{bA}
No	75.0^{aA}	67.3^{aA}	77.3^{aA}
Causes of extubation failure recorded, %			
Yes	56.9^{aA}	65.4^{aA}	59.1^{aA}
No	43.1^{aA}	34.6^{bA}	40.9^{aA}

NICU: neonatal ICU; PICU: pediatric ICU; NPICU: (mixed) neonatal/pediatric ICU; SBT: spontaneous breathing trial; CPAP: continuous positive airway pressure; PSV: pressure-support ventilation; PEEP: positive end-expiratory pressure; and MV: mechanical ventilation. Proportions followed by the same superscript letters (in lower case for columns and in upper case for rows) did not differ statistically from each other in the multiple comparison tests, $p < 0.05$ being considered significant.

stability/hemodynamics (in 86%).[11] However, other studies involving pediatric patients have shown that ventilatory parameters prior to extubation and arterial blood gas values were not associated with the success or failure of extubation.[8,36] Another study involving pediatric patients in Brazil,[37] observed that the rapid shallow breathing index and blood gas analyses were not predictors of extubation failure in the postoperative period after cardiac surgery. There are as yet no accurate, reliable criteria to predict success in weaning and extubation in neonatal and pediatric populations.[33,35] Therefore, subjective rather than evidence-based criteria are employed in most ICUs around the world.[2,32]

A variety of ventilation modes are used for MV weaning in pediatric patients.[5] A survey carried out in PICUs in Italy[38] found that SIMV+PSV was the ventilation mode most commonly used for weaning, whereas another study[9] reported that the PSV weaning mode was more

Table 4. Comparison between ICUs with protocolized ventilator weaning and those without.

Criteria and other variables	Use of a weaning protocol	
	Yes	No
Weaning and extubation readiness criteria, %		
Clinical criteria	8.3[c]	6.7[c]
Clinical and biochemical criteria	59.6[a]	83.3[a]
Clinical criteria, biochemical criteria, and predictive indices, %	32.1[b]	10.0[b]
Clinical criteria and predictive indices	---	---
Time frame considered for extubation failure, %		
24 h	34.5[a]	14.7[c]
48 h	42.9[a]	52.5[a]
72 h	14.3[b]	3.3[c]
Undefined	8.3[b]	29.5[b]
Frequency of extubation attempts, %		
Patients successfully extubated on the first attempt	92.9[a]	87.9[a]
Patients required up to 3 extubation attempts	7.1[b]	12.1[b]
Use of a weaning protocol after extubation failure on the first attempt, %		
Yes	46.4[a]	3.3[b]
No	47.6[a]	88.5[a]
In some cases	6.0[b]	8.2[b]
Time on MV recorded, %		
Yes	94.0[a]	96.7[a]
No	6.0[b]	3.3[b]
Weaning time recorded, %		
Yes	36.9[b]	14.8[b]
No	63.1[a]	85.2[a]
Causes of extubation failure recorded, %		
Yes	71.4[a]	45.9[a]
No	28.6[b]	54.1[a]

MV: mechanical ventilation. Proportions followed by the same superscript lowercase letters in columns did not differ statistically from each other in the multiple comparison tests, $p < 0.05$ being considered significant.

widely used in PICUs in other countries. However, other surveys showed that SIMV is the preferential weaning or pre-extubation ventilation mode in NICUs in the United Kingdom[13] and Canada.[12] The best ventilation mode for weaning from MV has not been established in the field of neonatology.[39]

The Weaning Survey-Brazil has some limitations. First, we were unable to obtain contact information for all of the relevant ICUs in Brazil, due to the absence of a single registry containing all such information. In addition, some ICU coordinators did not sign the authorization form. Another limitation is that each questionnaire was completed by only one individual. However, we believe that the questionnaire reliably evaluated the practices in each ICU, because it was completed by the coordinator or intensivist responsible for the unit. In fact, it is possible that the respondents adopted better weaning and extubation practices as they completed the questionnaire. This is a limitation of surveys. Nonetheless, it is noteworthy that this was the first survey to evaluate the profile, in terms of weaning and extubation practices, of NICUs and PICUs in Brazil. In addition, our survey included all of the states and regions of the country. Furthermore, the size of the survey sample (n = 146) was larger than the minimum calculated (n = 82) as being required to be representative of all ICUs in Brazil. The results allow us to understand the practices related to the weaning and extubation processes in the NICUs and PICUs of Brazil, enabling the planning and development of future standardized protocols for the MV weaning in each age group. Optimization of the weaning process could reduce variations in clinical practice, as well as reducing the time on MV, thus reducing the risks associated with ventilation and the costs to the public health system.

In conclusion, the present survey showed that the weaning and extubation practices in Brazil vary widely as a function of the age group served by the ICU. The most common weaning strategy in Brazil is a gradual withdrawal from ventilatory support, and protocolized weaning is more common in PICUs. In PICUs, an SBT is more often performed in the PSV+PEEP ventilation mode, although the duration of the trial was quite variable. In most NICUs and PICUs in Brazil, readiness for extubation is further assessed by clinical and blood gas analysis.

Further studies are needed in order to evaluate the clinical impact of the methods and strategies adopted for MV weaning and extubation of pediatric and neonatology patients in Brazil. Such studies should be

based on the safety, quality, and productivity indicators applicable in ICUs.

ACKNOWLEDGMENTS

The authors are especially grateful to the Research Committee of the *Associação de Medicina Intensiva Brasileira* (AMIB, Brazilian Association of Intensivists) and the AMIB Department of Physiotherapy in Intensive Care, for their guidance and commitment to the dissemination of research, as well as to the ICU professionals who completed the questionnaires. We would also like to thank Professor Suzana Lobo, President of the AMIB Fund (2014-2015), for her guidance during the survey, Dr. Fernando Dias Suprarregui, President of the AMIB (2014-2015), for authorizing this research project and for his collaboration, and Professor Débora Feijó Villas Bôas Vieira, of the University of Rio Grande do Sul, for her assistance with the ICU data collection.

REFERENCES

1. Soo Hoo GW, Park L. Variations in the measurement of weaning parameters: a survey of respiratory therapists. Chest. 2002;121(6):1947-1955. https://doi.org/10.1378/chest.121.6.1947
2. Johnston C, da Silva PSL. Weaning and Extubation in Pediatrics. Curr Respir Med Rev. 2012;8(1):68-78. https://doi.org/10.2174/157339812798868852
3. Newth CJL, Venkataraman S, Willson DF, Meert KL, Harrison R, Dean JM, et al. Weaning and extubation readiness in pediatric patients. Pediatr Crit Care Med. 2009;10(1):1-11. https://doi.org/10.1097/PCC.0b013e318193724d
4. Mhanna MJ, Anderson IM, Iyer NP, Baumann A. The Use of Extubation Readiness Parameters: A Survey of Pediatric Critical Care Physicians. Respir Care. 2014;59(3):334-339. https://doi.org/10.4187/respcare.02469
5. Blackwood B, Murray M, Chisakuta A, Cardwell CR, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of invasive mechanical ventilation in critically ill paediatric patients. Cochrane Database Syst Rev. 2013;2013(7):CD009082. https://doi.org/10.1002/14651858.CD009082.pub2
6. Andrade LB, Melo TM, Morais DF, Lima MR, Albuquerque EC, Martimiano PH. Spontaneous breathing trial evaluation in preterm newborns extubation. Rev Bras Ter Intensiva. 2010;22(2):159-165. https://doi.org/10.1590/S0103-507X2010000200010
7. Kamlin CO, Davis PG, Argus B, Mills B, Morley CJ. A trial of spontaneous breathing to determine the readiness for extubation in very low birth weight infants: a prospective evaluation. Arch Dis Child Fetal Neonatal Ed. 2008;93(4):F305-F306. https://doi.org/10.1136/adc.2007.129890
8. Laham JL, Breheny PJ, Rush A. Do clinical parameters predict first planned extubation outcome in the pediatric intensive care unit? J Intensive Care Med. 2015;30(2):89-96. https://doi.org/10.1177/0885066613494338
9. Farias JA, Fernández A, Monteverde E, Flores JC, Baltodano A, Menchaca A, et al. Mechanical ventilation in pediatric intensive care units during the season for acute lower respiratory infection: a multicenter study. Pediatr Crit Care Med. 2012;13(2):158-164. https://doi.org/10.1097/PCC.0b013e3182257b82
10. Blackwood B, Tume L. The implausibility of "usual care" in an open system: sedation and weaning practices in Paediatric Intensive Care Units (PICUs) in the United Kingdom (UK). Trials. 2015;16:325. https://doi.org/10.1186/s13063-015-0846-3
11. Al-Mandari H, Shalish W, Dempsey E, Keszler M, Davis PG, Sant'Anna G. International survey on periextubation practices in extremely preterm infants. Arch Dis Child Fetal Neonatal Ed. 2015;100(5):F428-F431. https://doi.org/10.1136/archdischild-2015-308549
12. Shalish W, Anna GM. The use of mechanical ventilation protocols in Canadian neonatal intensive care units. Paediatr Child Health. 2015;20(4):e13-e19. https://doi.org/10.1093/pch/20.4.e13
13. Sharma A, Greenough A. Survey of neonatal respiratory support strategies. Acta Paediatr. 2007;96(8):1115-1117. https://doi.org/10.1111/j.1651-2227.2007.00388.x
14. Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária [homepage on the Internet]. Brasília: o Ministério; [cited 2017 Jun 8]. Resolução Nº 7, de 24 de fevereiro de 2010. Dispõe sobre os requisitos mínimos para funcionamento de Unidades de Terapia Intensiva e dá outras providências. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2010/res0007_24_02_2010.html
15. Miot HA. Sample size in clinical and experimental trials. J Vasc Bras. 2011;10(4):275-8. http://dx.doi.org/10.1590/S1677-54492011000400001 https://doi.org/10.1590/S1677-54492011000400001
16. Biase N, Ferreira D. Comparações múltiplas e testes simultâneos para parâmetros binomiais de K populações independentes. Rev Bras Biometria. 2009;27(3):301-323.
17. R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: The R Project for Statistical Computing; 2017.
18. Teixeira C, Maccari JG, Vieira SR, Oliveira RP, Savi A, Machado AS, et al. Impact of a mechanical ventilation weaning protocol on the extubation failure rate in difficult-to-wean patients. J Bras Pneumol. 2012;38(3):364-371. https://doi.org/10.1590/S1806-37132012000300012
19. Wielenga JM, van den Hoogen A, van Zanten HA, Helder O, Bol B, Blackwood B. Protocolized versus non-protocolized weaning for reducing the duration of invasive mechanical ventilation in newborn infants. Wielenga JM, editor. Cochrane Database Syst Rev. 2016;3:CD011106. https://doi.org/10.1002/14651858.CD011106.pub2
20. Tume LN, Kneyber MC, Blackwood B, Rose L. Mechanical Ventilation, Weaning Practices, and Decision Making in European PICUs. Pediatr Crit Care Med. 2017;18(4):e182-e188. https://doi.org/10.1097/PCC.0000000000001100
21. Farias JA, Retta A, Alía I, Olazarri F, Esteban A, Golubicki A, et al. A comparison of two methods to perform a breathing trial before extubation in pediatric intensive care patients. Intensive Care Med. 2001;27(10):1649-1654. https://doi.org/10.1007/s001340101035
22. Foronda FK, Troster EJ, Farias JA, Barbas CS, Ferraro AA, Faria LS, et al. The impact of daily evaluation and spontaneous breathing test on the duration of pediatric mechanical ventilation: a randomized controlled trial. Crit Care Med. 2011;39(11):2526-2533. https://doi.org/10.1097/CCM.0b013e3182257520
23. Chavez A, dela Cruz R, Zaritsky A. Spontaneous breathing trial predicts successful extubation in infants and children. Pediatr Crit Care Med. 2006;7(4):324-328. https://doi.org/10.1097/01.PCC.0000225001.92994.29
24. Faustino EV, Gedeit R, Schwarz AJ, Asaro LA, Wypij D, Curley MA, et al. Accuracy of an Extubation Readiness Test in Predicting Successful Extubation in Children With Acute Respiratory Failure From Lower Respiratory Tract Disease. Crit Care Med. 2017;45(1):94-102. https://doi.org/10.1097/CCM.0000000000002024
25. Kamlin CO, Davis PG, Morley CJ. Predicting successful extubation of very low birthweight infants. Arch Dis Child Fetal Neonatal Ed. 2006;91(3):F180-F183. https://doi.org/10.1136/adc.2005.081083
26. Chawla S, Natarajan G, Gelmini M, Kazzi SN. Role of spontaneous breathing trial in predicting successful extubation in premature infants. Pediatr Pulmonol. 2013;48(5):443-448. https://doi.org/10.1002/ppul.22623
27. Randolph AG, Wypij D, Venkataraman ST, Hanson JH, Gedeit RG, Meert KL, et al. Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. JAMA. 2002;288(20):2561-2568. https://doi.org/10.1001/jama.288.20.2561
28. Farias JA, Alía I, Retta A, Olazarri F, Fernández A, Esteban A, et al. An evaluation of extubation failure predictors in mechanically ventilated infants and children. Intensive Care Med. 2002;28(6):752-757. https://doi.org/10.1007/s00134-002-1306-6
29. Ferguson LP, Walsh BK, Munhall D, Arnold JH. A spontaneous

breathing trial with pressure support overestimates readiness for extubation in children. Pediatr Crit Care Med. 2011;12(6):e330-e335. https://doi.org/10.1097/PCC.0b013e3182231220

30. Gillespie LM, White SD, Sinha SK, Donn SM. Usefulness of the minute ventilation test in predicting successful extubation in newborn infants: a randomized controlled trial. J Perinatol. 2003;23(3):205-207. https://doi.org/10.1038/sj.jp.7210886
31. Hermeto F, Bottino MN, Vaillancourt K, Sant'Anna GM. Implementation of a respiratory therapist-driven protocol for neonatal ventilation: impact on the premature population. Pediatrics. 2009;123(5):e907-e916. https://doi.org/10.1542/peds.2008-1647
32. Giaccone A, Jensen E, Davis P, Schmidt B. Definitions of extubation success in very premature infants: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2014;99(2):F124-F127. https://doi.org/10.1136/archdischild-2013-304896
33. Sant'Anna GM, Keszler M. Weaning Infants from Mechanical Ventilation. Clin Perinatol. 2012;39(3):543-562. https://doi.org/10.1016/j.clp.2012.06.003
34. Nemer SN, Barbas CS. Predictive parameters for weaning from mechanical ventilation. J Bras Pneumol. 2011;37(5):669-679. https://doi.org/10.1590/S1806-37132011000500016
35. Valenzuela J, Araneda P, Cruces P. Weaning from mechanical ventilation in paediatrics. State of the art. Arch Bronconeumol. 2014;50(3):105-112. https://doi.org/10.1016/j.arbres.2013.02.003
36. Johnston C, de Carvalho WB, Piva J, Garcia PC, Fonseca MC. Risk factors for extubation failure in infants with severe acute bronchiolitis. Respir Care. 2010;55(3):328-333.
37. Johnston C, Piva JP, Carvalho WB, Garcia PC, Fonseca MC, Hommerding PX. Post Cardiac Surgery In Children: Extubation Failure Predictor's [Article in Portuguese]. Rev Bras Ter Intensiva. 2008;20(1):57-62. https://doi.org/10.1590/S0103-507X2008000100009
38. Wolfler A, Calderoni E, Ottonello G, Conti G, Baroncini S, Santuz P, et al. Daily practice of mechanical ventilation in Italian pediatric intensive care units: a prospective survey. Pediatr Crit Care Med. 2011;12(2):141-146. https://doi.org/10.1097/PCC.0b013e3181dbaeb3
39. Sant'Anna GM, Keszler M. Developing a neonatal unit ventilation protocol for the preterm baby. Early Hum Dev. 2012;88(12):925-929. https://doi.org/10.1016/j.earlhumdev.2012.09.010

J Bras Pneumol. 2020;46(4):e20190295
https://dx.doi.org/10.36416/1806-3756/e20190295

ORIGINAL ARTICLE

Comparison of the effects of voluntary and involuntary breath stacking techniques on respiratory mechanics and lung function patterns in tracheostomized patients: a randomized crossover clinical trial

Luciano Matos Chicayban[1,2,3], Alice Campos Hemétrio[3], Liz Tavares Rangel Azevedo[3]

1. Laboratório de Pesquisa em Fisioterapia Pneumofuncional e Intensiva, Institutos Superiores de Ensino do Centro Educacional Nossa Senhora Auxiliadora – ISECENSA – Campos dos Goytacazes (RJ) Brasil.
2. Unidade de Terapia Intensiva, Hospital Geral de Guarus – HGG – Campos dos Goytacazes (RJ) Brasil.
3. Curso de Fisioterapia, Institutos Superiores de Ensino do Centro Educacional Nossa Senhora Auxiliadora – ISECENSA – Campos dos Goytacazes (RJ) Brasil.

Submitted: 27 August 2019.
Accepted: 29 October 2019.

Study carried out in the Laboratório de Pesquisa em Fisioterapia Pneumofuncional e Intensiva, Institutos Superiores de Ensino do Centro Educacional Nossa Senhora Auxiliadora – ISECENSA – Campos dos Goytacazes (RJ) Brasil.
(ClinicalTrials.gov identifier: NCT04012489 [http://www.clinicaltrials.gov/])

ABSTRACT

Objective: To compare the effects of voluntary breath stacking (VBS) and involuntary breath stacking (IBS) techniques on respiratory mechanics, lung function patterns, and inspiratory capacity in tracheostomized patients. **Methods:** This was a randomized crossover clinical trial involving 20 tracheostomized patients admitted to the ICU and submitted to the VBS and IBS techniques, in random order, with an interval of 5 h between each. Ten cycles of each technique were performed with an interval of 30 s between each cycle. In VBS, patients performed successive inspirations for up to 30 s through a one-way valve, whereas in IBS, successive slow insufflations were performed with a resuscitator bag until the pressure reached 40 cmH_2O. Respiratory mechanics, inspiratory capacity, and the lung function pattern were evaluated before and after the interventions. **Results:** After IBS, there was an increase in static compliance ($p = 0.007$), which was also higher after IBS than after VBS ($p = 0.03$). There was no significant difference between the pre-VBS and post-VBS evaluations in terms of static compliance ($p = 0.42$). Inspiratory capacity was also greater after IBS than after VBS (2,420.7 ± 480.9 mL vs. 1,211.3 ± 562.8 mL; $p < 0.001$), as was airway pressure (38.3 ± 2.6 cmH_2O vs. 25.8 ± 5.5 cmH_2O; $p < 0.001$). There were no changes in resistance or lung function pattern after the application of either technique. **Conclusions:** In comparison with VBS, IBS promoted greater inspiratory capacity and higher airway pressure, resulting in an increase in static compliance.

Keywords: Mucociliary clearance; Respiratory care units; Respiratory mechanics; Physical therapy modalities.

INTRODUCTION

Patients admitted to the ICU show increased mucus production and impaired mucociliary clearance. The deleterious effects of prolonged bed rest, acquired muscle weakness, and advanced age make it difficult to mobilize and eliminate mucus.[1] Acquired respiratory muscle weakness due to long ICU stays reduces lung volume, sighing, and peak cough flow (PCF), resulting in decreased expansion of the lungs and rib cage.[2] The progressive loss of inspiratory muscle strength leads to a restrictive pattern of lung function, causing complications such as atelectasis, pulmonary infection, and gas exchange dysfunction. In addition, deterioration of the expiratory muscles decreases cough effectiveness.[1] The combination of a restrictive pattern of lung function and the inability to adequately clear pulmonary secretions increases the incidence of respiratory complications.[3,4] In patients with neuromuscular disease, increased survival is related to bronchial hygiene measures, such as assisted cough and manual hyperinflation.[4]

Involuntary breath stacking (IBS) can be defined as a technique of pulmonary insufflation through multiple inspiratory efforts achieved with the assistance of a resuscitator bag. IBS is performed with a one-way valve and has the objective of producing volumes greater than the resting inspiratory capacity (IC).[2] The benefits of IBS include increased inspiratory volume, improved thoracic mobility, prevention of atelectasis, and mobilization of secretions. IBS is widely used in order to improve cough effectiveness in patients with neuromuscular diseases, such as Duchenne muscular dystrophy, quadriplegia, and amyotrophic lateral sclerosis, because of the associated respiratory muscle weakness.[2,5]

Voluntary breath stacking (VBS) is based on encouraging inspiration by occluding the expiratory port of the one-way valve and allowing only the inspiratory flow.[6] However, the patient should actively recruit progressively increasing volumes of air, via contraction of respiratory muscles. The VBS technique came to be widely used after it was shown to produce higher vital

Correspondence to:
Luciano Matos Chicayban. Rua Doutor Augusto Bessa, 324, Parque Turf Club, CEP 28015-150, Campos dos Goytacazes, RJ, Brasil.
Tel.: 55 22 99803-0510. E-mail: lucianochicayban@gmail.com
Financial support: None.

ISSN 1806-3713

capacity values than did the conventional method in patients with an obstructive or restrictive pattern of lung function, in those with neuromuscular disease, and in healthy individuals.[7]

We have found no studies that compared the therapeutic effects of the VBS and IBS techniques or analyzed the volumes recruited and pressures achieved by the two techniques in tracheostomized patients admitted to the ICU. The hypothesis of the present study was that IBS would increase IC, with clinically relevant effects on lung compliance. Therefore, the objective of the present study was to compare the effects of VBS and IBS on respiratory mechanics, lung function patterns, and IC in tracheostomized patients admitted to the ICU.

METHODS

This was a randomized crossover clinical trial involving 20 tracheostomized adults admitted to the ICU of the Guarus General Hospital, in the city of Campos dos Goytacazes, Brazil, all of whom had been breathing spontaneously, with no need for ventilatory support, for at least 96 h. Patients with undrained pleural effusion or undrained pneumothorax were excluded from the study, as were those with static compliance values less than 25 mL/cmH_2O and those who were unable to undergo measurement of respiratory mechanics (Figure 1). The study was approved by the Research Ethics Committee of the Institutes of Higher Education of the Our Lady of Perpetual Help Education Center (Reference no. 93156718.0.0.0000.5524), in the city of Campos dos Goytacazes. Written informed consent was obtained from the legal guardians of all participating patients.

Intervention

All patients were submitted to the VBS and IBS techniques with an interval of 5 h between each. The order in which the two techniques were applied was determined by using a computer-generated random permutation, and the results were placed into envelopes numbered from 1 to 10, totaling 20 envelopes. The envelopes were opened sequentially at the time of data collection. The randomization process was performed by a second investigator, and the principal investigator was blinded to the order in which the two techniques were applied.

To perform the interventions, we placed the patients in the supine position with the head of the bed elevated 45°, and cuff pressure was increased to prevent leaks. Before the interventions, patients underwent endotracheal suctioning, in accordance with the recommendations of the American Association for Respiratory Care.[8] The protocol for the VBS and IBS techniques consisted of a series of ten cycles of each with an interval of at least 30 s between each cycle. For VBS and IBS, the system was connected to the tracheostomy tube at basal end expiration (i.e., at functional residual capacity). As shown in Figure 2, the system (for both techniques) consisted of a one-way valve, a manometer, and a digital respirometer, connected to a bacterial filter for the purpose of being coupled to the tracheostomy tube.

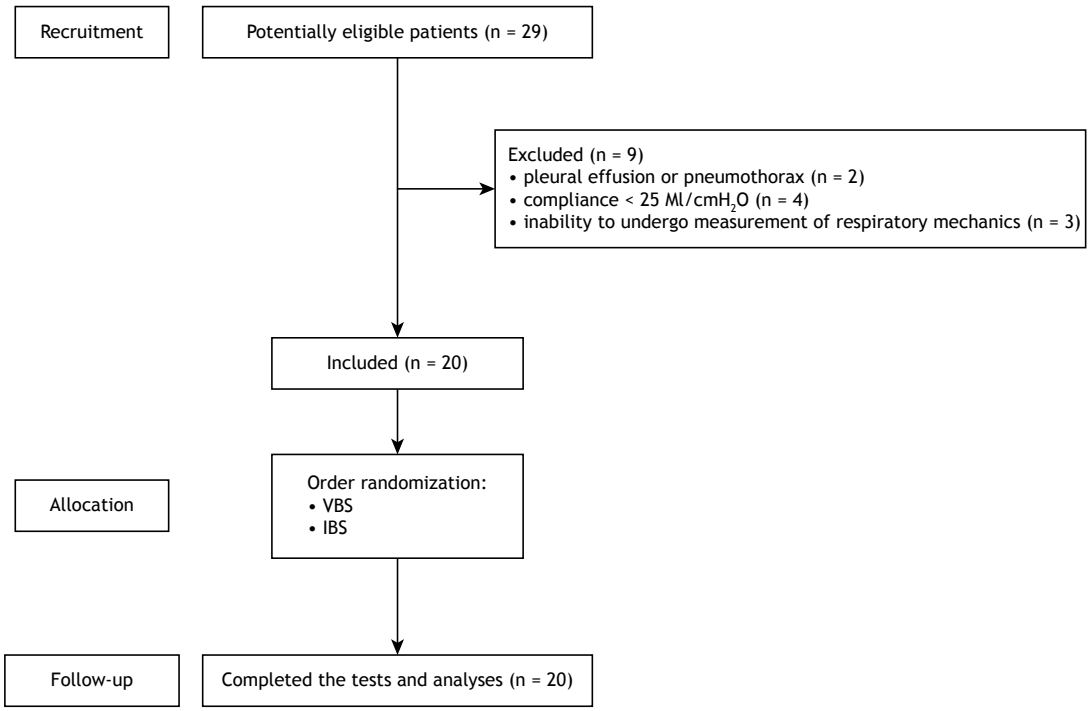


Figure 1. Study patient flowchart. VBS: voluntary breath stacking; and IBS: involuntary breath stacking.

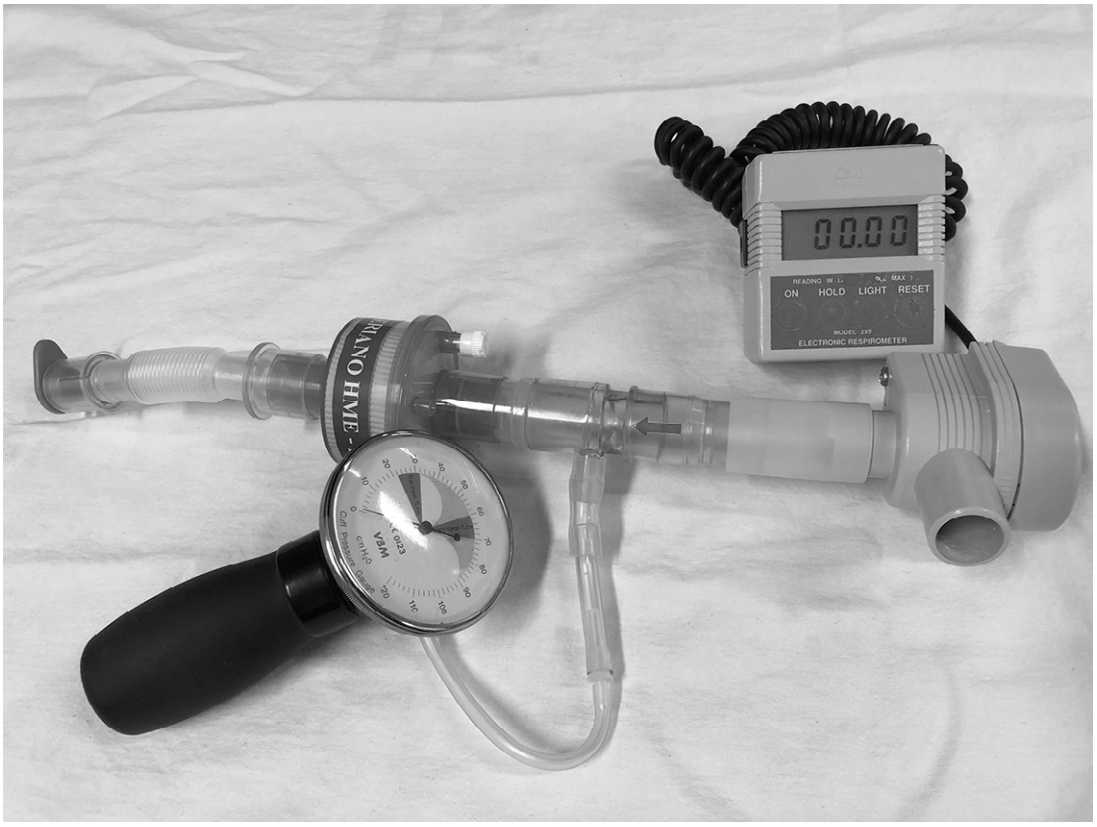


Figure 2. Experimental setup used for voluntary breath stacking. The monitoring system, based on inspiratory capacity (measured with a respirometer), was coupled to a one-way valve connected to an analog manometer. A bacterial filter was used for patient coupling. For involuntary breath stacking, a resuscitator bag was connected to the respirometer outlet.

In VBS, patients took successive inspirations for up to 30 s or until no one-way valve opening or inspiratory volume increase (measured with a respirometer) was observed over two consecutive efforts. In IBS, a resuscitator bag (RWR, São Paulo, Brazil) was connected to the respirometer. Successive slow insufflations were performed, by slowly compressing the resuscitator bag, until the MIP reached 40 cmH_2O.

Evaluation

Before and after the interventions, respiratory mechanics, lung function patterns, IC, and airway pressure were evaluated.

Respiratory mechanics

Respiratory mechanics were assessed with a Vela ventilator (Bird Products Corp., Palm Springs, CA, USA), by using the end-inspiratory occlusion maneuver. The maneuver was performed in volume-controlled ventilation, at a constant flow rate of 40 L/min with an inspiratory pause of 3 s. Prior to the maneuver, all patients underwent 30 s of hyperventilation, which was achieved by increasing the RR to 35 breaths/min. The ventilator screen was "frozen" so that MIP, plateau pressure, and positive end-expiratory pressure could be recorded, making it possible to calculate static respiratory system compliance (C_{st},rs) and total respiratory system resistance (R,rs). Three consecutive, acceptable measurements were made at each time point, and we used the mean of the two measurements with the lowest standard deviations. Measurements were considered acceptable if we detected no deflections in the flow or pressure curves and no plateau during the inspiratory pause, because such changes would suggest patient interference and the presence of leaks, respectively.[9-12]

IC

The maximum volume recruited during VBS and IBS was measured from functional residual capacity, determining IC. In VBS, IC was measured at 30 s of expiratory port occlusion or at the time point when the patient had not recruited volume over two consecutive cycles. In IBS, IC was recorded when the airway pressure reached 40 cmH_2O. IC was measured with a digital respirometer (Ohmeda, Oxnard, CA, USA), in three cycles, and the highest value was used.[5,6,13]

Airway pressure

In VBS and IBS, airway pressure was measured at IC, in the absence of respiratory muscle effort. In VBS, airway pressure was recorded after 30 s of expiratory port occlusion or when the patient had not recruited any volume over two consecutive cycles.

In IBS, airway pressure was recorded at the time point when MIP reached 40 cmH_2O. The maximum pressures achieved by VBS and IBS were recorded in three cycles, and we used the arithmetic mean of the two measurements with the lowest standard deviations.[14]

Lung function pattern

Minute volume (V_E) and RR were measured before and after the interventions. The digital respirometer was coupled to the tracheostomy tube, and the volume of air exhaled in 60 s (V_E) was recorded. The mean basal tidal volume (V_T) was calculated as the ratio of V_E to RR (V_E/RR), making it possible to calculate the rapid shallow breathing index (defined as the RR/V_T ratio).[15]

Statistical analysis

The data obtained were organized and reviewed in Microsoft Excel® spreadsheets, making it possible to calculate the mean and standard deviation for each variable. Results were analyzed and graphs were created using SigmaPlot software, version 12.01 (Systat Software Inc., Richmond, CA, USA). When the results of the pre- and post-intervention measurements of respiratory mechanics (C_{st},rs and R,rs) and lung function pattern (V_T, V_E, RR, and RR/V_T ratio) showed normal distribution or homogeneity of variances, as determined by the Shapiro-Wilk test and Levene's test, respectively, they were analyzed by two-way repeated-measures ANOVA with Tukey's post-test. When they showed non-normal distribution, the Friedman test was used. The pre- and post-intervention IC values were compared by using a paired t-test, as were the pre- and post-intervention changes (absolute and relative) in respiratory mechanics and lung function pattern variables. The level of significance was set at 5% for all tests. The clinical effects of VBS and IBS were compared on the basis of the effect size, as determined by calculating Cohen's d. The effect size was calculated on the basis of the difference in absolute and relative changes between pre- and post-intervention measurements.

RESULTS

A total of 20 tracheostomized patients were evaluated between August of 2018 and March of 2019. On the day of the interventions, all of the patients were breathing spontaneously with the aid of nebulization of oxygen. The characteristics of the sample are presented in Table 1. Analysis of the respiratory mechanics showed that only IBS increased C_{st},rs relative to the pre-intervention value ($p = 0.007$), and there was a significant difference between post-VBS and post-IBS values for C_{st},rs ($p = 0.03$; $d = 0.11$). Relative changes in C_{st},rs were greater after IBS than after VBS (13.1 ± 11.9% vs. 1.3 ± 8.8%; $p = 0.008$; $d = 0.49$), as were absolute changes (4.6 ± 4.8 mL/cmH_2O vs. 0.3 ± 4.0 mL / cmH_2O; $p = 0.043$; $d = 0.44$).

No significant differences were observed between pre-VBS and pre-IBS values for C_{st},rs or R,rs or between post-VBS and pre-VBS values for C_{st},rs ($p = 0.85$). Neither technique produced changes in R,rs—there were no significant differences between pre-VBS and pre-IBS values ($p = 0.69$) or between post-VBS and post-IBS values ($p = 0.30$; $d = 0.14$), nor were there significant differences in absolute changes between post-VBS and post-IBS measurements ($p = 0.41$; $d = 0.17$) or in relative changes between post-VBS and post-IBS measurements ($p = 0.16$; $d = 0.01$). Results for respiratory mechanics are presented in Table 2.

IC was greater after IBS than after VBS (2,420.7 ± 480.9 mL vs. 1,211.3 ± 562.8 mL; $p < 0.001$; $d = 0.76$). Inspiratory volume, relative to V_T, increased from 396.1 ± 94.5 mL to 2,420.7 ± 480.9 mL after IBS ($p < 0.001$) and from 398.0 ± 83.3 mL to 1,211.3 ± 562.8 mL after VBS (Figure 3). The difference in recruited volume was 2,024.6 ± 445.1 mL for IBS, compared with 813.3 ± 530.9 mL for VBS ($p < 0.001$). At IC, IBS promoted higher airway pressure than did VBS (38.3 ± 2.6 cmH_2O vs. 25.8 ± 5.5 cmH_2O; $p < 0.001$). No significant difference was observed in the number of cycles required to reach IC ($p = 0.36$). To achieve an inspiratory pressure of approximately 40 cmH_2O, IBS required 4.8 ± 0.9 cycles of insufflation with the resuscitator bag, whereas VBS required 5.0 ± 2.3 cycles.

Regarding the lung function pattern, no significant changes were observed between pre- and post-intervention values for V_E, RR, V_T, or the RR/V_T ratio. The lung function pattern was assessed by comparing pre-VBS with post-VBS values and pre-IBS with post-IBS values, by comparing pre-VBS with pre-IBS values and post-VBS with post-IBS values, and by comparing absolute and relative changes in values between post-VBS and post-IBS measurements. Those data are presented in Table 3.

DISCUSSION

The major findings of the present study were that IBS increased C_{st},rs, as well as promoting greater IC

Table 1. Characteristics of the sample (N = 20).[a]

Characteristic	Result
Age, years	62.5 ± 14.3
Male gender	10 (50)
Duration of mechanical ventilation, days	26.9 ± 4.8
C_{st},rs, mL/cmH_2O	40.2 ± 14.9
R,rs, cmH_2O/L.s^{-1}	12.3 ± 3.3
Diagnosis	
Pulmonary sepsis	8 (40)
Stroke	6 (30)
Postoperative abdominal surgery	8 (40)
Pneumonia	8 (40)
Acute renal failure	2 (10)

C_{st},rs: static respiratory system compliance; and R,rs: total respiratory system resistance. [a]Values expressed as mean ± SD or as n (%).

Table 2. Results for the effects of voluntary breath stacking and involuntary breath stacking on respiratory mechanics.[a]

Variable	Pre-intervention	Post-intervention	p	Absolute change	Relative change
C_{st},rs, mL/cmH_2O					
Voluntary breath stacking	40.2 ± 14.9	40.4 ± 14.0	0.85	0.3 ± 4.0	1.3 ± 8.6
Involuntary breath stacking	38.8 ± 14.0	43.4 ± 13.6	0.007	4.6 ± 4.8	13.1 ± 11.9
p	0.27	0.03	-	0.043	0.008
Effect size	-	0.11	-	0.44	0.49
R,rs, cmH_2O/L.s^{-1}					
Voluntary breath stacking	12.9 ± 4.1	12.7 ± 4.1	0.37	−0.3 ± 0.9	−2.2 ± 6.7
Involuntary breath stacking	13.8 ± 5.9	14.0 ± 5.3	0.73	0.1 ± 1.3	2.8 ± 8.5
p	0.69	0.30	-	0.41	0.16
Effect size	-	0.14	-	0.17	0.01

C_{st},rs: static respiratory system compliance; and R,rs: total respiratory system resistance. [a]Values expressed as mean ± SD.

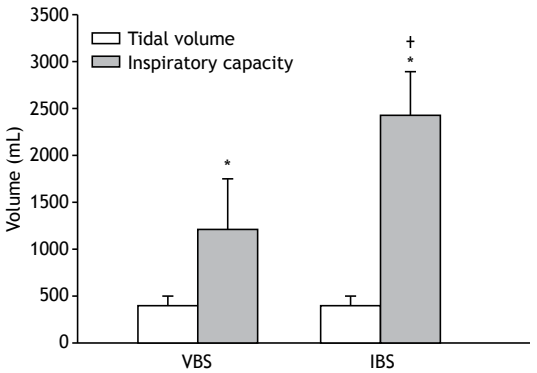


Figure 3. Basal tidal volume (white bar) and the inspiratory capacity (gray bar) obtained by voluntary breath stacking (VBS) and involuntary breath stacking (IBS). *p < 0.001 vs. basal tidal volume. †p < 0.001 vs. inspiratory capacity in the voluntary breath stacking group.

and higher airway pressure than did VBS. Neither technique produced changes in R,rs or in the pattern of lung function.

Bronchial hygiene techniques that recruit higher lung volumes have a greater potential for eliminating secretions. Higher inspiratory volume translates to higher elastic recoil pressure, higher PEF, and lower R,rs. Therefore, inspiratory volume appears to be the main factor in determining exhaled volume and PCF.[16] Achieving maximum insufflation capacity can confer some benefits, such as increased cough effectiveness, decreased atelectasis, increased compliance, and increased amplitude of chest movement,[17] as well as delaying mechanical ventilation or reducing the time on mechanical ventilation.[18] The two techniques studied here make it possible to maintain lung expansion longer, allowing additional time for the forces of interdependence to recruit volume, a process that does not usually take place during a single inspiratory effort.[19]

Increases in PCF during IBS can be obtained in various populations, including healthy individuals, individuals with respiratory muscle weakness, and patients with an obstructive pattern of lung function.[20] The patients who benefit most from IBS are those with a restrictive pattern of lung function, as well as those with neuromuscular disease, such as Duchenne muscular dystrophy,[21] spinal muscular atrophy,[22] congenital muscular dystrophy,[22] and amyotrophic lateral sclerosis.[5,23,24] Other indications include the postoperative period after cardiac surgery[25] and Parkinson's disease.[26]

In a study of 61 patients with Duchenne muscular dystrophy, PCF was compared among four conditions: during unassisted coughing; during IBS alone; with abdominal thrusts; and during IBS combined with abdominal thrusts. IBS promoted PCF values higher than those obtained during unassisted cough or with abdominal thrusts. However, IBS combined with abdominal thrusts was the most effective technique in increasing PCF.[21] Although the present study did not assess PCF, the larger increase in lung volume achieved by IBS appears to have been crucial for the increase in lung compliance and in the prevalence of productive cough. One study involving healthy individuals demonstrated that insufflations from a resuscitator bag promoted a mean increase in IC of 599 mL (20.4%) relative to the resting IC.[5] In the present study, VBS increased mean basal inspiratory volume by 813 mL, totaling a mean resting IC of 1,211 mL, whereas IBS increased mean basal inspiratory volume by 2,024 mL, resulting in a mean resting IC of 2,420 mL. Because our sample consisted of patients with respiratory muscle weakness due to prolonged hospitalization and mechanical ventilation, the resting IC was considerably smaller than that reported for healthy young adults. The improvements in volume and pressure obtained through the use of breath stacking techniques have been associated with increased PCF, greater mobilization of secretions, and increased cough effectiveness.[2,5]

In addition to producing higher lung volumes, IBS has the advantage of not requiring great muscle effort to achieve maximum IC, because it is a passive/assisted pulmonary insufflation technique. However, insufflation from a resuscitator bag should be performed in synchrony with inspiratory muscle contractions. Insufflations during the expiratory phase cause asynchrony and spikes in airway pressure. However, complications such as barotrauma

Table 3. Results for the effects of voluntary breath stacking and involuntary breath stacking on respiratory patterns.[a]

Variable	Pre-intervention	Post-intervention	p	Absolute change	Relative change
V_E, L					
Voluntary breath stacking	9.0 ± 1.9	8.5 ± 2.8	0.43	−0.5 ± 1.7	−6.2 ± 21.1
Involuntary breath stacking	9.5 ± 3.0	9.1 ± 3.0	0.43	−0.5 ± 1.9	−3.8 ± 16.4
p	0.39	0.39	-	0.99	0.39
Effect size	-	0.10	-	0.00	0.06
V_T, mL					
Voluntary breath stacking	398.0 ± 83.3	388.0 ± 84.2	0.61	−10.1 ± 71.7	−1.5 ± 16.5
Involuntary breath stacking	396.1 ± 94.5	378.2 ± 91.8	0.36	−17.9 ± 47.0	−4.2 ± 11.4
p	0.94	0.69	-	0.78	0.34
Effect size	-	0.05	-	0.06	0.09
RR, breaths/min					
Voluntary breath stacking	23.1 ± 5.4	22.4 ± 7.4	0.55	−0.7 ± 3.9	−3.4 ± 18.5
Involuntary breath stacking	24.1 ± 6.2	25.2 ± 7.2	0.32	1.1 ± 2.7	4.8 ± 12.1
p	0.53	0.10	-	0.26	0.13
Effect size	-	0.19	-	0.26	0.25
RR/V_T ratio, breaths/min/L					
Voluntary breath stacking	62.3 ± 23.4	62.4 ± 30.9	0.98	0.1 ± 17.6	1.9 ± 29.8
Involuntary breath stacking	64.0 ± 23.8	69.1 ± 24.9	0.29	5.1 ± 11.6	9.0 ± 20.3
p	0.81	0.34	-	0.46	0.27
Effect size	-	0.12	-	0.16	0.14

V_E: minute volume; and V_T: tidal volume. [a]Values expressed as mean ± SD.

have not been observed in neuromuscular patients after IBS.[2] The same is true for the use of IBS in healthy individuals with no primary intrinsic lung disease. One study reported that the resuscitator bag was well calibrated and that the safety valve opened automatically when the pressure reached 40 cmH_2O.[5] In the present study, in addition to the use of a safety valve, pressure was monitored by a manometer incorporated into the system, and the slow manual insufflations were stopped when the pressure reached 40 cmH_2O. Nevertheless, pressure spikes were observed during cough in patients who mobilized secretions, especially after IBS. Of the 20 patients evaluated, 17 (85%) coughed and required suctioning during IBS, compared with only 2 (10%) during VBS.

Another benefit of IBS is that it can be performed by the patients themselves through self-insufflation from a resuscitator bag. It is indicated for patients with reduced vital capacity, reduced PCF, secretion retention, or difficulty in eliminating secretions, as well as for those who are at high risk for atelectasis.[17] In one study, 18 patients with spinal muscular atrophy or congenital muscular dystrophy engaged in daily IBS training and were followed at home for 4-6 months to assess the effects.[22] The prescribed daily regimen was 10 series of 3-4 insufflations. There were increases in assisted and unassisted PCF, although the increases were less pronounced in the patients with associated scoliosis. In addition, FVC was found to have increased in the patients without scoliosis.[22]

IBS consists of consecutive insufflations from a resuscitator bag and consequent stacking of breaths. In contrast, manual hyperinflation consists of a single slow insufflation from a resuscitator bag, followed by an inspiratory pause.[27] Therefore, the volume recruited during IBS is probably higher than that recruited during manual hyperinflation. Several authors have used manual hyperinflation in mechanically ventilated patients, assessing its therapeutic effects or comparing its therapeutic effects with those of ventilator hyperinflation. Studies[10,28-30] have demonstrated that manual hyperinflation improves respiratory mechanics, without causing hemodynamic changes, and have used C_{st},rs to assess therapeutic effects, as in the present study. The mobilization of secretions leads to expansion/recruitment of collapsed lung units or lung units with high time constants, resulting in an increase in C_{st},rs. That effect is due to increases in collateral ventilation, elastic recoil pressure, and expiratory flow, resulting in an increase in gas-liquid interaction.[28]

During VBS, occlusion of the airways in the expiratory phase triggers compensatory mechanisms by progressively increasing central drive. The airflow resulting from each inspiratory effort increases the lung volume and stacks breaths. Over the course of successive inspiratory efforts, the volume increments tend to decrease, because the respiratory muscles are placed at a biomechanical disadvantage and compliance decreases. The inspiratory flow continues until the inspiratory effort becomes insufficient to open the one-way valve. At this point, the lung volume is close to total lung capacity.[7,19] One study compared the resting IC, the resting IC with a breath hold, and VBS in 26 cooperative patients in whom pain or muscle weakness resulted in impaired ability to achieve or sustain deep inspiration. VBS increased inspiratory

volume, indicating that the addition of a one-way valve is effective in increasing IC.[13] One other study compared the effects of incentive spirometry and VBS on FVC and recruited volume in 35 patients in the first five days after cardiac surgery. The authors reported that VBS completely restored inspiratory volume by postoperative day 2, in addition to having promoted greater lung volume recruitment over the five days of treatment, although they did not observe differences between the two techniques in terms of the FVC.[6]

The one-way valve allows the patient to relax the inspiratory muscles without exhaling and allows volume to increase during successive breaths. Two mechanisms can help to explain volume recruitment during VBS: increased neural stimulation and increased lung recruitment. In most patients, relatively high inspiratory volumes can be achieved with moderate pressures. However, patients whose respiratory mechanics are impaired by dyspnea or pain are unable to sustain the effort needed to achieve maximum volume recruitment.[13] The volume recruited during VBS depends exclusively on respiratory muscle contraction, and that dependency is a limiting factor for volume recruitment and the consequent therapeutic efficacy. Respiratory muscle weakness reduces the effectiveness of the inspiratory phase of cough, there being a direct relationship between MIP and cough flow, which emphasizes the need to strengthen the respiratory muscles.[17] In the present study, we observed that some patients were able to open the inspiratory valve after 30 s of occlusion. Those patients might have achieved greater IC.

IBS promoted greater IC and higher airway pressure than did VBS, resulting in an increase in C_{st},rs. However, neither technique had any effect on the lung function pattern.

REFERENCES

1. Strickland SL, Rubin BK, Drescher GS, Haas CF, O'Malley CA, Volsko TA, et al. AARC clinical practice guideline: effectiveness of nonpharmacologic airway clearance therapies in hospitalized patients. Respir Care. 2013;58(12):2187-2193. https://doi.org/10.4187/respcare.02925
2. Kang SW, Bach JR. Maximum insufflation capacity. Chest. 2000;118(1):61-65. https://doi.org/10.1378/chest.118.1.61
3. Torres-Castro R, Vilaró J, Vera-Uribe R, Monge G, Avilés P, Suranyi C. Use of air stacking and abdominal compression for cough assistance in people with complete tetraplegia. Spinal Cord. 2014;52(5):354-357. https://doi.org/10.1038/sc.2014.19
4. Brito MF, Moreira GA, Pradella-Hallinan M, Tufik S. Air stacking and chest compression increase peak cough flow in patients with Duchenne muscular dystrophy. J Bras Pneumol. 2009;35(10):973-979. https://doi.org/10.1590/S1806-37132009001000005
5. Sarmento A, de Andrade AF, Lima ÍN, Aliverti A, de Freitas Fregonezi GA, Resqueti VR. Air Stacking: A Detailed Look Into Physiological Acute Effects on Cough Peak Flow and Chest Wall Volumes of Healthy Subjects. Respir Care. 2017;62(4):432-443. https://doi.org/10.4187/respcare.05189
6. Dias CM, Vieira Rde O, Oliveira JF, Lopes AJ, Menezes SL, Guimarães FS. Three physiotherapy protocols: effects on pulmonary volumes after cardiac surgery. J Bras Pneumol. 2011;37(1):54-60. https://doi.org/10.1590/S1806-37132011000100009
7. Marini JJ, Rodriguez RM, Lamb VJ. Involuntary breath-stacking. An alternative method for vital capacity estimation in poorly cooperative subjects. Am Rev Respir Dis. 1986;134(4):694-698. https://doi.org/10.1164/arrd.1986.134.5.902
8. American Association for Respiratory Care. AARC Clinical Practice Guidelines. Endotracheal suctioning of mechanically ventilated patients with artificial airways 2010. Respir Care. 2010;55(6):758-764.
9. Chicayban LM, Zin WA, Guimarães FS. Can the Flutter Valve improve respiratory mechanics and sputum production in mechanically ventilated patients? A randomized crossover trial. Heart Lung. 2011;40(6):545-553. https://doi.org/10.1016/j.hrtlng.2011.05.008
10. Ahmed F, Shafeeq AM, Moiz JA, Geelani MA. Comparison of effects of manual versus ventilator hyperinflation on respiratory compliance and arterial blood gases in patients undergoing mitral valve replacement. Heart Lung. 2010;39(5):437-443. https://doi.org/10.1016/j.hrtlng.2009.10.006
11. Berney S, Denehy L. A comparison of the effects of manual and ventilator hyperinflation on static lung compliance and sputum production in intubated and ventilated intensive care patients. Physiother Res Int. 2002;7(2):100-108. https://doi.org/10.1002/pri.246
12. Chicayban LM. Acute effects of ventilator hyperinflation with increased inspiratory time on respiratory mechanics: randomized crossover clinical trial. Rev Bras Ter Intensiva. 2019;31(3):289 - 295. https://doi.org/10.5935/0103-507X.20190052
13. Baker WL, Lamb VJ, Marini JJ. Breath-stacking increases the depth and duration of chest expansion by incentive spirometry. Am Rev Respir Dis. 1990;141(2):343-346. https://doi.org/10.1164/ajrccm/141.2.343
14. Sarmento A, Resqueti V, Dourado-Júnior M, Saturnino L, Aliverti A, Fregonezi G, et al. Effects of Air Stacking Maneuver on Cough Peak Flow and Chest Wall Compartmental Volumes of Subjects With Amyotrophic Lateral Sclerosis. Arch Phys Med Rehabil. 2017;98(11):2237-2246.e1. https://doi.org/10.1016/j.apmr.2017.04.015
15. Barcelar Jde M, Aliverti A, Rattes C, Ximenes ME, Campos SL, Brandão DC, et al. he expansion of the pulmonary rib cage during breath stacking is influenced by age in obese women. PLoS One. 2014;9(11):e110959. https://doi.org/10.1371/journal.pone.0110959
16. Smith JA, Aliverti A, Quaranta M, McGuinness K, Kelsall A, Earis J, et al. Chest wall dynamics during voluntary and induced cough in healthy volunteers. J Physiol. 2012;590(3):563-574. https://doi.org/10.1113/jphysiol.2011.213157
17. Armstrong A. Developing a breath-stacking system to achieve lung volume recruitment. Br J Nurs. 2009;18(19):1166-1169. https://doi.org/10.12968/bjon.2009.18.19.44820
18. Bach JR, Bianchi C, Vidigal-Lopes M, Turi S, Felisari G. Lung inflation by glossopharyngeal breathing and "air stacking" in Duchenne muscular dystrophy. Am J Phys Med Rehabil. 2007;86(4):295-300. https://doi.org/10.1097/PHM.0b013e318038d1ce
19. Faria IC, Freire LM, Sampaio WN. Inspiration boosters: technical updates in incentive spirometers and breath-stacking. Rev Med Minas Gerais. 2013;23(2):228-234. https://doi.org/10.5935/2238-3182.20130035
20. Sivasothy P, Brown L, Smith IE, Shneerson JM. Effect of manually assisted cough and mechanical insufflation on cough flow of normal subjects, patients with chronic obstructive pulmonary disease (COPD), and patients with respiratory muscle weakness. Thorax. 2001;56(6):438-444. https://doi.org/10.1136/thorax.56.6.438
21. Ishikawa Y, Bach JR, Komaroff E, Miura T, Jackson-Parekh R. Cough augmentation in Duchenne muscular dystrophy. Am J Phys Med Rehabil. 2008;87(9):726-730. https://doi.org/10.1097/PHM.0b013e31817f99a8
22. Marques TB, Neves Jde C, Portes LA, Salge JM, Zanoteli E, Reed UC. Air stacking: effects on pulmonary function in patients with spinal muscular atrophy and in patients with congenital muscular dystrophy. J Bras Pneumol. 2014;40(5):528-534. https://doi.org/10.1590/S1806-37132014000500009
23. Sferrazza Papa GF, Pellegrino GM, Shaikh H, Lax A, Lorini L, Corbo M. Respiratory muscle testing in amyotrophic lateral sclerosis: a practical approach. Minerva Med. 2018;109(6 Suppl 1):11-19. https://doi.org/10.23736/S0026-4806.18.05920-7

24. Rafiq MK, Bradburn M, Proctor AR, Billings CG, Bianchi S, McDermott CJ, et al. A preliminary randomized trial of the mechanical insufflator-exsufflator versus breath-stacking technique in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(7-8):448-455. https://doi.org/10.3109/21678421.2015.1051992
25. Dias CM, Plácido TR, Ferreira MFB, Guimarães FS, Menezes SLS. Incentive spirometry and breath stacking: effects on the inspiratory capacity of individuals submitted to abdominal surgery. Rev Bras Fisioter. 2008;12(2):94-99. https://doi.org/10.1590/S1413-35552008000200004
26. Ribeiro BS, Lopes AJ, Menezes SLS, Guimarães FS. Selecting the best ventilator hyperinflation technique based on physiologic markers: A randomized controlled crossover study. Heart Lung. 2019;48(1):39-45. https://doi.org/10.1016/j.hrtlng.2018.09.006
27. Anderson A, Alexanders J, Sinani C, Hayes S, Fogarty M. Effects of ventilator vs manual hyperinflation in adults receiving mechanical ventilation: a systematic review of randomised clinical trials. Physiotherapy. 2015;101(2):103-110. https://doi.org/10.1016/j.physio.2014.07.006
28. Berney S, Denehy L. A comparison of the effects of manual and ventilator hyperinflation on static lung compliance and sputum production in intubated and ventilated intensive care patients. Physiother Res Int. 2002;7(2):100-108. https://doi.org/10.1002/pri.246
29. Dennis DM, Duncan CN, Pinder M, Budgeon CA, Jacob WJ. Performance of manual hyperinflation: consistency and modification of the technique by intensive care unit nurses during physiotherapy. J Clin Nurs. 2016;25(15-16):2295-2304. https://doi.org/10.1111/jocn.13190
30. Savian C, Paratz J, Davies A. Comparison of the effectiveness of manual and ventilator hyperinflation at different levels of positive end-expiratory pressure in artificially ventilated and intubated intensive care patients. Heart Lung. 2006;35(5):334-341. https://doi.org/10.1016/j.hrtlng.2006.02.003

J Bras Pneumol. 2020;46(4):e20190145
https://dx.doi.org/10.36416/1806-3756/e20190145

BRIEF COMMUNICATION

Sublobar resection in the treatment of elderly patients with early-stage non-small cell lung cancer

Margarida Afonso[1], Carlos Branco[2], Tiago Manuel Alfaro[1]

1. Serviço de Pneumologia, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.
2. Centro de Cirurgia Cardiotorácica, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

Submitted: 2 May 2019.
Accepted: 20 September 2019.

Study carried out at the Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

ABSTRACT

Surgical resection is the primary treatment option for early-stage non-small cell lung cancer, lobectomy being considered the standard of care. In elderly patients, physiological characteristics can limit the suitability for surgery and the extent of resection. Sublobar resection (SLR) can be offered as an alternative. The aim of this real-world analysis was to compare lobectomy and SLR in terms of recurrence and survival rates in patients over 70 years of age.

Keywords: Carcinoma, non-small-cell lung/mortality; Carcinoma, non-small-cell lung/surgery; Recurrence; Aged; Aged, 80 and over.

The incidence of non-small cell lung cancer (NSCLC) increases with age, 40% of cases occurring in patients over 70 years of age. For early-stage disease, surgical resection is the primary option, lobectomy being considered the standard of care. According to the National Comprehensive Cancer Network (NCCN) guidelines, sublobar resection (SLR) is appropriate in cases of reduced pulmonary reserve or major comorbidities and smaller tumors (< 2 cm).[1] Notably, recommendations for lobectomy are based on only one randomized controlled trial, conducted by the Lung Cancer Study Group, which showed that, in comparison with lobectomy, SLR resulted in a 3-fold increase in local recurrence, a 30% increase in overall mortality, and a 50% increase in cancer-related mortality.[2] In elderly patients, physiological limitations and comorbidities can limit surgical eligibility and the extent of resection. Retrospective studies have produced conflicting results regarding the benefits of lobectomy, although only a few have focused on the elderly. Advanced age has been associated with higher morbidity and mortality after lobectomy. In older patients, the risk of death from comorbidities can exceed that of death from cancer.[3] The greater parenchymal preservation in limited resection can challenge the gains achieved in lobectomy.[4] However, questions remain regarding recurrence and survival. In this study, we aimed to compare SLR and lobectomy in patients over 70 years of age with early-stage (stage I or II) NSCLC in a real-life context. We hypothesized that limited resection would produce outcomes similar to those obtained with lobectomy.

We retrospectively studied all patients over 70 years of age undergoing curative lung resection for NSCLC between January of 2012 and December of 2017. Surgery was performed in the thoracic surgery department of a university hospital, and treatment plans were discussed in multidisciplinary meetings. After surgery, all patients were followed at the same hospital. We excluded patients submitted to neoadjuvant treatment because that could indicate a more advanced clinical stage (≥ stage II), which would make them unsuitable candidates for SLR. Patients were divided into groups by the type of procedure they had undergone: SLR and lobectomy.

We reviewed clinical records to collect demographic data, as well as data regarding smoking status; performance status, as determined with the Eastern Cooperative Oncology Group (ECOG) scale; comorbidities, as determined with the Charlson comorbidity index (CCI); lung function, including FVC, FEV_1, and DLCO (all as percentages of the predicted value), as well as the FEV_1/FVC ratio; preoperative blood test results; histology findings; clinical staging; resected lymph nodes (LN); margin status; length of hospital stay; postoperative complications, in the immediate postoperative period and within the first 30 days, as determined with the Clavien-Dindo classification; time to recurrence; and overall survival (OS). For the calculation of the CCI, lung cancer was not considered a comorbidity. Staging was reviewed according to the 8th edition of the International Association for the Study of Lung Cancer tumor-node-metastasis classification of malignant tumors. For each patient, the time to recurrence and the OS were both calculated in months. The time to recurrence was defined as the time from surgery to recurrence, whereas the OS was defined as the time from surgery to death. Data related to patients who did not experience recurrence or die during the study period were censored at the end of the study.

The statistical analysis was performed with the Stata statistical software package, version 13 (StataCorp LP, College Station, TX, USA). Continuous variables were characterized with measures of central tendency (mean or median) and dispersion (standard deviation or interquartile range), according to the normality of the data, as determined with the Shapiro-Wilk test. Categorical

Correspondence to:
Margarida Afonso. Serviço de Pneumologia, Centro Hospitalar e Universitário de Coimbra, Rua Prof. Mota Pinto, 3075, Praceta, Coimbra, Portugal.
Tel.: 351 23 940-0400. E-mail: margaridaiafonso@gmail.com
Financial support: None.

ISSN 1806-3713

variables were characterized as absolute and relative frequencies. Intergroup differences in categorical variables were evaluated with Student's t-tests for independent variables or Wilcoxon rank-sum tests, according to the normality of the data. For comparisons among groups, ANOVA or the Kruskal-Wallis test was used. Relationships between categorical variables were tested by using chi-square tests. A two-tailed $p < 0.05$ was considered significant.

For the analysis of recurrence-free survival and OS, we calculated estimated values for postoperative months 12, 24, 36, 48, and 60. A univariate analysis was performed by using log-rank tests for dichotomized variables, including demographic characteristics, blood test results, lung function parameters, the ECOG performance status score, the CCI, histology findings, clinical stage, length of hospital stay, and complications. In a multivariate analysis, factors showing a $p < 0.25$ were used in order to construct an initial Cox proportional hazard model, after which a step-down procedure was used in order to select predictors with a $p < 0.05$.

A total of 72 patients were included: 18 (25.0%) were in the SLR group (all 18 underwent wedge resection); and 54 (75.0%) were in the lobectomy group. The choice of wedge resection over segmentectomy was based on the experience at the hospital. Table 1 shows the characteristics of the sample as a whole and of each group. With the exception of lung function, which was slightly worse in the SLR group, there were no significant differences between the two groups.

The mean age of the patients was 78.4 years. Of the 72 patients evaluated, 49 (68.1%) were male, 38 (52.8%) were never smokers, and 70 (97.2%) had an ECOG performance status score of 0 or 1. The most common histological diagnosis was adenocarcinoma. The SLR and lobectomy groups were identical in terms of comorbidities, with a median CCI of 5 (range, 4-8) in both groups, as well as in terms of the mean tumor size and the tumor location. The clinical stage was determined to be IA1 in 26 patients (36.1%), IA2 in 4 (5.6%), IB in 36 (50.0%), IIA in 4 (5.6%), and IIB in 2 (2.8%).

The number of LNs resected was higher in the lobectomy group than in the SLR group (15.6 ± 11.0 vs. 7.4 ± 7.0; $p = 0.005$). Pleural invasion was observed in 28 cases (38.9%) overall, being more common in the lobectomy group, occurring in 23 (42.6%) of the 54 patients in that group, compared with only 5 (27.8%) of the 18 patients in the SLR group, although the difference was not significant. Negative margins were achieved in all cases. The mean hospital stay (in days) was shorter in the SLR group (6.7 ± 3.3 vs. 8.0 ± 3.5), although that difference was also not significant.

Surgical complications in the immediate postoperative period were reported in 18 (25%) of the 72 cases evaluated, 14 complications occurring in the lobectomy group and 4 occurring in the SLR group. Of those 18 complications, 17 were categorized as Clavien-Dindo grade I, the remaining complication (nosocomial pneumonia requiring antibiotic therapy, in an SLR group patient) being categorized as Clavien-Dindo grade II. The SLR group patient with pneumonia died after discharge (on postoperative day 10). One lobectomy group patient developed a late complication (residual pleural effusion).

In the sample as a whole, the mean follow-up period was 33.5 ± 24.3 months, being 35.5 ± 24.3 months in the SLR group and 32.9 ± 22.0 months in the lobectomy group ($p > 0.05$). The recurrence rate was lower in the SLR group than in the lobectomy group, although the difference was not significant ($p = 0.12$). In the univariate analysis, a platelet density $> 200 \times 10^9$/L, pleural invasion, and a tumor stage > I were found to be significant predictors of recurrence and mortality. In the multivariate analysis, only pleural invasion and platelet density retained their significance. Only a tumor stage > I and pleural invasion were found to be significant predictors of OS in the univariate and multivariate analyses. Although recurrence was a strong predictor of mortality, it was not included in the model, because it was considered part of the causal pathway. Notably, SLR was not associated with a higher risk of recurrence or mortality. The results from the recurrence and survival analyses are reported in Table 2.

The main finding of our study was that, among older patients with early-stage NSCLC, the recurrence and mortality rates observed after SLR were similar to those observed after lobectomy. The length of hospital stay and the rate of postoperative complications were slightly better among the patients undergoing SLR. These results are relevant, because a less invasive approach may be preferable in older patients with NSCLC if it minimizes postoperative mortality and recurrence. Our conclusions are limited by the small size of the sample and retrospective nature. Because this was a retrospective study, it is possible that there was a selection bias. However, it mirrors real-world practice.

Our results complement those obtained by Mery et al.,[5] who showed that the benefits of lobectomy do not extend to patients over 71 years of age.[5] In contrast, Razi et al.[6] found that, in patients over 75 years of age with stage IA NSCLC, cancer-specific survival and OS were lower after wedge resection than after segmentectomy or lobectomy. Nevertheless, the 5-year cancer-specific survival rate was similar among the three groups.

Some aspects of our findings merit special considerations. Having a stage II tumor was found to be associated with higher mortality, with an adjusted hazard ratio (HR) of 4.96 (95% CI: 1.20-24.08). That corresponds to the worse prognosis associated with tumors ≥ 4 cm (stage cT2b).[7] However, the tumor characteristics (histology, size, and location) and tumor stage were equivalent between the two groups, none of those variables being prognostic. Although the NCCN recommends that the use SLR be limited to tumors ≤ 2 cm (stage IA1 or IA2),[1] SLR was performed for larger tumors, with no apparent impact on outcomes,

Table 1. Characteristics of elderly patients with early-stage non-small cell lung cancer, by type of surgical procedure performed.[a]

Characteristic	SLR (n = 18)	Lobectomy (n = 54)	Total (n = 72)	p
Male	14 (77.8)	35 (64.8)	49 (68.1)	NS
Mean age, years	77.2 ± 2.8	78.9 ± 3.2	78.4 ± 3.2	NS
Smoking status				
Never smoker	8 (44.4)	30 (55.6)	38 (52.8)	
Former smoker	8(44.4)	20 (37.0)	28 (38.9)	NS
Current smoker	2 (11.1)	4(7.4)	6 (8.3)	
ECOG performance status score				
0	9 (50.0)	30 (55.6)	39 (54.1)	
1	8 (44.4)	23 (42.6)	31 (43.0)	NS
2	1 (5.6)	1 (1.9)	2 (2.8)	
Charlson comorbidity index	4.9 ± 1.1	4.9 ± 0.7	4.9 ± 0.8	NS
Lung function parameters				
FEV_1, % of predicted	79.1 ± 25.5	103.2 ± 29.1	98.0 ± 29.9	< 0.01
FVC, % of predicted	94.7 ± 22.4	106.6 ± 26.3	104.0 ± 25.8	NS
FEV_1/FVC ratio	64.4 ± 10.6	79.2 ± 16.8	76.0 ± 16.7	< 0.01
Single-breath DLCO, % of predicted	66.3 ± 17.7	75.5 ± 15.9	73.6 ± 16.5	NS
Preoperative blood test results				
BUN, mg/dL	25.1 ± 12.7	20.1 ± 7.6	21.4 ± 9.3	NS
Creatinine, mg/dL	1.07 ± 0.42	0.95 ± 0.44	0.98 ± 0.43	NS
Albumin, g/dL	4.2 ± 0.3	4.3 ± 0.4	4.3 ± 0.4	NS
LDH (U/L)	216.0 ± 63.3	241.8 ± 107.8	235.3 ± 98.6	NS
CRP (U/L)	0.61 ± 0.83	0.69 ± 0.88	0.66 ± 0.86	NS
Leukocyte density, g/L	7.8 ± 2.8	7.2 ± 2.4	7.3 ± 2.5	NS
Hemoglobin, g/dL	13.5 ± 1.5	13.4 ± 1.5	13.4 ± 1.5	NS
Platelet density, g/L	225.0 ± 92.7	209.2 ± 54.2	213.2 ± 65.5	NS
Tumor size, mm	20.6 ± 12.6	23.7 ± 9.9	22.9 ± 10.6	NS
Tumor location				
Right upper lobe	6 (33.3)	14 (25.9)	20 (27.8)	
Right middle lobe	2 (11.1)	2 (3.7)	4 (5.6)	
Right lower lobe	2 (11.1)	12 (22.2)	14 (19.4)	NS
Left upper lobe	4 (22.2)	12 (22.2)	16 (22.2)	
Left lower lobe	4 (22.2)	14 (25.9)	18 (25.0)	
Histology				
Adenocarcinoma	9 (50.0)	44 (81.5)	53 (73.6)	
Squamous cell carcinoma	4 (22.2)	4 (7.4)	8 (11.1)	
Adenosquamous carcinoma	2 (11.1)	4 (7.4)	6 (8.3)	NS
Pleomorphic carcinoma	2 (11.1)	1 (1.9)	3 (4.2)	
Sarcomatoid carcinoma	0	1 (1.9)	1 (1.4)	
Combined tumor type	1 (5.6)	0	1 (1.4)	
Clinical stage				
IA1	4 (22.2)	3 (5.6)	7 (9.7)	
IA2	6 (33.3)	22 (40.7)	28 (38.9)	
IA3	5 (27.8)	20 (37.0)	25 (34.7)	NS
IB	3 (16.7)	5 (9.3)	8 (11.1)	
IIA	0	4 (7.4)	4 (5.6)	
Number of lymph nodes	7.4 ± 7.0	15.6 ± 11.0	13.6 ± 11.0	< 0.05
Pleural invasion	5 (27.8)	23 (42.6)	28 (38.9)	NS
Hospital stay, days	6.7 ± 3.3	8.0 ± 3.5	7.7 ± 3.5	NS
Complications rate	4 (22.2)	14 (25.9)	18 (25.0)	NS

SLR: sublobar resection; NS: nonsignificant; ECOG: Eastern Cooperative Oncology Group; BUN: blood urea nitrogen; LDH: lactate dehydrogenase; and CRP: C-reactive protein. [a]Values expressed as n (%) or mean ± SD.

Table 2. Univariate and multivariate analyses of dichotomized variables to identify predictors of recurrence, mortality, and survival.

Variable	Univariate analysis		Multivariate analysis	
	Recurrence	Mortality	Recurrence	Survival
	p	p	p	p
Male gender	0.94	0.24		
Age ≥ 80 years	0.48	0.56		
Any smoking history	0.75	0.59		
Married	0.11	0.57		
ECOG performance status score > 0	0.46	0.79		
Charlson comorbidity index > 4	0.90	0.36		
FVC < 80% of the predicted value	0.85	0.17		
BUN > 21 mg/dL	0.29	0.21		
Albumin < 4.2 g/dL	0.07	0.08		
Hb < 12 g/dL	0.43	0.74		
Platelet density > 200 g/L	0.03	0.92	0.04	
Tumor size > 20 mm	0.20	0.46		
Tumor located in the right lung	0.11	0.09		
Tumor stage > I	< 0.01	0.03		0.05
SLR	0.12	0.31		
≥ 10 lymph nodes resected	0.62	0.58		
Pleural invasion	< 0.01	< 0.01	0.01	< 0.01
Postoperative complications	0.24	0.37		

ECOG: Eastern Cooperative Oncology Group; BUN: blood urea nitrogen; Hb: hemoglobin; and SLR: sublobar resection.

in our sample. As shown by Harada et al.,[8] SLR may reduce the lung cancer-induced loss of lung function, thus possibly improving survival. In our patient sample, the predictive value of pleural invasion was confirmed; we found that pleural invasion was associated with higher recurrence rates (adjusted HR = 4.67; 95% CI: 1.46-14.98) and lower survival rates (adjusted HR = 3.81; 95% CI: 1.44-10.12). Although a platelet density > 200 g/L has been associated with a risk of disease progression after surgical treatment of NSCLC,[9] further validation is needed.

Surgical margins and LN sampling during SLR warrant discussion. Although the objective of SLR, as defined by the NCCN, should be to achieve surgical margins ≥ 2 cm or that are greater than the size of the nodule,[1] detailed measures were not were not available in the pathology reports for the cases evaluated in the present study. As expected, the number of LNs resected was significantly higher among our lobectomy group patients (p = 0.041), although it did not correlate with recurrence or survival. Because we analyzed the number of LNs but not the number of stations, we cannot determine whether the NCCN recommendation to remove LNs from at least three stations, always including station 7, was followed. Less invasive procedures have been associated with postoperative benefits such as shorter hospital stays and fewer complications.[10] We identified such benefits in our patient sample, which could be explained, in part, by the fact that all of the procedures were performed with an open approach.

Preoperative exclusion of patients with lower lung reserve and more comorbidities, as recommended in the European Respiratory Society/European Society of Thoracic Surgeons guidelines on fitness for radical therapy,[11] should be considered. The fact that those guidelines were followed at the facility under study could explain the lack of any significant impact of those variables in the present study. In our sample, a case-by-case multidisciplinary discussion resulted in a higher proportion of patients being selected for lobectomy than for SLR (75% vs. 25%). This can be interpreted as reflecting the fact that lobectomy is the current standard of care, SLR being a compromise between lobectomy and nonsurgical treatment. However, on the basis of the data available, we cannot draw a definitive conclusion regarding whether SLR was the procedure of choice or was chosen as a compromise solution. Nevertheless, in elderly patients with early-stage NSCLC, the results achieved with SLR appear to be equivalent to those achieved with lobectomy.

REFERENCES

1. National Comprehensive Cancer Network (NCCN) [homepage on the Internet]. Brussels: NCCN; c2019 [cited 2019 Jan 18]. Non-small cell lung cancer (version 3.2019). Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
2. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg. 1995;60(3):615-623. https://doi.org/10.1016/0003-4975(95)00537-U
3. Guerra M, Neves P, Miranda J. Surgical treatment of non-small-cell lung cancer in octogenarians. Interact Cardiovasc Thorac Surg.

2013;16(5):673-680. https://doi.org/10.1093/icvts/ivt020

4. Groth SS, Rueth NM, Hodges JS, Habermann EB, Andrade RS, D'Cunha J, et al. Conditional cancer-specific versus cardiovascular-specific survival after lobectomy for stage I non-small cell lung cancer. Ann Thorac Surg. 2010;90(2):375-382. https://doi.org/10.1016/j.athoracsur.2010.04.100
5. Mery CM, Pappas AN, Bueno R, Colson YL, Linden P, Sugarbaker DJ, et al. Similar long-term survival of elderly patients with non-small cell lung cancer treated with lobectomy or wedge resection within the surveillance, epidemiology, and end results database. Chest. 2005;128(1):237-245. https://doi.org/10.1378/chest.128.1.237
6. Razi SS, John MM, Sainathan S, Stavropoulos C. Sublobar resection is equivalent to lobectomy for T1a non-small cell lung cancer in the elderly: a Surveillance, Epidemiology, and End Results database analysis. J Surg Res. 2016;200(2):683-689. https://doi.org/10.1016/j.jss.2015.08.045
7. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93-99. https://doi.org/10.3322/caac.21388
8. Harada H, Okada M, Sakamoto T, Matsuoka H, Tsubota N. Functional advantage after radical segmentectomy versus lobectomy for lung cancer. Ann Thorac Surg. 2005;80(6):2041-2045. https://doi.org/10.1016/j.athoracsur.2005.06.010
9. Yu D, Liu B, Zhang L, DU K. Platelet count predicts prognosis in operable non-small cell lung cancer. Exp Ther Med. 2013;5(5):1351-1354. https://doi.org/10.3892/etm.2013.1003
10. Kilic A, Schuchert MJ, Pettiford BL, Pennathur A, Landreneau JR, Landreneau JP, et al. Anatomic segmentectomy for stage I non-small cell lung cancer in the elderly. Ann Thorac Surg. 2009;87(6):1662-1668. https://doi.org/10.1016/j.athoracsur.2009.02.097
11. Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy) [published correction appears in Eur Respir J. 2009 Sep;34(3):782]. Eur Respir J. 2009;34(1):17-41. https://doi.org/10.1183/09031936.00184308

J Bras Pneumol. 2020;46(4):e20200204
https://dx.doi.org/10.36416/1806-3756/e20200204

SPECIAL ARTICLE

Brazilian Thoracic Society recommendations for the diagnosis and treatment of chronic thromboembolic pulmonary hypertension

Caio Julio Cesar dos Santos Fernandes[1], Jaquelina Sonoe Ota-Arakaki[2], Frederico Thadeu Assis Figueiredo Campos[3], Ricardo de Amorim Correa[4], Marcelo Basso Gazzana[5], Carlos Vianna Poyares Jardim[1], Fábio Biscegli Jatene[1], Jose Leonidas Alves Junior[1], Roberta Pulcheri Ramos[2], Daniela Tannus[6], Carlos Teles[2], Mario Terra Filho[1], Daniel Waetge[7], Rogerio Souza[1]

1. Grupo de Circulação Pulmonar, Divisão de Cardiopneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Disciplina de Pneumologia. Hospital São Paulo, Escola Paulista de Medicina. Universidade Federal de São Paulo, São Paulo (SP) Brasil.
3. Serviço de Pneumologia e Cirurgia Torácica, Hospital Júlia Kubistchek, Belo Horizonte (MG) Brasil.
4. Serviço de Pneumologia e Cirurgia Torácica, Hospital das Clínicas, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.
5. Serviço de Pneumologia, Hospital de Clínicas de Porto Alegre, Porto Alegre (RS) Brasil.
6. Hospital das Clínicas, Faculdade de Medicina, Universidade Federal de Goiás, Goiânia (GO) Brasil.
7. Disciplina de Pneumologia, Faculdade de Medicina, Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.

Submitted: 30 April 2020.
Accepted: 22 May 2020.

ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious and debilitating disease caused by occlusion of the pulmonary arterial bed by hematic emboli and by the resulting fibrous material. Such occlusion increases vascular resistance and, consequently, the pressure in the region of the pulmonary artery, which is the definition of pulmonary hypertension. The increased load imposed on the right ventricle leads to its progressive dysfunction and, finally, to death. However, CTEPH has a highly significant feature that distinguishes it from other forms of pulmonary hypertension: the fact that it can be cured through treatment with pulmonary thromboendarterectomy. Therefore, the primary objective of the management of CTEPH should be the assessment of patient fitness for surgery at a referral center, given that not all patients are good candidates. For the patients who are not good candidates for pulmonary thromboendarterectomy, the viable therapeutic alternatives include pulmonary artery angioplasty and pharmacological treatment. In these recommendations, the pathophysiological bases for the onset of CTEPH, such as acute pulmonary embolism and the clinical condition of the patient, will be discussed, as will the diagnostic algorithm to be followed and the therapeutic alternatives currently available.

Keywords: Hypertension, pulmonary/diagnosis; Hypertension, pulmonary/surgery; Hypertension, pulmonary/therapy; Hypertension, pulmonary/drug therapy; Pulmonary artery/pathology; Pulmonary embolism/complications.

DEFINITION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension (PH) that results from occlusion of the pulmonary circulation by residual organized thromboembolic material, with consequent pulmonary microvasculature remodeling, which is induced or enhanced by a combination of imperfect angiogenesis, reduced endogenous fibrinolysis, and endothelial dysfunction. In this process, there is a gradual replacement of the normal intimal endothelial layer, causing a reduction in the pulmonary vascular bed and a consequent increase in its resistance and, therefore, in the afterload of the right ventricle. The increased load imposed on the right ventricle leads to progressive right ventricular failure, which is the major factor responsible for the mortality associated with CTEPH.[1]

The definition of CTEPH is based on objective criteria (Chart 1).[2] Conceptually, the diagnostic criteria aim to exclude a potential component related to acute embolic material (hence the requirement of at least three months of full anticoagulation), to confirm occlusion with imaging methods (rather than only on the basis of clinical suspicion), and, finally, to confirm the presence of PH. It is important to understand this concept in the broader context of other causes of PH.

Multiple etiological processes may be responsible for the elevation of pressure in the pulmonary vascular system as opposed to the normal condition of low pressure and low vascular resistance. By definition, PH occurs when mean pulmonary artery

Correspondence to:
Rogerio Souza, Avenida Enéas de Carvalho Aguiar, 44, 5º andar, Bloco II, CEP 05403-900, São Paulo, SP, Brasil.
Tel./Fax: 55 11 3069-5695. E-mail: rogerio.souza@incor.usp.br
Financial support: None.

Chart 1. Diagnostic criteria for chronic thromboembolic pulmonary hypertension (all are required).

Diagnostic criterion
Invasive confirmation of pulmonary hypertension: mean pulmonary artery pressure > 20 mmHg[a]
Confirmation of pulmonary thromboembolism by pulmonary artery CT angiography, ventilation/perfusion lung scintigraphy, or pulmonary arteriography
At least three months of effective anticoagulation

Adapted from Galiè et al.[2] [a]Simonneau et al.[3]

pressure (mPAP) exceeds 20 mmHg.[3] This pressure threshold for defining PH has recently been set; most evidence regarding all forms of PH considers an mPAP ≥ 25 mmHg as a diagnostic criterion. Therefore, although the present recommendations adopt the current criterion for defining PH, it should be understood that the scientific evidence is quite limited in patients with an mPAP between 21 and 24 mmHg.

There are various pathophysiological mechanisms that might cause PH: increased pulmonary vascular hydrostatic pressure, as in mitral stenosis; vascular bed loss associated with hypoxic vasoconstriction, as in lung parenchymal diseases; pulmonary vascular remodeling with endothelial and middle layer proliferation, as in idiopathic pulmonary arterial hypertension (PAH); or even mechanical obstruction of the vascular bed, as previously mentioned in CTEPH.[4] Therefore, the first step in dealing with a patient with PH is to determine the predominant pathophysiological mechanism. This will allow adequate classification of the patient according to the current system (Chart 2), which is based on grouping patients by the major pathophysiological mechanism, clinical presentation, and response to treatment; that is, when a patient with PH is adequately classified, there is an associated treatment plan available.[3]

In accordance with the current classification of PH, CTEPH is in group 4.[3] As previously mentioned, adequate classification of CTEPH is particularly significant, because the therapeutic approach to CTEPH is completely different from that to other forms of PH, given that surgical treatment might be curative.[5]

PATHOPHYSIOLOGY: FROM ACUTE PULMONARY THROMBOEMBOLISM TO CTEPH

In up to approximately 80% of the cases of CTEPH, the disease is preceded by an identified episode of acute pulmonary thromboembolism (PTE).[6] During the acute event, there are several changes resulting from the presence of emboli, changes that are outside the scope of these recommendations.[7] However, it is worth noting that an acute PTE episode can have three possible clinical outcomes[8]: 1) right ventricular failure due to an acute increase in the afterload of the right ventricle, which can lead to death; 2) complete reperfusion of the pulmonary circulation in the medium term, which can be spontaneous (resulting from the action of endogenous thrombolytics) or secondary to treatment; or 3) partial reperfusion of the pulmonary circulation, with residual occlusion of part of the pulmonary circulation. It is believed that one year after an acute PTE episode adequately treated with anticoagulants, approximately 30% of patients will continue to have filling defects in the pulmonary circulation when reevaluated with ventilation/perfusion lung scintigraphy,[9] although not all of those will be symptomatic. Patients with perfusion defects after an episode of acute pulmonary embolism who continue to have dyspnea but do not have PH at rest are classified as having chronic pulmonary thromboembolic disease (CPTED).[1] In this group, symptoms are due to PH on exertion or to changes in ventilation and gas exchange. In contrast, patients with residual perfusion defects, symptoms of even greater relevance, and PH are characterized as having CTEPH.

Unlike patients with CPTED, patients with CTEPH have marked hemodynamic dysfunction not only because of the hypoperfused vascular region (due to chronic pulmonary artery occlusion), but also because of clot-free lung regions, which are subjected to relatively increased flow, given that the blood flow diverted from the obstructed regions.[10] In addition, it is speculated that bronchial circulation, whose flow is increased in such cases, may also lead to further increased flow in the vascular bed distal to the obstruction because of the presence of collateral circulation. This increased flow leads to endothelial dysfunction, with consequent vascular remodeling.

As a result of this condition of regional hypoperfusion/increased flow, susceptible patients develop PH and subsequent right ventricular failure. Therefore, endothelial dysfunction in CTEPH is found not only in the pulmonary artery region but also in the capillary and venous regions.[11] This could explain why a considerable number of patients continue to have residual PH after pulmonary thromboendarterectomy (PTEA),[12] a surgical procedure that is intended to cure CTEPH but that would not interfere with the disease affecting the pulmonary capillary and venous systems because it addresses only the fibrous material that is obstructing the pulmonary arteries.

EPIDEMIOLOGY

The prevalence of CTEPH after acute PTE is highly debatable, with rates ranging from 0.7% to 10% in the literature.[13-15] A meta-analysis of 16 studies, involving 4,407 patients followed for more than two years, reported an overall incidence of 0.56% (95% CI: 0.1-1.0%). When only the patients who survived for at least six months after the embolic event were considered, the incidence was 3.2% (95% CI:

Chart 2. Current classification of pulmonary hypertension.

Classification of pulmonary hypertension
1. Pulmonary arterial hypertension
1.1 Idiopathic pulmonary arterial hypertension
1.2 Heritable pulmonary arterial hypertension
1.3 Drug- or toxin-induced pulmonary arterial hypertension
1.4 Pulmonary arterial hypertension associated with:
1.4.1 Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1.5 Responders to calcium channel blockers
1.6 Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1.7 Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1 Heart failure with preserved EF
2.2 Heart failure with reduced EF
2.3 Valvular disease
2.4 Congenital or acquired heart diseases leading to post-capillary pulmonary hypertension
3. Pulmonary hypertension due to lung disease and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung diseases with mixed restrictive and obstructive patterns
3.4 Hypoxia without structural lung disease
3.5 Lung developmental disorders
4. Pulmonary hypertension due to pulmonary artery obstructions
4.1 Pulmonary hypertension due to chronic pulmonary thromboembolism
4.2 Other pulmonary artery obstructions: sarcoma or angiosarcoma; other malignant tumors (renal carcinoma, uterine carcinoma, gem cell tumors of the testis); non-malignant tumors (leiomyoma); arteritis without connective tissue disease; congenital pulmonary artery stenoses; parasitosis (hydatidosis)
5. Pulmonary hypertension due to unclear and/or multifactorial mechanisms
5.1 Hematological disorders: chronic hemolytic anemia; myeloproliferative disorders
5.2 Systemic and metabolic disorders: pulmonary Langerhans cell histiocytosis; Gaucher disease; glycogen storage disease; neurofibromatosis; and sarcoidosis
5.3 Others: fibrosing mediastinitis; chronic renal failure with or without hemodialysis
5.4 Complex congenital heart disease

Adapted from Simonneau et al.[3] EF: ejection fraction.

2.0-4.4%), and, among these patients, when only those without major comorbidities were considered, the incidence was 2.8% (95% CI: 1.5-4.1%).[16] The incidence of CTEPH in the global population is reported to be 5 new cases/million population per year,[17] the mean age at diagnosis being 63 years and men and women being equally affected.[18] Time to diagnosis is long, having been reported to be, on average, 14 months in a European cohort.[19]

Contrary to what might be supposed, the risk factors for CTEPH are different from the classic predisposing factors for acute PTE, which have been associated with the classic triad described by Virchow: hypercoagulability; endothelial lesion; and venous stasis.[20] Deficiencies of antithrombin, protein C, and protein S, as well as factor V Leiden mutation, have not been associated with the presence of CTEPH.[21] However, high serum concentrations of factor VIII and the presence of lupus anticoagulant and antiphospholipid antibodies have been associated with the development of CTEPH, as has the presence of genetic variants that lead to fewer sites of binding of clots to plasmin, making the thrombi more resistant to lysis by endogenous thrombolytics.[22] The identification of familial clusters of CTEPH cases has also corroborated the role of genetic changes in the genesis of this disease.[23]

Various clinical comorbidities have also been associated with CTEPH: neoplasms; arteriovenous shunts; splenectomy; and chronic inflammatory diseases (such as inflammatory bowel disease, osteomyelitis, and rheumatoid arthritis).[24-26] Very curiously, chronic infectious diseases, particularly bacterial ones, associated with infection with *Staphylococcus aureus*, appear to be related to the development of CTEPH. Fragments of *S. aureus* DNA have been isolated in the peripheral blood of patients with CTEPH, but not in patients with acute PTE.[27] The greatest risk factor for the development of CTEPH in a European cohort was infection of cardiac pacemakers.[24] In addition, in experimental models, the presence of *S. aureus* resulted in delayed recanalization of induced thrombi.[27] Thyroid dysfunction, particularly that caused by thyroid hormone replacement therapy, has been identified as an independent risk factor for CTEPH. A recent study identified thyroid dysfunction in 10.5% of the patients with scheduled surgery, and, in 54.8% of those patients, there was no history of

thyroid disease.[28] Elevated levels of (endogenous or exogenous) thyroid hormones are associated with a higher risk of thrombosis secondary to an increase in factor VIII and von Willebrand factor, as well as with deficient fibrinolysis. The major risk factors for the development of CTEPH are described in Table 1.

DIAGNOSIS

The diagnosis of CTEPH is based on clinical status, imaging studies, and hemodynamic data. The main complaint is progressive dyspnea, most often preceded by an episode of acute PTE or deep vein thrombosis in the lower limbs. Physical examination can reveal a loud pulmonary component of the second heart sound and signs of right heart failure, with leg edema, ascites, and jugular stasis. Episodes of syncope may also be present. Hemoptysis is a more common symptom than in other forms of PH, being secondary to rupture of hypertrophied bronchial arteries.[29]

Chest X-ray is of very limited importance in assessing CTEPH because it yields nonspecific findings, and echocardiography is commonly used as a screening test to investigate the presence of PH. One of the tests that can add sensitivity to the diagnosis of PH is cardiopulmonary exercise testing (CPET). CPET seeks to identify changes in oxygen consumption and carbon dioxide output during exercise, identifying the mechanism causing dyspnea; in early cases of PH, CPET can identify exertional limitation and increased physiological dead space.[30]

Ventilation/perfusion lung scintigraphy (Figure 1) remains to be the test of choice for the investigation of cases of suspected CTEPH because of its high sensitivity (96-97%) and high specificity (90-95%),[31] both of which are higher than those of conventional CT angiography (Figure 2). A meta-analysis evaluating CT angiography for the diagnosis of CTEPH reported an aggregate sensitivity of 76% (95% CI: 69-82%), despite a high specificity of 96% (95% CI: 93-98%).[32] Low probability scintigraphic findings exclude the diagnosis of CTEPH, which is not true for conventional CT angiography. More recent techniques, such as dual-energy CT angiography with iodine maps, have shown sensitivity and specificity similar to those of lung scintigraphy.[33]

The most significant role of chest CT angiography is the diagnosis of acute PTE. In CTEPH, the greatest importance of chest CT angiography does not lie in excluding the diagnosis, but rather in making the differential diagnosis of CTEPH from other causes of vascular obstruction,[34] as well as from lung parenchymal changes that might suggest the presence of heterogeneous perfusion (Figure 3). In addition, chest CT angiography has been a strategic tool for evaluating treatment options for CTEPH, together with lung scintigraphy and digital pulmonary angiography. In conjunction with hemodynamic data, these tests can define the best therapeutic strategy: PTEA, considered the treatment of choice; balloon pulmonary angioplasty (BPA); or pharmacological treatment.

Chest CT angiography can also be useful in differentiating between acute PTE and CTEPH. There are radiological signs of chronicity of pulmonary vascular impairment that are identifiable on CT angiography and that make it possible to prevent inappropriate use of treatments for primary pulmonary reperfusion injury (thrombolytics or embolectomy)[35,36] in cases initially diagnosed as acute events (Chart 3). Only patients with acute PTE and signs of hemodynamic instability should receive these treatments,[8,37] not those with newly diagnosed CTEPH.

Magnetic resonance imaging (MRI) can be used for the differential diagnosis of CTEPH (from pulmonary artery sarcoma, for instance).[38] In addition, cardiac MRI provides reliable information on cardiac chambers, allowing prognostic evaluation and the follow-up of interventions such as PTEA.[39] Pulmonary artery magnetic resonance angiography is not usually used for the diagnosis of CTEPH for reasons of spatial resolution and logistics, although new techniques and equipment have improved its accuracy.[40]

Similarly to MRI, positron-emission tomography-CT (PET-CT) can contribute to the differential diagnosis of CTEPH from diseases mimicking CTEPH. The role of PET-CT has been described in the identification of pulmonary artery sarcomas[41] and Takayasu's arteritis involving the pulmonary arteries.[42] In both conditions, the uptake of glucose labeled with ^{18}F-fluorodeoxyglucose measured with PET-CT is substantially increased in the vascular obstruction

Table 1. Major risk factors for the development of chronic thromboembolic pulmonary hypertension.

Risk factor	OR (95% CI)
Infected pacemaker/arteriovenous shunts	76.40 (7.67-10.351)
Splenectomy	17.87 (1.56-2.438)
Recurrent venous thromboembolism events	14.49 (5.4-43.08)
Thyroid hormone replacement therapy	6.10 (2.73-15.05)
Previous venous thromboembolism event	4.52 (2.35-9.12)
Antiphospholipid antibodies and lupus anticoagulant antibodies	4.20 (1.56-12.21)
History of malignancy	3.76 (1.47-10.43)
Blood type other than O	2.09 (1.12-3.94)

Based on data from Bonderman et al.[24],[a] [a]Independent risk factors when compared with those of patients with nonthromboembolic pulmonary hypertension; in that study,[24] most patients had pulmonary arterial hypertension (group 1).

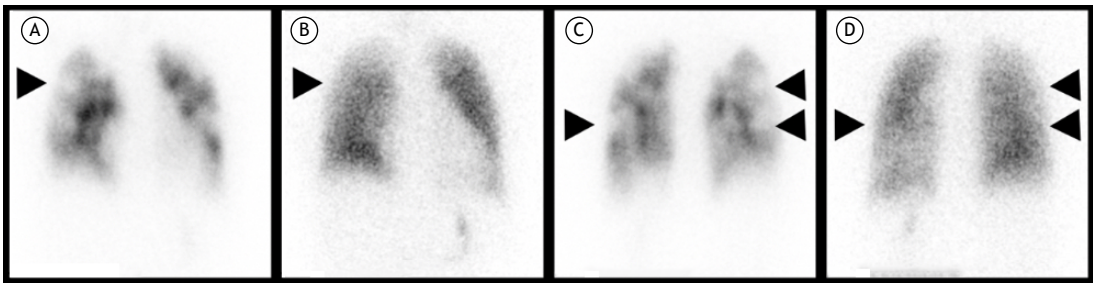


Figure 1. Ventilation/perfusion scintigraphy of a patient with chronic thromboembolic pulmonary hypertension. Note that ventilation is homogeneous (B and D), but perfusion is heterogeneous, with several segmental defects (A and C). There are regions that receive ventilation but not perfusion (arrowhead), suggesting vascular occlusion.

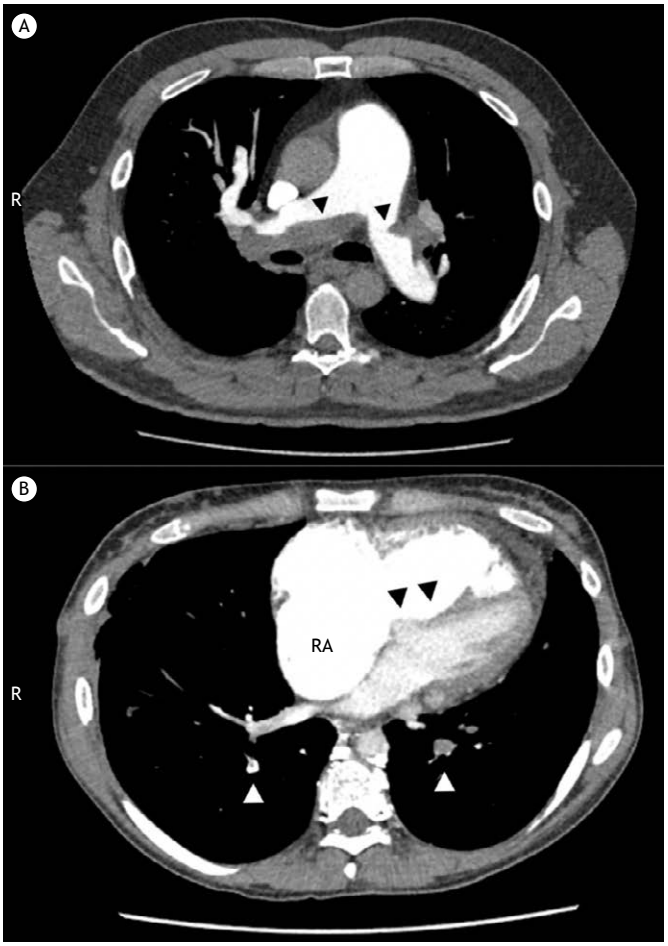


Figure 2. Chest CT angiography of a patient with chronic thromboembolic pulmonary hypertension. Note in A the eccentric clots that adhere to the pulmonary artery walls; in B, in addition to the clots, the dilated right atrium (RA) and the flattening of the interventricular septum (black arrowheads), suggesting pulmonary hypertension and right ventricular dysfunction.

and distinguishes these conditions from CTEPH, given that the vascular occlusions in CTEPH generally do not show uptake of labeled glucose on PET-CT.

Invasive tests, such as right heart catheterization (RHC) and digital subtraction pulmonary arteriography (Figure 4), are key to preoperative assessment and to stratification of clinical and surgical risk in patients with CTEPH. RHC is mandatory to confirm the presence of PH, typically precapillary PH.[1] Although some patients with CTEPH may show vasoreactivity, which may indicate a better prognosis, RHC is not performed at the treatment level, because it does not alter therapy.[2,43] Given the complexity of these tests and their importance in defining the therapeutic approach, they should be performed at referral centers for CTEPH. The sequence of tests recommended for the investigation of CTEPH can be seen in Figure 5.

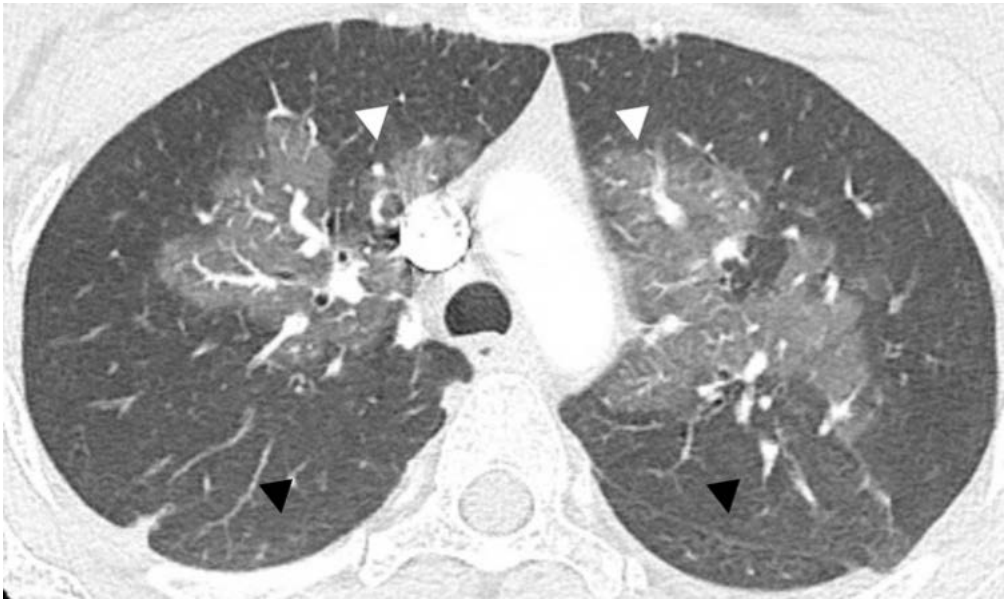


Figure 3. CT image on lung parenchymal window setting in a patient with chronic thromboembolic pulmonary hypertension. Note the mosaic perfusion pattern, with hypoperfused areas (black arrowheads) and hyperperfused areas (white arrowheads).

Chart 3. Pulmonary artery CT angiography findings suggestive of pre-existing chronic vascular disease.

Direct vascular signs
Eccentric filling defects that adhere to the vascular wall and may show calcification, being different from filling defects in the center of blood vessels, within the dilated lumen, which are suggestive of acute pulmonary thromboembolism Abrupt termination of a vessel Complete vascular occlusion or concave or pouch-like filling defects Intimal irregularity Linear intraluminal filling defects (such as bands or webs) Stenosis or poststenotic dilatation Vascular tortuosity
Indirect vascular signs
Significant right ventricular hypertrophy, right atrial dilatation Pericardial effusion Pulmonary arterial dilatation (> 29 mm in men and > 27 mm in women) or pulmonary arterial wall calcification Poststenotic dilation of bronchial arteries resulting from obstructed vessels
Parenchymal changes
Mosaic attenuation of the parenchyma as a consequence of geographic variation in perfusion

Modified from Dias et al.[34]

Regardless of the imaging method used, it is important to consider other diagnoses that can mimic CTEPH. As highlighted above, differentiation from acute PTE should always be sought. Large unilateral filling defects and/or intravascular lobulation suggest pulmonary artery sarcomas. The presence of multiple aneurysms and/or arterial wall thickening should raise the suspicion of pulmonary arterial vasculitis. Sometimes, abrupt termination of a major branch of the pulmonary artery, the causes of which can be a central thrombus, hypoplasia, or agenesis of the pulmonary artery, can be a diagnostic challenge. Large thrombi in situ, especially at bifurcation of pulmonary arteries and their branches, occurring more frequently in conditions of increased flow, such as in congenital heart disease with shunt, can also cause diagnostic difficulties in CTEPH.[38]

TREATMENT OF CTEPH

General approach

Some approaches suggested for other forms of PH are also recommended for patients with CTEPH, although most of them have a low level of evidence. Chief among them are[2]: 1) female patients should avoid pregnancy and should be enrolled in specific education and follow-up programs, given the increased complexity associated with the use of hormonal contraceptive methods in this population; 2) physical

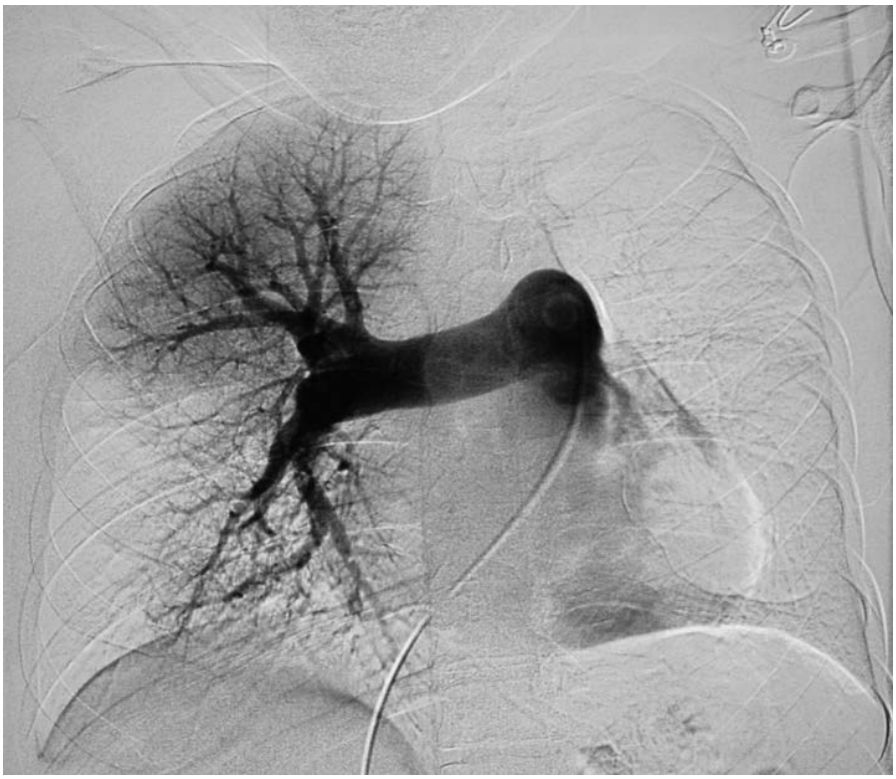


Figure 4. Pulmonary arteriography showing various filling defects, with exclusion of the left lung and of various segments in the right lower lobe, consistent with chronic thromboembolic pulmonary hypertension.

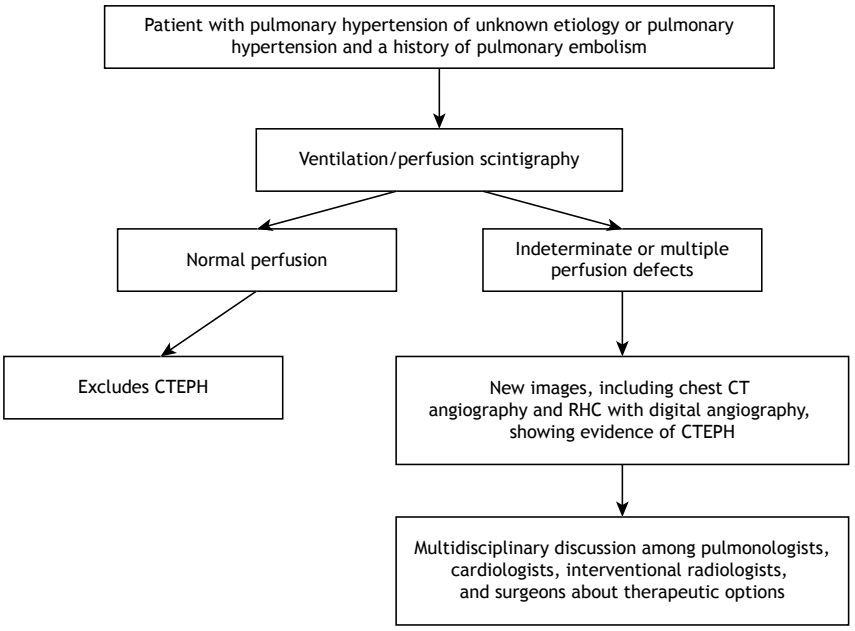


Figure 5. Investigation algorithm for chronic thromboembolic pulmonary hypertension (CTEPH). RHC: right heart catheterization.

training programs can improve patient functional capacity; however, such programs should be started only after the use of specific treatments and under the supervision of teams with experience in caring for patients with PH; 3) immunization against influenza and pneumococcal infection should be performed during outpatient follow-up; 4) psychological and social support is desirable; 5) patients should be

advised of the risks of elective surgery and long air travel; 6) diuretics should be used in the presence of circulatory congestion associated with right ventricular failure; 7) the criteria for recommending home oxygen therapy are the same as those in patients with COPD, although there is no specific evidence for its use; and 8) it should be emphasized that there is no indication for the use of calcium channel blockers in CTEPH patients.

Anticoagulation

All patients with CTEPH should receive full anticoagulation indefinitely as from the time of diagnostic suspicion. Confirmation of the diagnosis should be made only after at least three months of anticoagulation so that any reversible vascular effect produced by anticoagulation will have occurred (i.e., so that any possible acute residual component will have been neutralized).[10] Anticoagulation should be continued also in the postoperative period if the patient undergoes PTEA, regardless of surgical success, and during clinical treatment of non-operated patients.[1]

The choice of an optimal anticoagulant for the treatment of CTEPH is still a subject of controversy in the literature. Vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) can be used. Traditionally, as well as in the major articles in the literature, VKAs are the most widely used, with a therapeutic target international normalized ratio between 2.0 and 3.0.[1,18] Despite the lack of specific studies about CTEPH, DOACs have been rapidly incorporated into the treatment of CTEPH worldwide because of their convenient dosing schedules, stable pharmacokinetic properties, safety profile in terms of major bleeding, and good results, as well as their good acceptance in the context of acute PTE.[44] In 2016 in Germany, 51.0% and 46.2% of 392 patients diagnosed with CTEPH received anticoagulation with DOACs and VKAs, respectively.[45] In Brazil, a case series of patients with CTEPH showed that the use of DOACs in this situation was safe and efficient, regardless of the surgical status of the patients.[46] However, a study conducted in the UK suggests caution in the use of DOACs in CTEPH.[47] In that multicenter, retrospective study, 794 and 206 patients were treated with VKAs and DOACs, respectively, after PTEA. There were no differences in improvement in hemodynamics or functional status after surgery between the two groups, nor were there differences in major bleeding over a follow-up of 612 ± 702 days (0.7% per person/year). However, venous thromboembolism recurrence was higher in those treated with DOACs than in those treated with VKAs (4.62% vs. 0.76% per person/year; p = 0.008), with no differences in survival. Definitive conclusions about the role of DOACs in CTEPH still require further evidence from prospective studies or data from large registries. Therefore, the use of DOACs as the drugs of choice for patients with CTEPH still cannot be recommended. In addition, it is worthy of note that the use of DOACs in patients with antiphospholipid syndrome is not recommended to date because some studies have reported an increased rate of thromboembolic events in the group treated with DOACs when compared with the group treated with VKAs.[48,49]

Surgical treatment: PTEA

The presence of fibrous material obstructing the vascular lumen (Figure 6) shows why PTEA is the treatment of choice for patients with CTEPH.[2] The surgical results are excellent, depending on the level of experience of the referral center, as well as on appropriate patient selection.[50] Patients with CTEPH who undergo PTEA have a better prognosis than do non-operated patients, even when we consider that up to half of the operated patients may still have some degree of PH after the surgical procedure.[51] It is important not to confuse PTEA with embolectomy, which consists in removing only acute (nonendothelialized) thrombi and is used as reperfusion therapy in acute PTE.

Referral centers

Facilities that have adequate infrastructure to perform PTEA and BPA and have a multidisciplinary team with clinicians, surgeons, radiologists, and intensivists, are considered referral centers for CTEPH.[51] The team should be experienced in the management of this condition, should be prepared for the perioperative management of patients with CTEPH, and should perform at least 10 PTEAs per year.[50] Less-experienced centers, which perform fewer than 10 PTEAs per year, reported higher mortality rates than did centers that perform more than 50 PTEAs per year (8.8% and 3.4%, respectively). Ideally, referral centers for CTEPH should strive for excellence, performing more than 20 PTEAs per year, with mortality rates < 10%.[52]

Patient selection

Patient selection considers the amount of surgically accessible thromboembolic material, as well as its effects on pulmonary vascular resistance (PVR), in order to determine the potential hemodynamic improvement that may result from the surgical intervention.[51] The concept of proportionality between the extent of obstruction and the hemodynamic presentation is somewhat subjective and is related to the level of experience of the center. In certain situations, getting a second opinion from experienced centers regarding operability might be useful for novice centers. In a study that evaluated pharmacological interventions in patients with CTEPH, in which assessment of operability was confirmed or not by centers with wide experience in the surgical management of CTEPH, 69 (22%) of 312 patients who were initially regarded as technically inoperable were reclassified as viable candidates for PTEA,[53] clearly demonstrating the role that the learning curve plays in the decision making of whether or not to recommend the surgical intervention and justifying the requirement that, in

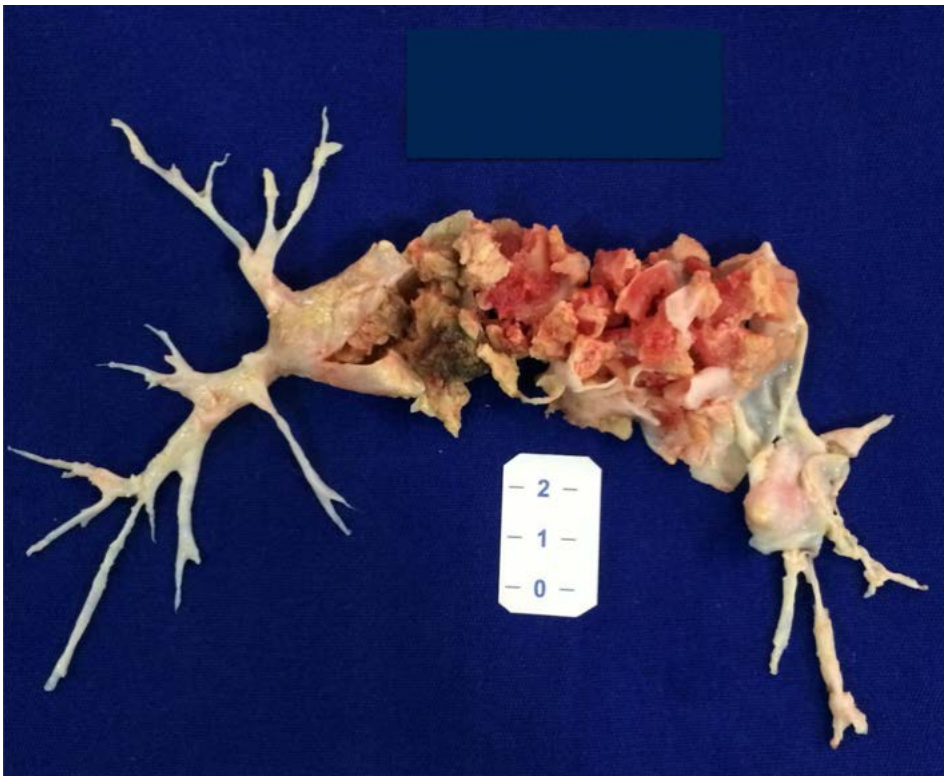


Figure 6. Surgical specimen obtained during pulmonary thromboendarterectomy.

order for a center to be classified as a referral center, it should perform a minimum number of PTEAs. ·In the decision making of whether or not to recommend PTEA, factors associated with favorable surgical results should be considered, such as a history of deep vein thrombosis/PTE, absence of comorbidities, absence of signs of right heart failure, functional class II or III status, clear proportionality between the imaging abnormalities and the hemodynamic data, bilateral lower lobe disease, PVR less than 1,000 dyn · s · cm^{-5}, and high pulse pressure.[1] The absence of these characteristics does not contraindicate PTEA, but indicates higher surgical risk, and should therefore be weighed against the level of experience of the center in performing the surgical procedure.

A specific population to be considered to be selected for PTEA is that of patients with unilateral occlusion of one of the main branches of the pulmonary artery, also known as complete pulmonary vascular exclusion (see Figure 4, left lung). In such cases, although the patients are usually younger and have lower pulmonary artery pressure and lower PVR, local factors can make it difficult to perform PTEA and can compromise the surgical result. It is not uncommon, in cases of complete unilateral pulmonary vascular exclusion, that the arterial bed distal to the obstruction shows severe postobstructive arteriopathy or remains hypoplastic, causing inadequate reperfusion despite PTEA.[54] Therefore, cases of unilateral pulmonary artery occlusion should be considered a priority for PTEA, which should be performed before the development of a postobstructive arteriopathy.[55]

Given the low rates of venous thromboembolism in the postoperative period after PTEA, most centers of excellence have abandoned the practice of inserting an inferior vena cava filter prior to surgery. The recommendation is to restart anticoagulation as early as possible, taking into account perioperative bleeding status and the presence of a coagulopathy, as well as the presence of other comorbidities.

Surgical procedure

PTEA is performed through a longitudinal median sternotomy using cardiopulmonary bypass (CPB), with the patient being cooled to 18-20°C. This is followed by a period of total circulatory arrest (TCA) of up to 20 min, during which either the right or the left pulmonary artery is approached (Figure 7) and the obstructive fibrous material is removed. Next, CPB is resumed, and blood is recirculated for 10 min, after which there is one more cycle of TCA for the contralateral approach.[56] In most cases, two periods of TCA are sufficient, one for each side approached, but, if necessary, more periods of TCA can be performed until the pulmonary arteries are completely unblocked. After the last period of TCA, CPB is resumed and the patient is slowly rewarmed, at which point other interventions can be made, such as coronary artery revascularization or correction of congenital malformations. Given the need for long CPB time with periods of TCA, measures such as protection

of the brain by local cooling and assessment of brain activity should be implemented to minimize adverse effects. In addition, anesthetic care, perioperative mechanical ventilation strategies, anticoagulation management, and adequate hemodynamic monitoring are of vital importance, as are anesthesiologists and intensivists trained in performing this type of surgery and in providing extracorporeal membrane oxygenation (ECMO), if necessary.[57] Despite the extent of the surgical procedure, the European registry shows that operated patients have significantly greater survival than non-operated patients, underscoring the role of PTEA as the first-line treatment for eligible patients.[50] On the basis of intraoperative findings, patients are classified into resection categories, which are associated with surgical benefit and long-term prognosis (Chart 4).[55]

The major complications of PTEA are hemodynamic and respiratory. Right ventricular dysfunction in the immediate postoperative period can make it difficult to discontinue CPB. Venoarterial ECMO, although rarely necessary, can provide a bridge to right ventricular recovery.[58] Another complication is residual PH, which occurs in up to 50% of the patients, although a recent meta-analysis involving 4,868 patients reported its presence in approximately 25% of the operated patients.[59] Pulmonary reperfusion injury is a severe respiratory complication that occurs most frequently in the first 48 h after surgery and can cause inflammatory pulmonary edema and severe hypoxemia. In some cases, venovenous ECMO may be necessary for ventilatory support.[57]

The impact of PTEA on the right ventricle suggests the presence of reverse remodeling,[60] with a reduction in ventricular volumes and mass, as well as an improvement in ventricular ejection fraction. Moderate to severe tricuspid insufficiency is common in patients with CTEPH but in general does not need to be corrected during PTEA, given the reduction in right ventricular dimensions after the reduction in PVR.[55] Bilateral lung transplantation (exceptionally heart-lung transplantation) is the surgical treatment for patients with PH refractory to other therapies who have no contraindications to this procedure. Patients with CTEPH rarely undergo lung transplantation, since they respond significantly to other therapies.[61]

BPA

For patients with CTEPH who have residual PH (after surgery) or for whom surgery is not feasible

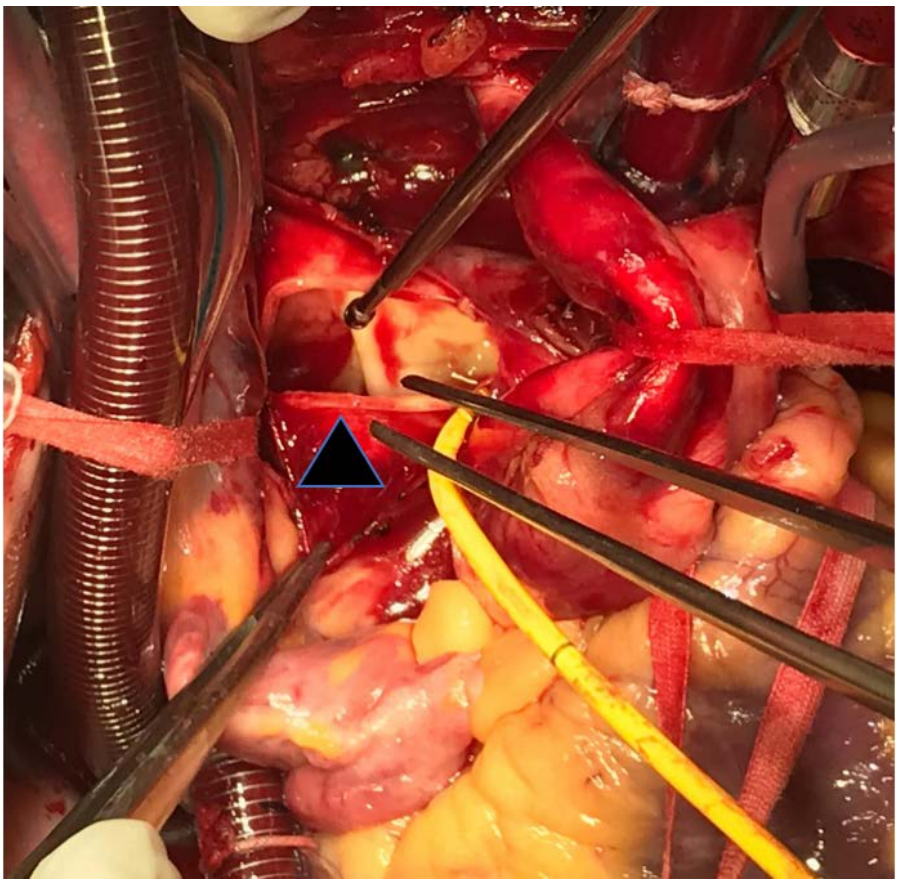


Figure 7. Image of the surgical field of a patient undergoing pulmonary thromboendarterectomy. The pulmonary artery is sectioned longitudinally (arrowhead); an organized white thrombus can be seen within the pulmonary artery, adjacent to the dissecting clamps. There is no blood flow through the pulmonary artery, given that the patient is on cardiopulmonary bypass during a period of total circulatory arrest (cannulas on the left).

(for technical reasons or because of thrombus inaccessibility), treatment options used to be limited to clinical treatment or pulmonary transplantation.[1,55] However, since the late 1990s, reports of pulmonary artery catheterization procedures for dilation of chronically obstructed branches have been published.[62] BPA, or simply pulmonary angioplasty, is currently an important resource for the treatment of patients with CTEPH.[1,63,64]

BPA consists in the insertion a balloon-tipped catheter that can be used to dilate systemic arteries (e.g., femoral, renal, or even coronary arteries) and the subsequent inflation of the balloon within the chosen vessel, without the need for prostheses, such as stents (Figure 8), or the use of thrombolytics or thrombus fragmentation techniques, as can occur in acute PTE. The balloon is inflated to generate enough pressure to disrupt the fibrin network or displace it radially, producing an improvement in local blood flow and an increase in the diameter of the treated vessel, thus leading to a reduction in PVR.[65-68]

Because the disease is rarely limited to a single area, this treatment is repeated approximately 6-8 times (sessions) for each patient, since approaching more than 4 segments in the same session increases the risk of complications, such as reperfusion edema or rupture of vessels (causing alveolar hemorrhage). From the first reports to more consistent studies,[65,67,68] BPA has gradually been incorporated into the treatment algorithm for CTEPH, because the results of this intervention have shown that it can improve hemodynamics, improve symptoms, and increase exercise capacity and right ventricular function, with significantly reduced rates of complications.[63,69,70] Retrospective studies have shown that the benefits of BPA also persist in the medium term,[71,72] and study groups outside Japan were able to reproduce encouraging results.[64,73] A meta-analysis of 12 observational studies (a total of 493 patients) reported a 2-year mortality rate of 1.3% in patients who underwent BPA, a rate that is significantly lower than that associated with the pharmacological treatment alone.[74] The role of BPA in patients with surgically resectable lesions but for whom surgery is contraindicated because of comorbidities or who refuse surgery has yet to be established.[1] BPA, as well as PTEA, should be performed at referral centers by professionals trained in the procedure.

Pharmacological treatment

Technically inoperable CTEPH

All patients with CTEPH should be assessed for eligibility for PTEA at a referral center, as defined previously, because PTEA is potentially curative. However, given that not all patients are eligible for PTEA, either because of the presence of inaccessible thrombi or because PVR is disproportionately high for the degree of vascular obstruction seen on imaging studies,[50] pharmacological treatment, such as BPA, is an alternative.

Three randomized, placebo-controlled clinical trials (Table 2) reported the benefits of using PAH-specific medications in patients with CTEPH who are inoperable (functional class II-IV).[75-77] The medications evaluated

Chart 4. Surgical classification of chronic thromboembolic pulmonary hypertension.

Surgical level	Location of thromboembolism
Level 0	No evidence of CTE in either lung
Level I	CTE starting in the main pulmonary arteries
Level IC	Complete occlusion of one main pulmonary artery with CTE
Level II	CTE starting at the level of lobar arteries or in the descending pulmonary artery
Level III	CTE starting at the level of segmental arteries
Level IV	CTE starting at the level of subsegmental arteries

Adapted from Galiè et al.[52] CTE: chronic thromboembolism.

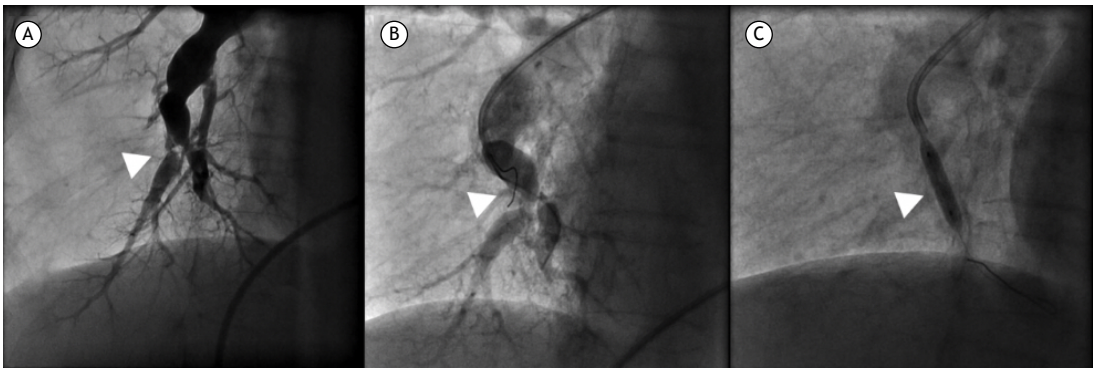


Figure 8. Pulmonary artery angioplasty. In A, multiple circumferential lesions in a segmental branch of the right pulmonary artery; in B, passage of a guidewire; and, in C, passage and inflation of a balloon to dilate the vascular lumen and reduce pulmonary vascular resistance.

were bosentan,[75] riociguat,[76] and macitentan.[77] Those trials showed different clinical endpoints. In the trial regarding bosentan,[75] the primary endpoint was a composite of an increase in six-minute walk distance (6MWD) and a reduction in PVR, whereas in the trial regarding riociguate,[76] it was an increase in 6MWD. In the trial regarding macitentan,[77] the primary endpoint was a reduction in PVR. In addition, two of the trials were phase III trials,[75,76] whereas one was a phase II trial.[77] The trials regarding riociguat and macitentan[76,77] showed positive outcomes, whereas that regarding bosentan,[75] which had a composite primary endpoint, the results cannot be considered positive because it showed an effect only in reducing PVR.

A meta-analysis involving 6 studies and 565 patients with CTEPH showed that the use of PAH-targeted drugs in this population led to a significant hemodynamic improvement, as well as to an improvement in symptoms, functional class, and exercise capacity. No differences were found in mortality or in the incidence of severe adverse events.[78]

Residual PH

Although PTEA can be curative, recent data suggest that approximately 25% of the operated patients have some degree of residual PH.[59] Some doubt exists regarding cutoff values for defining residual PH after PTEA. Whereas prospective studies have used the traditional cutoff value of 25 mmHg for defining it,[76] a cohort study of 880 patients who had been operated on at one of eight centers in the United Kingdom reported that a postoperative mPAP of 38 mmHg and postoperative PVR > 425 dyn · s · cm^{-5} correlated with a worse prognosis.[12] Currently, it is recommended that an mPAP value of 30 mmHg, invasively determined 3-6 months after PTEA,[79] be used to define the presence of significant residual PH. This value comes from the data analysis carried out in that cohort study,[12] which showed that an mPAP > 30 mmHg in the postoperative period after PTEA was associated with higher long-term mortality. The aforementioned trials[75,76] included patients with residual PH, defined as an mPAP ≥ 25 mmHg and PVR ≥ 300 dyn · s · cm^{-5}, more than six months after PTEA. In the trial regarding bosentan,[75] a reduction in PVR was observed also in the patients with residual PH, but there was no improvement in exercise capacity. In that regarding riociguat,[76] there was an improvement in 6MWD and a reduction in PVR also in the subgroup of patients who had previously been operated on. Macitentan was not evaluated in patients with residual PH.[77] Currently, riociguat is the only medication that has been approved by the American, European, and Brazilian regulatory agencies for the treatment of technically inoperable CTEPH or residual PH.

Combined pharmacological treatment

Regarding the macitentan trial,[77] 61% of the patients had already been treated with a phosphodiesterase-5 inhibitor and/or an oral or inhaled prostacyclin when they were started on either macitentan or placebo. The efficacy of macitentan was similar between those who had previously been treated and those who had not.[77] Other combinations of PH-targeted drugs have not been prospectively studied in CTEPH. The combination of riociguat and a phosphodiesterase-5 inhibitor is contraindicated; a study of one such combination reported a lack of benefit and a high rate of discontinuation due to systemic arterial hypotension in patients with PAH.[80]

Table 2. Randomized, double-blind, placebo-controlled clinical trials of drugs for the treatment of technically inoperable chronic thromboembolic pulmonary hypertension.[a]

Study	Jaïs et al.[75],[b]	Ghofrani et al.[76],[b]	Ghofrani et al.[77]
Drug	Bosentan	Riociguat	Macitentan
Dosing schedule	125 mg p.o., bid	0.5-2.5 mg p.o., tid	10 mg/day p.o., qd
Number of patients	157	261	80
Duration, weeks	16	16	16 and 24[c]
Residual or recurrent PH	41 (29.9%)	72 (27.6%)	–
Previous use of PH-specific medication	-	-	49 (61.3%)
Baseline 6MWD, m	342 ± 84	347 ± 80	352 ± 81
Effect on 6MWD, m	+2	+46	+34
Baseline PVR, dyn · s · cm^{-5}	783 (95% CI: 703-861)	787 ± 422	957 ± 435
Effect on PVR, %	−24	−31	−16
Major adverse effects[d]	Peripheral edema (13% vs. 7.5%) Hepatotoxicity (7.8% vs. 1.3%)	Headache (25% vs. 14%) Hypotension (9% vs. 3%)	Peripheral edema (23% vs. 10%) ↓ hemoglobin (15% vs. 0)

bid: twice a day; tid: three times a day; qd: every day; PH: pulmonary hypertension; 6MWD: six-minute walk distance; and PVR: pulmonary vascular resistance. [a]Values expressed as n or as mean ± SD. [b]We also included patients with residual PH after pulmonary thromboendarterectomy. [c]PVR at week 16 and 6MWD at week 24. [d]Drug versus placebo.

PH medications as "bridging to surgery"

The evidence supporting pharmacological treatment as bridging to surgery is scarce. International registry data have shown delayed referral to surgery and worse outcomes in those patients treated prior to referral.[50,81] Recently, a case series has demonstrated some benefit of using pharmacological therapy as bridging to surgery in a population with more severe hemodynamic impairment.[82] Nevertheless, clinical treatment for improving the hemodynamic status of patients prior to the surgical procedure is not recommended as part of the routine treatment of CTEPH. Clinical treatment can be considered in selected cases only at referral centers with wide experience in the surgical treatment of patients with CTEPH, so that it will not lead to a delay in accessing the treatment of choice.

Patients either not eligible for surgery because of comorbidities or who refuse surgery

Patients with accessible thrombi but who were either not eligible for surgery because of comorbidities or refused to undergo surgery were not included in the studies presented above; such patients require an individualized approach.

Pharmacological treatment or angioplasty

One study included 105 patients with CTEPH not undergoing PTEA who were randomized either to receive riociguat or to undergo BPA in one of 14 centers in France.[83] In that study, the efficacy of BPA was greater, given that it reduced PVR by 60%, compared with 32% for riociguat ($p < 0.0001$). In addition, the proportion of patients who improved at least one functional class was higher among those undergoing BPA than among those treated with riociguat (88% vs. 49%; $p < 0.0001$). The reduction in brain natriuretic peptide levels was also 67% higher in the BPA group than in the riociguate group ($p < 0.0001$). There was no difference in 6MWD between the groups. The benefits of BPA came at a price. The proportion of patients with at least one adverse event was higher among those undergoing BPA than among those treated with riociguat (50% vs. 26%), as was the proportion of patients with at least one severe adverse event directly related to treatment (14% vs. 9%). None of the patients discontinued treatment because of adverse events, and there were no deaths during the 26 weeks of the study. These data suggest that BPA should be tried before pharmacological treatment with riociguat in patients with CTEPH who are not eligible for surgery. If BPA is not completely successful in normalizing the patient's pressure, pharmacological treatment with riociguat would then be indicated.[1] It should be emphasized, however, that that study[83] was the first to propose such an approach and that the long-term results of BPA as an initial treatment option if PTEA is not possible—results that would define the role of BPA in this setting—remain unknown. Nevertheless, this treatment option can be accepted as a possibility for patients who are not candidates for surgery. If BPA is not readily available, it is advisable to start pharmacological therapy so that there is no delay in initiating treatment.

Multimodal treatment

The combination of different therapeutic modalities is already a reality in CTEPH. There are reports and case series on different combinations of therapeutic strategies, such as PTEA plus pre- and/or post-operative drugs, BPA plus drugs, and, more recently, the combination of PTEA, BPA, and drugs. This last combination is still an individualized approach and depends on the location of the obstruction, the severity of hemodynamic impairment, and the expertise of the team.[84] Ongoing long-term prospective studies may clarify the role of combined methods in the treatment of CTEPH, as well as the indications and the appropriate timing for each intervention.

The algorithm proposed for the therapeutic approach to CTEPH is described in Figure 9.

Follow-up

Patients with CTEPH, whether they undergo PTEA or not, should be evaluated at least every 3-6 months. The factors assessed include clinical variables (functional class, symptom progression, signs of right heart failure); biochemical markers (natriuretic peptides); cardiac echocardiography and/or cardiac MRI (right ventricular function by tricuspid annular plane systolic excursion [TAPSE] or ejection fraction, atrial dilatation, presence of pericardial effusion); exercise testing (either 6MWD or oxygen consumption and ventilatory equivalent during CPET); and hemodynamic variables (right atrial pressure, cardiac index, and mixed venous oxygen saturation). At each visit, patient risk should be stratified on the basis of these variables.[85] There are some risk stratification models that were initially used in PAH and have currently been validated in CTEPH,[86,87] and the therapeutic target is to maintain patients in the low-risk category all the time (Table 3), with an increase in quality of life.[88] CPET can also be used in the assessment of the severity of CTEPH and in the follow-up of patients with CTEPH, but therapeutic target thresholds have yet to be defined for this population.

Screening for CTEPH after acute PTE

All patients who had acute PTE should be clinically evaluated at 3-6 months of follow-up. At follow-up visits, in addition to the assessment of symptoms, attention should be paid to risk factors that are present and are predictors of an increased risk of CTEPH, such as recurrent venous thromboembolism, young age, unprovoked venous thromboembolism, extensive filling defects, signs of right ventricular dysfunction (e.g., pulmonary artery systolic pressure > 60 mmHg and/or right ventricular hypertrophy), and previous

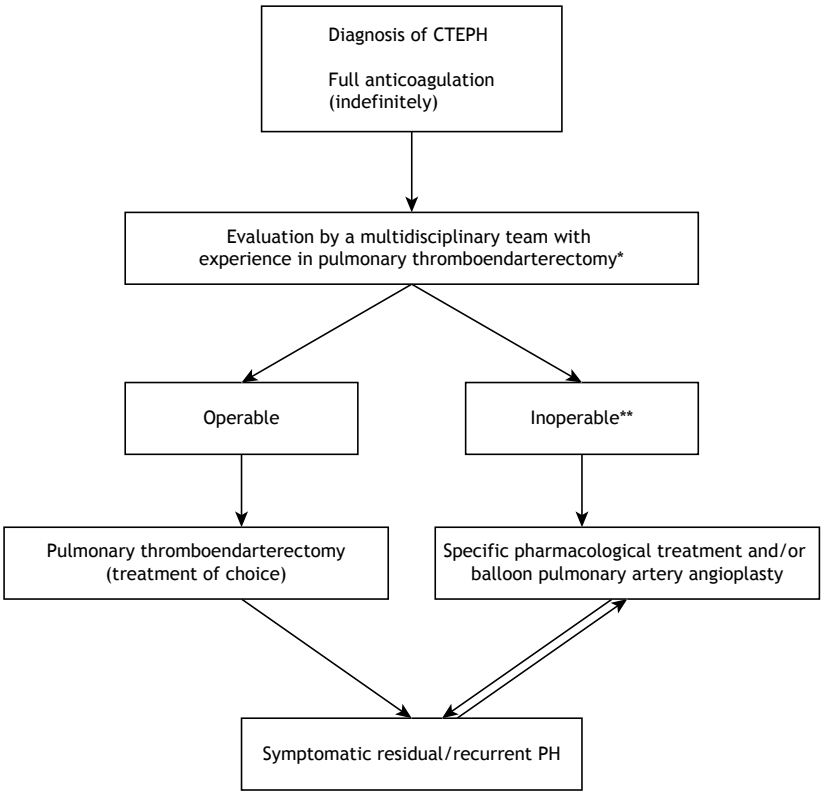


Figure 9. Treatment algorithm for chronic thromboembolic pulmonary hypertension (CTEPH). PH: pulmonary hypertension. *Multidisciplinary team: a surgeon, a radiologist, and a clinician with experience in pulmonary hypertension. **Depending on the level of experience of the center, consider getting a second opinion from another team specializing in pulmonary thromboendarterectomy.

Table 3. Risk stratification.

Determinants of prognosis	Estimated one-year mortality		
	Low risk < 5%	Intermediate risk 5-10%	High risk > 10%
Clinical signs of right ventricular failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasionally[a]	Repeatedly[b]
WHO-FC	I, II	III	IV
6MWD	> 440 m	165-440 m	< 165 m
Plasma levels of NT-proBNP/ BNP	BNP < 50 ng/L NT-proBNP < 300 ng/L	BNP 50-300 ng/L NT-proBNP 300-1,400 ng/L	BNP > 300 ng/L NT-proBNP > 1,400 ng/L
Imaging (ECHO, chest MRI)	RA area < 18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or minimal pericardial effusion	RA area > 26 cm^2 Pericardial effusion
Hemodynamic parameters	RA pressure < 8 mmHg CI ≥ 2.5 L · min · m^2 SvO_2 > 65%	RA pressure 8-14 mmHg CI 2.0-2.4 L · min · m^2 SvO_2 60-65%	RA pressure > 14 mmHg CI < 2.0 L · min · m^2 SvO_2 < 60%

Adapted from Galiè et al.[2] WHO-FC: World Health Organization functional class; 6MWD: six-minute walk distance; NT-proBNP: N-terminal pro-B-type natriuretic peptide; ECHO: echocardiography; MRI: magnetic resonance imaging; RA: right atrial; CI: cardiac index; and SvO_2: mixed venous oxygen saturation. [a]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient. [b]Repeated episodes of syncope, even with little or regular physical activity.

pulmonary artery CT angiography findings of CTEPH (see Chart 3).[36]

There is no recommendation that all survivors of acute PTE should be actively investigated.[89] However, patients with persistent or recurrent dyspnea or with limited exercise capacity three months after treatment of the acute event should be assessed for CTEPH. The initial test is echocardiography. If

Chart 5. Recommendations for the management of chronic thromboembolic pulmonary hypertension.

Diagnosis
• For a diagnosis of CTEPH, the following three diagnostic criteria must be met: at least three months of effective anticoagulation; invasive confirmation of pulmonary hypertension: mean pulmonary artery pressure > 20 mmHg; and confirmation of chronic thromboembolism by chest CT angiography, ventilation/perfusion lung scintigraphy, and/or pulmonary arteriography
• Every patient under investigation for pulmonary hypertension should be evaluated for the possibility of CTEPH via ventilation/perfusion lung scintigraphy
Screening
• There is no recommendation that all patients with PTE should be investigated for CTEPH
• Patients with a history of VTE (DVT or PTE) who, after 3-6 months of anticoagulation, present with dyspnea should be investigated for CTEPH
• Patients with a history of PTE and multiple risk factors for CTEPH, even if asymptomatic, can be investigated for CTEPH
• Echocardiography is the initial screening test for CTEPH
• In the presence of echocardiographic findings that are suggestive of pulmonary hypertension, the screening test for CTEPH is ventilation/perfusion lung scintigraphy
Treatment
• All patients with CTEPH should be maintained on full anticoagulation indefinitely
• All patients with CTEPH should be evaluated for pulmonary thromboendarterectomy at a referral center (see definition for referral center)
• It is suggested that less-experienced centers request a second opinion from a more experienced center before contraindicating the surgical procedure
• If surgery is contraindicated by an established referral center or by the presence of postoperative residual pulmonary hypertension (mean pulmonary artery pressure > 30 mmHg, measured 3-6 months after surgery), patients should undergo pharmacological treatment and/or balloon pulmonary angioplasty
• Supportive care, including diuretics and long-term home oxygen therapy, should be implemented on a case-by-case basis

CTEPH: chronic thromboembolic pulmonary hypertension; PTE: pulmonary thromboembolism; VTE: venous thromboembolism; and DVT: deep vein thrombosis.

there are findings indicating intermediate or high likelihood of PH, ventilation/perfusion lung scintigraphy should be performed. In cases with a low likelihood of PH, additional factors should be observed, such as natriuretic peptide levels, risk factors for CTEPH both during the acute event and within the context of the patient, and, eventually, CPET results. CPET is a maximal exercise test, the results of which may be suggestive of CTEPH, which would then indicate the need for further investigation with echocardiography and, subsequently, RHC.[90] In addition, CPET allows the identification of other mechanisms that cause dyspnea in this population of patients who do not have CTEPH.

There is as yet no defined approach to patients with pulmonary thromboembolic disease, that is, those with residual thrombi and no PH at rest. It is suggested that such patients also be referred to referral centers for an individualized approach.

FINAL CONSIDERATIONS

Chart 5 summarizes the recommendations for the management of CTEPH.

REFERENCES

1. 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
2. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 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
3. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1):1801913. https://doi.org/10.1183/13993003.01913-2018
4. Hoette S, Jardim C, Souza Rd. Diagnosis and treatment of pulmonary hypertension: an update. J Bras Pneumol. 2010;36(6):795-811. https://doi.org/10.1590/S1806-37132010000600018
5. Gopalan D, Delcroix M, Held M. Diagnosis of chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2017;26(143):160108. https://doi.org/10.1183/16000617.0108-2016
6. Fernandes T, Auger W, Fedullo P. Epidemiology and risk factors for chronic thromboembolic pulmonary hypertension. Thromb Res. 2018;164:145-149. https://doi.org/10.1016/j.thromres.2018.01.012
7. Fernandes CJ, Luppino Assad AP, Alves-Jr JL, Jardim C, de Souza R. Pulmonary Embolism and Gas Exchange. Respiration. 2019;98(3):253-262. https://doi.org/10.1159/000501342
8. Fernandes CJCDS, Jardim CVP, Alves JL Jr, Oleas FAG, Morinaga LTK, Souza R. Reperfusion in acute pulmonary thromboembolism [published online ahead of print, 2018 Jun 7]. J Bras Pneumol. 2018;44(3):0. https://doi.org/10.1590/s1806-37562017000000204
9. Urokinase pulmonary embolism trial. Phase 1 results: a cooperative study. JAMA. 1970;214(12):2163-2172. https://doi.org/10.1001/jama.214.12.2163
10. Simonneau G, Torbicki A, Dorfmüller P, Kim N. The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2017;26(143):160112. https://doi.org/10.1183/16000617.0112-2016

11. Dorfmüller P, Günther S, Ghigna MR, Thomas de Montpréville V, Boulate D, Paul JF, et al. Microvascular disease in chronic thromboembolic pulmonary hypertension: a role for pulmonary veins and systemic vasculature. Eur Respir J. 2014;44(5):1275-1288. https://doi.org/10.1183/09031936.00169113
12. Cannon JE, Su L, Kiely DG, Page K, Toshner M, Swietlik E, et al. Stratification of Patient Long-Term Outcome After Pulmonary Endarterectomy: Results From the United Kingdom National Cohort. Circulation. 2016;133(18):1761-1771. https://doi.org/10.1161/CIRCULATIONAHA.115.019470
13. Coquoz N, Weilenmann D, Stolz D, Popov V, Azzola A, Fellrath JM, et al. Multicentre observational screening survey for the detection of CTEPH following pulmonary embolism. Eur Respir J. 2018;51(4):1702505. https://doi.org/10.1183/13993003.02505-2017
14. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004;350(22):2257-2264. https://doi.org/10.1056/NEJMoa032274
15. Martí D, Gómez V, Escobar C, Wagner C, Zamarro C, Sánchez D, et al. Incidence of symptomatic and asymptomatic chronic thromboembolic pulmonary hypertension [Article in Spanish]. Arch Bronconeumol. 2010;46(12):628-633. https://doi.org/10.1016/j.arbres.2010.07.012
16. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, Delcroix M, Pruszczyk P, Mairuhu AT, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. Eur Respir J. 2017;49(2):1601792. https://doi.org/10.1183/13993003.01792-2016
17. Pepke-Zaba J, Jansa P, Kim NH, Naeije R, Simonneau G. Chronic thromboembolic pulmonary hypertension: role of medical therapy. Eur Respir J. 2013;41(4):985-990. https://doi.org/10.1183/09031936.00201612
18. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011;124(18):1973-1981. https://doi.org/10.1161/CIRCULATIONAHA.110.015008
19. Hoeper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. Circulation. 2006;113(16):2011-2020. https://doi.org/10.1161/CIRCULATIONAHA.105.602565
20. Fernandes CJ, Morinaga LTK, Alves JL Jr, Castro MA, Calderaro D, Jardim CVP, et al. Cancer-associated thrombosis: the when, how and why. Eur Respir Rev. 2019;28(151):180119. https://doi.org/10.1183/16000617.0119-2018
21. Lang IM, Pesavento R, Bonderman D, Yuan JX. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. Eur Respir J. 2013;41(2):462-468. https://doi.org/10.1183/09031936.00049312
22. Morris TA, Marsh JJ, Chiles PG, Auger WR, Fedullo PF, Woods VL Jr. Fibrin derived from patients with chronic thromboembolic pulmonary hypertension is resistant to lysis. Am J Respir Crit Care Med. 2006;173(11):1270-1275. https://doi.org/10.1164/rccm.200506-916OC
23. Dodson MW, Allen-Brady K, Brown LM, Elliott CG, Cannon-Albright LA. Chronic Thromboembolic Pulmonary Hypertension Cases Cluster in Families. Chest. 2019;155(2):384-390. https://doi.org/10.1016/j.chest.2018.10.004
24. Bonderman D, Wilkens H, Wakounig S, Schäfers HJ, Jansa P, Lindner J, et al. Risk factors for chronic thromboembolic pulmonary hypertension. Eur Respir J. 2009;33(2):325-331. https://doi.org/10.1183/09031936.00087608
25. Bonderman D, Jakowitsch J, Adlbrecht C, Schemper M, Kyrle PA, Schönauer V, et al. Medical conditions increasing the risk of chronic thromboembolic pulmonary hypertension. Thromb Haemost. 2005;93(3):512-516. https://doi.org/10.1160/TH04-10-0657
26. Delcroix M, Kerr K, Fedullo P. Chronic Thromboembolic Pulmonary Hypertension. Epidemiology and Risk Factors. Ann Am Thorac Soc. 2016;13 Suppl 3:S201-S206. https://doi.org/10.1513/AnnalsATS.201509-621AS
27. Bonderman D, Jakowitsch J, Redwan B, Bergmeister H, Renner MK, Panzenböck H, et al. Role for staphylococci in misguided thrombus resolution of chronic thromboembolic pulmonary hypertension. Arterioscler Thromb Vasc Biol. 2008;28(4):678-684. https://doi.org/10.1161/ATVBAHA.107.156000
28. Krieg VJ, Hobohm L, Liebetrau C, Guth S, Kölmel S, Troidl C, et al. Risk factors for chronic thromboembolic pulmonary hypertension - Importance of thyroid disease and function. Thromb Res. 2020;185:20-26. https://doi.org/10.1016/j.thromres.2019.10.025
29. Lang IM, Simonneau G, Pepke-Zaba JW, Mayer E, Ambroz D, Blanco I, et al. Factors associated with diagnosis and operability of chronic thromboembolic pulmonary hypertension. A case-control study. Thromb Haemost. 2013;110(1):83-91. https://doi.org/10.1160/TH13-02-0097
30. Herdy AH, Ritt LE, Stein R, Araujo 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
31. Tunariu N, Gibbs SJ, Win Z, Gin-Sing W, Graham A, Gishen P, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med. 2007;48(5):680-684. https://doi.org/10.2967/jnumed.106.039438
32. Dong C, Zhou M, Liu D, Long X, Guo T, Kong X. Diagnostic accuracy of computed tomography for chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis. PLoS One. 2015;10(4):e0126985. https://doi.org/10.1371/journal.pone.0126985
33. Masy M, Giordano J, Petyt G, Hossein-Foucher C, Duhamel A, Kyheng M, et al. Dual-energy CT (DECT) lung perfusion in pulmonary hypertension: concordance rate with V/Q scintigraphy in diagnosing chronic thromboembolic pulmonary hypertension (CTEPH). Eur Radiol. 2018;28(12):5100-5110. https://doi.org/10.1007/s00330-018-5467-2
34. Dias BA, Jardim C, Hovnanian A, Fernandes CJ, Souza R. Chronic thromboembolic pulmonary hypertension: diagnostic limitations [Article in Portuguese]. J Bras Pneumol. 2008;34(7):532-536. https://doi.org/10.1590/S1806-37132008000700014
35. Fernandes TM, Pretorius VG, Kim NH. Caution Regarding Catheter-directed Thrombolysis: Chronic Thromboembolic Pulmonary Hypertension Mistaken for Acute Submassive Pulmonary Embolism. Am J Respir Crit Care Med. 2017;195(8):1066-1067. https://doi.org/10.1164/rccm.201611-2193IM
36. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J. 2019;54(3):1901647. https://doi.org/10.1183/13993003.01647-2019
37. Fernandes CJCdS, Jardim CVP, Alves-Jr JL, Oleas FAG, Morinaga LTK, Souza Rd. Authors reply: Reflections on the use of thrombolytic agents in acute pulmonary embolism. J Bras Pneumol. 2019;45(1):e20180297.
38. Ruggiero A, Screaton NJ. Imaging of acute and chronic thromboembolic disease: state of the art. Clin Radiol. 2017;72(5):375-388. https://doi.org/10.1016/j.crad.2017.02.011
39. Waziri F, Ringgaard S, Mellemkjaer S, Bogh N, Kim WY, Clemmensen TS, et al. Long-term changes of right ventricular myocardial deformation and remodeling studied by cardiac magnetic resonance imaging in patients with chronic thromboembolic pulmonary hypertension following pulmonary thromboendarterectomy. Int J Cardiol. 2020;300:282-288. https://doi.org/10.1016/j.ijcard.2019.09.038
40. Rajaram S, Swift AJ, Telfer A, Hurdman J, Marshall H, Lorenz E, et al. 3D contrast-enhanced lung perfusion MRI is an effective screening tool for chronic thromboembolic pulmonary hypertension: results from the ASPIRE Registry. Thorax. 2013;68(7):677-678. https://doi.org/10.1136/thoraxjnl-2012-203020
41. Ito K, Kubota K, Morooka M, Shida Y, Hasuo K, Endo H, et al. Diagnostic usefulness of 18F-FDG PET/CT in the differentiation of pulmonary artery sarcoma and pulmonary embolism. Ann Nucl Med. 2009;23(7):671-676. https://doi.org/10.1007/s12149-009-0292-y
42. Kerr KM, Auger WR, Fedullo PF, Channick RH, Yi ES, Moser KM. Large vessel pulmonary arteritis mimicking chronic thromboembolic disease. Am J Respir Crit Care Med. 1995;152(1):367-373. https://doi.org/10.1164/ajrccm.152.1.7599847
43. Skoro-Sajer N, Hack N, Sadushi-Koliçi R, Bonderman D, Jakowitsch J, Klepetko W, et al. Pulmonary vascular reactivity and prognosis in patients with chronic thromboembolic pulmonary hypertension: a pilot study. Circulation. 2009;119(2):298-305. https://doi.org/10.1161/CIRCULATIONAHA.108.794610
44. Fernandes CJ, Alves Júnior JL, Gavilanes F, Prada LF, Morinaga LK, Souza R. New anticoagulants for the treatment of venous thromboembolism. J Bras Pneumol. 2016;42(2):146-154. https://doi.

org/10.1590/S1806-37562016042020068

45. Kramm T, Wilkens H, Fuge J, Schäfers HJ, Guth S, Wiedenroth CB, et al. Incidence and characteristics of chronic thromboembolic pulmonary hypertension in Germany. Clin Res Cardiol. 2018;107(7):548-553. https://doi.org/10.1007/s00392-018-1215-5
46. Gavilanes-Oleas FA, Alves JL Jr, Fernandes CJC, Prada LFL, Salibe Filho W, Terra Filho M, et al. Use of direct oral anticoagulants for chronic thromboembolic pulmonary hypertension. Clinics (Sao Paulo). 2018;73:e216. https://doi.org/10.6061/clinics/2018/e216
47. Bunclark K, Newnham M, Chiu YD, Ruggiero A, Villar SS, Cannon JE, et al. A multicenter study of anticoagulation in operable chronic thromboembolic pulmonary hypertension. J Thromb Haemost. 2020;18(1):114-122. https://doi.org/10.1111/jth.14649
48. Pengo V, Denas G, Zoppellaro G, Jose SP, Hoxha A, Ruffatti A, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood. 2018;132(13):1365-1371. https://doi.org/10.1182/blood-2018-04-848333
49. Uthman I, Noureldine MHA, Ruiz-Irastorza G, Khamashta M. Management of antiphospholipid syndrome. Ann Rheum Dis. 2019;78(2):155-161. https://doi.org/10.1136/annrheumdis-2018-213846
50. Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, et al. Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension: Results From an International Prospective Registry. Circulation. 2016;133(9):859-871. https://doi.org/10.1161/CIRCULATIONAHA.115.016522
51. Jenkins D, Madani M, Fadel E, D'Armini AM, Mayer E. Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2017;26(143):160111. https://doi.org/10.1183/16000617.0111-2016
52. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the 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 the International Society of Heart and Lung Transplantation (ISHLT) [published correction appears in Eur Heart J. 2011 Apr;32(8):926]. Eur Heart J. 2009;30(20):2493-2537.
53. Jenkins DP, Biederman A, D'Armini AM, Dartevelle PG, Gan HL, Klepetko W, et al. Operability assessment in CTEPH: Lessons from the CHEST-1 study. J Thorac Cardiovasc Surg. 2016;152(3):669-674.e3. https://doi.org/10.1016/j.jtcvs.2016.02.062
54. Hirsch AM, Moser KM, Auger WR, Channick RN, Fedullo PF. Unilateral pulmonary artery thrombotic occlusion: is distal arteriopathy a consequence?. Am J Respir Crit Care Med. 1996;154(2 Pt 1):491-496. https://doi.org/10.1164/ajrccm.154.2.8756827
55. Madani M, Mayer E, Fadel E, Jenkins DP. Pulmonary Endarterectomy. Patient Selection, Technical Challenges, and Outcomes. Ann Am Thorac Soc. 2016;13 Suppl 3:S240-S247. https://doi.org/10.1513/AnnalsATS.201601-014AS
56. Jamieson SW, Kapelanski DP. Pulmonary endarterectomy. Curr Probl Surg. 2000;37(3):165-252. https://doi.org/10.1016/S0011-3840(00)80005-2
57. Kratzert WB, Boyd EK, Saggar R, Channick R. Critical Care of Patients After Pulmonary Thromboendarterectomy. J Cardiothorac Vasc Anesth. 2019;33(11):3110-3126. https://doi.org/10.1053/j.jvca.2019.03.005
58. Sugiyama K, Suzuki S, Fujiyoshi T, Koizumi N, Sato M, Ogino H. Extracorporeal membrane oxygenation after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. J Card Surg. 2019;34(6):428-434. https://doi.org/10.1111/jocs.14052
59. Hsieh WC, Jansa P, Huang WC, Nižnanský M, Omara M, Lindner J. Residual pulmonary hypertension after pulmonary endarterectomy: A meta-analysis. J Thorac Cardiovasc Surg. 2018;156(3):1275-1287. https://doi.org/10.1016/j.jtcvs.2018.04.110
60. D'Armini AM, Zanotti G, Ghio S, Magrini G, Pozzi M, Scelsi L, et al. Reverse right ventricular remodeling after pulmonary endarterectomy. J Thorac Cardiovasc Surg. 2007;133(1):162-168. https://doi.org/10.1016/j.jtcvs.2006.08.059
61. Yusen RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Levvey BJ, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Lung and Heart-Lung Transplant Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. J Heart Lung Transplant. 2016;35(10):1170-1184. https://doi.org/10.1016/j.healun.2016.09.001
62. Feinstein JA, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. Circulation. 2001;103(1):10-13. https://doi.org/10.1161/01.CIR.103.1.10
63. Ogo T. Balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension. Curr Opin Pulm Med. 2015;21(5):425-431. https://doi.org/10.1097/MCP.0000000000000188
64. Olsson KM, Wiedenroth CB, Kamp JC, Breithecker A, Fuge J, Krombach GA, et al. Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension: the initial German experience. Eur Respir J. 2017;49(6):1602409. https://doi.org/10.1183/13993003.02409-2016
65. Ogawa A, Satoh T, Fukuda T, Sugimura K, Fukumoto Y, Emoto N, et al. Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension: Results of a Multicenter Registry. Circ Cardiovasc Qual Outcomes. 2017;10(11):e004029. https://doi.org/10.1161/CIRCOUTCOMES.117.004029
66. Kawakami T, Ogawa A, Miyaji K, Mizoguchi H, Shimokawahara H, Naito T, et al. Novel Angiographic Classification of Each Vascular Lesion in Chronic Thromboembolic Pulmonary Hypertension Based on Selective Angiogram and Results of Balloon Pulmonary Angioplasty. Circ Cardiovasc Interv. 2016;9(10):e003318. https://doi.org/10.1161/CIRCINTERVENTIONS.115.003318
67. Mizoguchi H, Ogawa A, Munemasa M, Mikouchi H, Ito H, Matsubara H. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv. 2012;5(6):748-755. https://doi.org/10.1161/CIRCINTERVENTIONS.112.971077
68. Kataoka M, Inami T, Hayashida K, Shimura N, Ishiguro H, Abe T, et al. Percutaneous transluminal pulmonary angioplasty for the treatment of chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv. 2012;5(6):756-762. https://doi.org/10.1161/CIRCINTERVENTIONS.112.971390
69. Fukui S, Ogo T, Goto Y, Ueda J, Tsuji A, Sanda Y, et al. Exercise intolerance and ventilatory inefficiency improve early after balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. Int J Cardiol. 2015;180:66-68. https://doi.org/10.1016/j.ijcard.2014.11.187
70. Fukui S, Ogo T, Morita Y, Tsuji A, Tateishi E, Ozaki K, et al. Right ventricular reverse remodelling after balloon pulmonary angioplasty. Eur Respir J. 2014;43(5):1394-1402. https://doi.org/10.1183/09031936.00012914
71. Sugimura K, Fukumoto Y, Satoh K, Nochioka K, Miura Y, Aoki T, et al. Percutaneous transluminal pulmonary angioplasty markedly improves pulmonary hemodynamics and long-term prognosis in patients with chronic thromboembolic pulmonary hypertension. Circ J. 2012;76(2):485-488. https://doi.org/10.1253/circj.CJ-11-1217
72. Inami T, Kataoka M, Yanagisawa R, Ishiguro H, Shimura N, Fukuda K, et al. Long-Term Outcomes After Percutaneous Transluminal Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension. Circulation. 2016;134(24):2030-2032. https://doi.org/10.1161/CIRCULATIONAHA.116.024201
73. Brenot P, Jaïs X, Taniguchi Y, Garcia Alonso C, Gerardin B, Mussot S, et al. French experience of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53(5):1802095. https://doi.org/10.1183/13993003.02095-2018
74. Tanabe N, Kawakami T, Satoh T, Matsubara H, Nakanishi N, Ogino H, et al. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: A systematic review. Respir Investig. 2018;56(4):332-341. https://doi.org/10.1016/j.resinv.2018.03.004
75. Jaïs X, D'Armini AM, Jansa P, Torbicki A, Delcroix M, Ghofrani HA, et al. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. J Am Coll Cardiol. 2008;52(25):2127-2134. https://doi.org/10.1016/j.jacc.2008.08.059
76. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med. 2013;369(4):319-329. https://doi.org/10.1056/NEJMoa1209657
77. Ghofrani HA, Simonneau G, D'Armini AM, Fedullo P, Howard LS, Jaïs X, et al. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. Lancet Respir Med. 2017;5(10):785-794. https://doi.org/10.1016/S2213-2600(17)30305-3

78. Zhang J, Li JM, Huang ZS, Xu JC, Fan Y. A meta-analysis of randomized controlled trials in targeted treatments of chronic thromboembolic pulmonary hypertension. Clin Respir J. 2019;13(7):467-479. https://doi.org/10.1111/crj.13034
79. Hoeper MM. Residual Pulmonary Hypertension After Pulmonary Endarterectomy: The Fog Is Clearing. Circulation. 2016;133(18):1731-1733. https://doi.org/10.1161/CIRCULATIONAHA.116.022595
80. Galiè N, Müller K, Scalise AV, Grünig E. PATENT PLUS: a blinded, randomised and extension study of riociguat plus sildenafil in pulmonary arterial hypertension. Eur Respir J. 2015;45(5):1314-1322. https://doi.org/10.1183/09031936.00105914
81. Jensen KW, Kerr KM, Fedullo PF, Kim NH, Test VJ, Ben-Yehuda O, et al. Pulmonary hypertensive medical therapy in chronic thromboembolic pulmonary hypertension before pulmonary thromboendarterectomy. Circulation. 2009;120(13):1248-1254. https://doi.org/10.1161/CIRCULATIONAHA.109.865881
82. Castro MA, Piloto B, Dos Santos Fernandes CJC, Jardim C, Filho WS, Oleas FG, et al. Use of medical therapies before pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension patients with severe hemodynamic impairment. PLoS One. 2020;15(5):e0233063. https://doi.org/10.1371/journal.pone.0233063
83. Jais X, Brenot P, Bouvaist H, Canuet M, Chabanne C, Chaouat A, et al. Late Breaking Abstract - Balloon pulmonary angioplasty versus riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension: results from the randomised controlled RACE study. Eur Respir J. 2019;54(Suppl 63):RCT1885. https://doi.org/10.1183/13993003.congress-2019.RCT1885
84. Madani M, Ogo T, Simonneau G. The changing landscape of chronic thromboembolic pulmonary hypertension management. Eur Respir Rev. 2017;26(146):170105. https://doi.org/10.1183/16000617.0105-2017
85. 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
86. Delcroix M, Staehler G, Gall H, Grünig E, Held M, Halank M, et al. Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients. Eur Respir J. 2018;52(5):1800248. https://doi.org/10.1183/13993003.00248-2018
87. Humbert M, Farber HW, Ghofrani HA, Benza RL, Busse D, Meier C, et al. Risk assessment in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53(6):1802004. https://doi.org/10.1183/13993003.02004-2018
88. Fernandes CJ, Martins BC, Jardim CV, Ciconelli RM, Morinaga LK, Breda AP, et al. Quality of life as a prognostic marker in pulmonary arterial hypertension. Health Qual Life Outcomes. 2014;12:130. https://doi.org/10.1186/s12955-014-0130-3
89. Wilkens H, Konstantinides S, Lang IM, Bunck AC, Gerges M, Gerhardt F, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): Updated Recommendations from the Cologne Consensus Conference 2018. Int J Cardiol. 2018;272S:69 - 78. https://doi.org/10.1016/j.ijcard.2018.08.079
90. Held M, Grün M, Holl R, Hübner G, Kaiser R, Karl S, et al. Cardiopulmonary exercise testing to detect chronic thromboembolic pulmonary hypertension in patients with normal echocardiography. Respiration. 2014;87(5):379-387. https://doi.org/10.1159/000358565

J Bras Pneumol. 2020;46(4):e20200094
https://dx.doi.org/10.36416/1806-3756/e20200094

What is the link between household garbage and tobacco control? The case of Brazil

André Salem Szklo[1], Maria Raquel Fernandes Silva[2], Bianca Ramalho Quintaes[3], Alessandra Trindade Machado[4]

TO THE EDITOR:

In recent years, the strategy of raising cigarette taxes has reduced the prevalence of smoking and the consumption of licit cigarettes in Brazil.[1] However, a certain fraction of smokers may have migrated to cheaper, illicit cigarettes in order to save money.[2] In many low- and middle-income countries, the tobacco industry is the only source of information on the illicit cigarette market, and this information can be used in order to weaken or delay the implementation of effective tobacco control policies.[3]

In 2018, the *Instituto Nacional de Câncer* (INCA, Brazilian National Cancer Institute) conducted a pragmatic study to gain a better understanding of the illicit cigarette trade in the city of Rio de Janeiro, Brazil, based on the characteristics and number of cigarette packs discarded with the household garbage. For that purpose, INCA worked in partnership with the *Companhia Municipal de Limpeza Urbana* (COMLURB, Municipal Urban Cleaning Company), which provides household waste collection services to the 156 neighborhoods in the city. Investigators in our research group took photographs of all stages of the study, thus allowing the images to "tell the story behind the numbers".

In addition to performing their regular recycling activities, COMLURB staff members were instructed to separate all cigarette packs discarded with the household garbage in each neighborhood (Figure 1A). A manual sieving method was used in order to separate discarded cigarette packs

Figure 1. In A, household garbage; in B, manual sieving to separate discarded cigarette packs from other materials; in C, discarded packs of "GIFT" cigarettes, the most commonly consumed illicit cigarette brand in the city of Rio de Janeiro, Brazil (brought into the country from Paraguay); and in D, discarded packs of "GIFT" cigarettes, some of which were legally manufactured in Brazil.

1. Divisão de Pesquisa Populacional, Coordenação de Prevenção e Vigilância, Instituto Nacional de Câncer José Alencar Gomes da Silva – INCA – Rio de Janeiro (RJ) Brasil
2. Divisão de Controle do Tabagismo e Outros Fatores de Risco, Coordenação de Prevenção e Vigilância, Instituto Nacional de Câncer José Alencar Gomes da Silva – INCA – Rio de Janeiro (RJ) Brasil.
3. Unidade de Pesquisa Aplicada, Companhia Municipal de Limpeza Urbana – COMLURB – Rio de Janeiro (RJ) Brasil.
4. Secretaria Executiva da Comissão Nacional para a Implementação da Convenção-Quadro para o Controle do Tabaco, Instituto Nacional de Câncer José Alencar Gomes da Silva – INCA – Rio de Janeiro (RJ) Brasil.

from other materials (Figure 1B). The packs that were found were classified as illicit or licit by INCA tobacco control analysts. For that purpose, they used the Brazilian National Health Surveillance Agency list of legal brands, as well as direct observation of the presence of Brazilian tobacco health warnings on the packs.[4] The most commonly consumed illicit cigarette brand in the city of Rio de Janeiro is called "GIFT" (Figure 1C) and is brought into the country from Paraguay, a known smuggling route. We also identified an odd situation that should be closely investigated by the Brazilian Secretariat of Federal Revenue: "GIFT" cigarettes legally manufactured in the city of Rio de Janeiro (with Brazilian pictorial health warnings displayed on cigarette packs; Figure 1D), as authorized by a court order.

Non-industry-funded studies are important to improve understanding of the illicit cigarette market and, as a consequence, help implement tobacco excise tax policies in Brazil and other low- and middle-income countries effectively.

ACKNOWLEDGMENTS

We would like to thank all COMLURB staff members who made this study possible.

AUTHOR CONTRIBUTIONS

All authors contributed to writing the manuscript. Silva MRF and Machado AT provided the photographs.

REFERENCES

1. Szklo AS, Yuan Z, Levy D. Update and extension of the Brazil SimSmoke model to estimate the health impact of cigarette smoking by pregnant women in Brazil. Cad Saude Publica. 2017;33(12):e00207416. https://doi.org/10.1590/0102-311x00207416
2. Iglesias RM, Szklo AS, Souza MC, de Almeida LM. Estimating the size of illicit tobacco consumption in Brazil: findings from the global adult tobacco survey. Tob Control. 2017;26(1):53-59. http://dx.doi.org/10.1136/tobaccocontrol-2015-052465
3. The World Bank [homepage on the Internet]. Washington DC: The World Bank; c2020 [updated 2019 Jan 1; cited 2020 Feb 1]. Confronting Illicit Tobacco Trade: A Global Review of Country Experiences. Available from: http://documents.worldbank.org/curated/en/677451548260528135/Confronting-Illicit-Tobacco-Trade-a-Global-Review-of-Country-Experiences
4. Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária [homepage on the Internet] Brasília: o Ministério; [cited 2020 Feb 2]. Consulta a registro. Available from: http://portal.anvisa.gov.br/tabaco/consulta-a-registro

J Bras Pneumol. 2020;46(4):e20200208
https://dx.doi.org/10.36416/1806-3756/e20200208

Spatiotemporal evolution of case fatality rates of COVID-19 in Brazil, 2020

Carlos Dornels Freire de Souza[1], João Paulo Silva de Paiva[1], Thiago Cavalcanti Leal[1], Leonardo Feitosa da Silva[1], Lucas Gomes Santos[1]

TO THE EDITOR:

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome (SARS) coronavirus 2, was initially identified in the city of Wuhan, capital of the Hubei province of China, in December of 2019.[1] On March 11, 2020, the World Health Organization characterized the disease as a pandemic.[2] As of April 26, there were approximately 3 million confirmed cases of COVID-19 and 206,000 deaths attributed to the disease worldwide. The highest numbers of confirmed cases were in the United States (n = 963,379) and Spain (n = 226,629), whereas the highest numbers of deaths were in Italy (n = 26,644) and France (n = 23,190).[3]

In Brazil, the first COVID-19 case was confirmed on February 26, 2020, in the city of São Paulo. On March 17, the first death from the disease was reported in the country. On April 24, Brazil already ranked 11th worldwide in terms of the number of confirmed cases (n = 52,995) and the number of deaths (n = 3,670).[4]

Given the continental dimensions of Brazil and its internal economic, social, and cultural inequalities, the impact of the disease might be heterogeneous. Therefore, the objective of the present study was to analyze the spatiotemporal distribution of case fatality rates (CFRs) of COVID-19 in the 26 Brazilian states and the Federal District of Brasília (all hereafter referred to as states) between epidemiological week (EW) 12 and EW 17 of 2020 (from March 17 to April 24).

This was an ecological study of all deaths due to COVID-19, by state and EW. Data were obtained from the Brazilian National Ministry of Health (https://covid.saude.gov.br/) on April 24, 2020. The CFRs for each state and EW were then calculated. The CFR is defined as the proportion of deaths from a given disease in relation to the total number of patients with that disease:

$$CFR = \frac{Number\ of\ deaths\ due\ to\ COVID\text{-}19}{Number\ of\ confirmed\ cases} \times 100$$

An exploratory spatiotemporal analysis was conducted, and choropleth maps were prepared in order to show the results. Because only secondary, public-domain data were used in the present study, the requirement for approval by the local research ethics committee was waived.

Between EW 9 and EW 17, Brazil reported 52,995 cases of COVID-19 and 3,670 deaths, with a CFR of 6.9%. The first deaths were reported on March 17 (in EW 12) in the states of Rio de Janeiro (n = 3) and São Paulo (n = 15), which subsequently accounted for 2,082 (56.7%) of the COVID-19-related deaths in the country during the period studied (Figure 1).

In EW 13, ten states accounted for 110 deaths: Santa Catarina, Rio Grande do Sul, Paraná, Rio de Janeiro, São Paulo, Goiás, Amazonas, Ceará, Pernambuco, and Piauí. The highest CFRs were found the states of Piauí (9.09%), Pernambuco (7.35%), and São Paulo (5.97%). In EW 14, there was an increase of 318 deaths and the number of accumulated deaths was 432, which was 3.8 times higher than in the previous week. Only the state of Tocantins reported no deaths. As can be seen in Figure 1, the highest CFRs were found in the states of Piauí (18.18%), Rondônia (9.09%), and Alagoas (8.70%).

In the following week (EW 15), 692 COVID-19-related deaths were added, bringing the national total to 1,124 (2.6 times higher than in EW 14). Of the ten states with the highest CFRs during that EW, six were in the northeastern region: Piauí (17.07%), Paraíba (12.94%), Sergipe (9.52%), Pernambuco (8.82%), Alagoas (6,25%), and Maranhão (6.10%). In EW 16, the cumulative number of deaths reached 2,346 (an increase of 1,222 in relation to the previous week), and COVID-19-related deaths had been reported in every state. The highest CFRs were observed in the states of Paraíba (12.68%), Pernambuco (9.35%), and Rio de Janeiro (8.52%). It is noteworthy that the state of Amazonas, which ranked 10th in CFR during EW 15 (5.05%), came to be ranked 4th by EW 16 (8.49%), as shown in Figure 1.

In EW 17, there were an additional 1,326 COVID-19-related deaths, bringing the total to 3,670. The numbers of confirmed deaths were highest in the states of São Paulo (n = 1,512), Rio de Janeiro (n = 570), and Pernambuco (n = 352), whereas the CFRs were highest in the states of Paraíba (11.40%), Rio de Janeiro (9.09%), and Pernambuco (8.80%), as can be seen in Figure 1.

Collectively, the states of São Paulo and Rio de Janeiro have a population of 63 million, which represents 29.7% of the population of Brazil. Although the first confirmed cases of COVID-19 and deaths from the disease were reported in those two states, it remains unclear whether they were the gateways for the disease to enter the country.[4]

It is of note that COVID-19-related mortality is determined not only by intrinsic characteristics of the infected individuals (age, previous diseases, and lifestyle)[5] but also by the access to and availability of therapeutic resources (hospital beds, health care staff, mechanical ventilators, and medications).[6] Therefore, the analysis of the lethality of the disease should take this combination of factors into account.

One study conducted in Brazil showed that the number of hospitalizations due to SARS between the confirmation

1. Departamento de Medicina, Universidade Federal de Alagoas, Arapiraca (AL) Brasil.

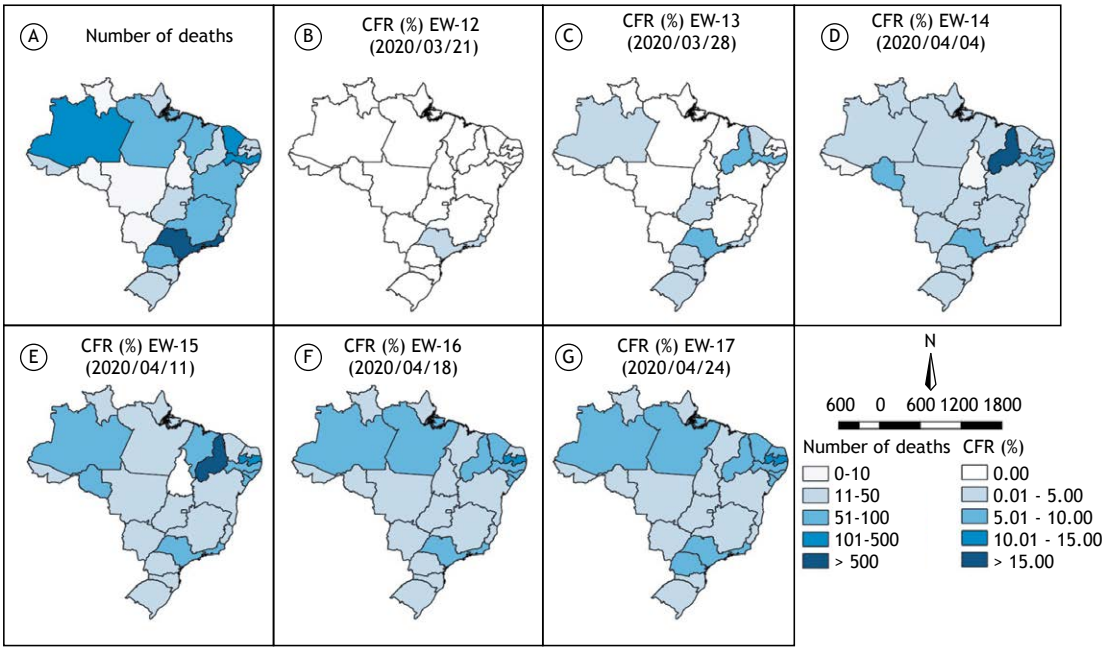


Figure 1. Spaciotemporal evolution of coronavirus disease 2019 in Brazil, regarding the number of deaths (A) and case fatality rates (CFRs, in B-G) from epidemiological week (EW) 12 to EW 17 of 2020.

of the first case of COVID-19 and EW 12 was higher than that found during the same period in previous years. The historical median of hospitalizations due to SARS in that EW is 299; in 2020, that number surpassed 1,000.[7]

By EW 13, all states in the southern region had reported COVID-19-related deaths. Those states (Rio Grande do Sul, Santa Catarina, and Paraná) have three important determinants of mortality[8]: their populations are older than are those of other regions of the country[9]; their historical incidence of SARS is the highest in the country[7]; and they have a fragile health care network, albeit more structured than those in other regions of the country.[6] In addition, their proximity to the states of São Paulo and Rio de Janeiro represents an additional complicating factor, because it facilitates travel between the two regions.

In the northern and northeastern regions, social vulnerability is a chronic problem. This might explain why the states in those regions ranked highest regarding CFRs. Currently, Brazil has 32,757 ICU beds for adults, of which 14,873 (45.4%) are managed by the Brazilian Unified Health Care System. Of those ICU beds, only 227 (0.69%) and 454 (1.38%) are in the states of Piauí and Paraíba (6.9 beds/100,000 population and 11.2 beds/100,000 population, respectively), which had the highest CFRs between EW 13 and EW 17. In the northern region, the situation is more critical: the state of Amazonas, one of the epicenters of the pandemic in Brazil, has only 271 ICU beds (6.5 beds/100,000 population).[8]

It should be borne in mind that the CFR is influenced by the underreporting of confirmed cases and deaths. States where there is little testing or where testing is targeted only at critically ill patients tend to generate higher CFRs, because the actual number of patients is not reflected. In addition, there have been a great number of deaths for which the cause has not been identified or confirmed, which also affects the quality of the records.[10] Recent investigations have suggested that the number of infected individuals in Brazil might be 10 to 15 times greater than the number of reported cases.[10] Not knowing the true magnitude of the pandemic is an obstacle to fighting the disease.

The present study showed that spatiotemporal differences in the CFR of COVID-19 among Brazilian states might reflect social, economic, cultural, and structural inequalities. Therefore, there is no single solution for the whole country and health care policies must take regional particularities into consideration.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733. https://doi.org/10.1056/NEJMoa2001017
2. World Health Organization [homepage on the Internet] Geneva: World Health Organization; c2020 [updated 2020 Mar 11, cited 2020 Apr 26]. Coronavirus disease 2019 (COVID-19): Situation Report - 51. [Adobe Acrobat document, 9p.]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10
3. Johns Hopkins University [homepage on the Internet]. Baltimore (MD): the University; c2020 [cited 2020 Apr 26]. COVID-19 Dashboard by the Center for Systems Science and Engineering

(CSSE). Available from: https://coronavirus.jhu.edu/map.html

4. Brasil. Ministério da Saúde. Centro de Operações de Emergência em Saúde Pública [homepage on the Internet]. Brasília: o Ministério; c2020 [updated 2020 Apr 20; cited 2020 Apr 26]. Boletim COE COVID-19 no. 13: Situação epidemiológica–Doença pelo coronavírus 2019. [Adobe Acrobat document, 18p.]. Available from: https://portalarquivos.saude.gov.br/images/pdf/2020/April/21/BE13---Boletim-do-COE.pdf
5. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with Different Severity: A Multi-center Study of Clinical Features. Am J Respir Crit Care Med. 2020 Apr 10 [Epub ahead of print]. https://doi.org/10.1164/rccm.202002-0445OC
6. Fundação Oswaldo Cruz (FIOCRUZ) [homepage da internet]. Rio de Janeiro: FIOCRUZ; c2020 [updated: 2020 Mar 19; cited 2020 Apr 26]. COVID-19: relatório apresenta estimativa de infecção pelo vírus no país e os impactos no SUS [about 3 screens]. Available from: https://portal.fiocruz.br/noticia/covid-19-relatorio-apresenta-estimativa-de-infeccao-pelo-virus-no-pais-e-os-impactos-no-sus
7. Bastos LS, Niquini RP, Lana RM, Villela DAM, Cruz OG, Coelho FC, et al. COVID-19 and hospitalizations for SARI in Brazil: a comparison up to the 12th epidemiological week of 2020. Cad Saude Publica. 2020;36(4):e00070120. https://doi.org/10.1590/0102-311x00070120
8. Rache B, Rocha R, Nunes L, Spinola P, Malik AM, Massuda A. Necessidades de Infraestrutura do SUS em Preparo à COVID-19: Leitos de UTI, Respiradores e Ocupação Hospitalar (Nota Técnica n. 3). Instituto de Estudos para Políticas de Saúde, 2020 Mar.
9. Miranda GM, Mendes AC, Silva AL. Population aging in Brazil: current and future social challenges and consequences. Rev Bras Geriatr Gerontol. 2016;19(3):507-519. https://doi.org/10.1590/1809-98232016019.150140
10. COVID-19 Brasil [homepage on the Internet]. Ribeirão Preto: COVID-19 Brasil [cited 2020 Apr 28]. Monitoramento e análises da situação do Coronavírus no Brasil. Available from: https://ciis.fmrp.usp.br/

J Bras Pneumol. 2020;46(4):e20200086
https://dx.doi.org/10.36416/1806-3756/e20200086

Prevalence of self-reported asthma in adults in the Brazilian Amazon: a population-based cross-sectional study

Gustavo Magno Baldin Tiguman[1], Raquel Rodrigues Ferreira Rocha de Alencar[2], Anderson da Paz Penha[3], Tais Freire Galvao[1], Marcus Tolentino Silva[4]

TO THE EDITOR:

The prevalence of asthma among adults is poorly known, especially in vulnerable regions, such as the Brazilian Amazon.[1] The objective of this study was to estimate the prevalence of self-reported asthma in adults living in the metropolitan area of Manaus, Brazil, in 2015.

We included individuals ≥ 18 years of age. We used a multistage probability cluster sampling design: stage 1, census tracts (random sampling); stage 2, households (systematic sampling); and stage 3, individuals (random sampling, based on age and sex quotas).[2] Experienced interviewers collected data at participant households.

The prevalence of self-reported asthma was assessed by the Brazilian Portuguese version of the European Community Respiratory Health Survey, a cutoff score ≥ 4 being used.[3] Individual variables included sex (male/female), age group (18-24, 25-34, 35-44, 45-59, or ≥ 60 years), marital status (married, separated, divorced, widowed, or single), level of education (college education or higher, high school education, middle school education, no formal education), socioeconomic class (A/B, C, or D/E, with A being the wealthiest and E being the poorest), health insurance (yes/no), use of health services in the last 12 months (visit to a physician, visit to a dentist, or hospitalization), place of residence (in the city of Manaus itself or in other cities within the metropolitan area of Manaus), chronic disease (COPD, depression, hypertension, diabetes, or hypercholesterolemia), and self-perception of health status (very good, good, fair, poor, or very poor).

All variables were evaluated by descriptive statistics with 95% CIs. Poisson regression with robust variance was used in order to estimate prevalence ratios (PRs) for asthma by independent variable. All of the variables showing $p < 0.20$ in the bivariate analysis were included in the multivariate analysis. Multicollinearity was assessed by the variance inflation factor (VIF), variables with a VIF > 10 being removed. All analyses were performed with the Stata statistical software package, version 14.2 (StataCorp LP, College Station, TX, USA), the complex sampling design being accounted for (using the *svy* command).

All participants gave written informed consent. The study protocol was approved by the Research Ethics Committee of the Federal University of Amazonas (Protocol no. 974,428).

Of the 4,001 study participants, 523 (13.1%; 95% CI, 12.0-14.1) were found to have asthma. Half of the participants were women, single, and in good health. Most were in the 18- to 44-year age bracket, had visited a physician in the previous 12 months, and resided in the city of Manaus (Table 1).

After adjustment, the prevalence of asthma was found to be significantly higher in women (PR, 1.84; 95% CI, 1.52-2.22), individuals living in the city of Manaus (PR, 1.70; 95% CI, 1.23-2.37), individuals with COPD (PR, 2.45; 95% CI, 1.93-3.10), individuals with depression (PR, 1.52; 95% CI, 1.20-1.93), individuals with hypertension (PR, 1.39; 95% CI, 1.16-1.68), individuals with hypercholesterolemia (PR, 1.33; 95% CI, 1.12-1.65), individuals in fair health (PR, 2.26; 95% CI, 1.51-3.38), individuals in poor health (PR, 3.30; 95% CI, 2.11-5.15), and individuals in very poor health (PR, 2.66; 95% CI, 1.54-4.63). None of the variables had a VIF > 10.

Although information bias resulting from self-report might limit the validity of our findings, clinical testing for asthma was beyond the scope of our study. Nevertheless, we employed a questionnaire that has been validated for the assessment of asthma in adults. Environmental factors were not assessed in this study and can be risk factors for asthma symptoms.[4] Given that only individuals who were at home at the time of data collection were included in the study, it is possible that selection bias influenced the results.

The prevalence of self-reported asthma in the present study was similar to the prevalence of asthma in the Brazilian adult population (12.4%) as assessed by the World Health Survey questionnaire in a multicountry study.[5] In contrast, the 2013 Brazilian National Health Survey found a low prevalence of self-reported physician-diagnosed asthma (4.4%), a finding that might be due to the fact that no screening tool was used for outcome assessment.[6]

In a cross-sectional study based on household surveys conducted in Brazil in 2003, 2008, and 2013, the prevalence of asthma was consistently higher in women,[1] as was the case in our study. This might be explained by biological differences, such as sex hormones and increased bronchial hyperresponsiveness, and social factors, such as different perceptions of airflow obstruction and medication compliance.[7] In addition, women seek medical attention and self-report health conditions more often than do men.[2]

1. Faculdade de Ciências Farmacêuticas, Universidade Estadual de Campinas, Campinas (SP) Brasil.
2. Faculdade de Medicina, Universidade Federal do Amazonas, Manaus (AM) Brasil.
3. University of California San Diego, San Diego (CA) USA.
4. Programa de Pós-Graduação em Ciências Farmacêuticas, Universidade de Sorocaba, Sorocaba (SP) Brasil.

ISSN 1806-3713

Table 1. Characteristics of the study participants and corresponding adjusted prevalence ratios for asthma (with 95% CIs) in the metropolitan area of Manaus, Brazil, in 2015 (N = 4,001).

Variable	n	%	PR (95% CI)	p
Sex				< 0.001
Male	1,888	47.2	1.00	
Female	2,113	52.8	1.84 (1.52-2.22)	
Age group, years				0.189
18-24	838	20.9	1.00	
25-34	1,152	28.8	0.83 (0.65-1.06)	
35-44	843	21.1	0.88 (0.68-1.15)	
45-59	772	19.3	0.71 (0.53-0.93)	
≥ 60	396	9.9	0.74 (0.53-1.03)	
Marital status				0.033
Married	1,409	35.2	1.00	
Separated	157	3.9	0.82 (0.53-1.26)	
Divorced	103	2.6	0.35 (0.17-0.72)	
Widowed	159	4.0	0.96 (0.70-1.31)	
Single	2,173	54.3	0.76 (0.64-0.90)	
Level of education				0.679
College or higher	158	4.0	1.00	
High school	1,903	47.5	1.07 (0.67-1.69)	
Middle school	649	16.2	1.12 (0.69-1.82)	
Elementary school or lower	1,291	32.3	0.98 (0.62-1.56)	
Socioeconomic class				0.026
A/B (the wealthiest)	629	15.7	1.00	
C	2,285	57.1	0.96 (0.73-1.22)	
D/E (the poorest)	1,087	27.1	1.19 (0.91-1.57)	
Health insurance				0.150
Yes	523	13.0	1.00	
No	3,478	87.0	1.22 (0.93-1.61)	
Use of health services in the last 12 months[a]				
Physician	3,066	76.6	1.13 (0.92-1.39)	0.247
Dentist	1,435	35.9	-[b]	-[b]
Hospitalization	273	6.8	1.22 (0.96-1.54)	0.099
Place of residence				0.001
In other cities within the metropolitan area of Manaus	522	13.2	1.00	
In the city of Manaus itself	3,479	86.9	1.70 (1.23-2.37)	
Chronic disease[a]				
COPD	99	2.5	2.45 (1.93-3.10)	< 0.001
Depression	214	5.4	1.52 (1.20-1.93)	0.001
Hypertension	787	19.7	1.39 (1.16-1.68)	< 0.001
Diabetes	245	6.2	0.78 (0.59-1.02)	0.073
Hypercholesterolemia	596	14.9	1.33 (1.12-1.65)	0.002
Health status				< 0.001
Very good	471	11.9	1.00	
Good	2,175	54.3	1.34 (0.90-1.98)	
Fair	1,108	27.7	2.26 (1.51-3.38)	
Poor	193	4.9	3.30 (2.11-5.15)	
Very poor	54	1.4	2.66 (1.54-4.63)	

PR: prevalence ratio. [a]The absence of this variable was used as reference for PR calculation. [b]Not included in the adjusted analysis (p = 0.234 in the bivariate analysis).

In the present study, the prevalence of asthma was found to be higher in individuals living in the city of Manaus itself than in those living in other cities within the metropolitan area of Manaus. In a cross-sectional study conducted in Peru in the 2000-2008 period, the prevalence of asthma was investigated in two different settings and was found to be higher in urban Lima than in rural Tumbes (12% vs. 3%).[8]

Adults with asthma are likely to report other chronic conditions. In a meta-analysis comparing 117,548 patients with asthma and 443,948 controls without asthma, it was shown that asthma, diabetes, cardiovascular diseases, hypertension, psychiatric disorders, neurological disorders, cancer, and respiratory diseases other than asthma share several common risk factors, including smoking, obesity, and lack of physical activity.[9] Given that asthma and COPD are both pulmonary diseases, there was a risk of collinearity between the two in our study. However, multicollinearity was ruled out by examining the VIF. In the present study, asthma was associated with worse health status, a finding that is consistent with those of a study showing severe problems related to symptoms, functional impairment, and quality of life in 167 asthma patients.[10]

In summary, over one tenth of adults living in the metropolitan area of Manaus have asthma, the prevalence of which was higher in women, individuals living in the city of Manaus itself, individuals with chronic conditions, and individuals with worse health status.

FINANCIAL SUPPORT

This study received financial support from the Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development; Grant nos. 404990/2013-4 and 448093/2014-6).

AUTHOR CONTRIBUTIONS

Silva MT and Galvao TF designed the work, analyzed and interpreted the data, and critically revised the work for important intellectual content. Tiguman GMB analyzed and interpreted the data and drafted the work. Alencar RRFR and Penha AP analyzed and interpreted the data and critically revised the work for important intellectual content. All authors approved the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Santos FMD, Viana KP, Saturnino LT, Lazaridis E, Gazzotti MR, Stelmach R, et al. Trend of self-reported asthma prevalence in Brazil from 2003 to 2013 in adults and factors associated with prevalence. J Bras Pneumol. 2018;44(6):491-497. https://doi.org/10.1590/s1806-37562017000000328
2. Silva MT, Galvão TF. Use of health services among adults living in Manaus Metropolitan Region, Brazil: population-based survey, 2015. Epidemiol Serv Saude. 2017;26(4):725-734. https://doi.org/10.5123/S1679-49742017000400005
3. Andrade E. Validação do questionário de triagem de asma do inquérito de saúde respiratória da Comunidade Européia (ECRHS) na cidade de Manaus-AM [thesis]. Porto Alegre: Universidade Federal do Rio Grande do Sul; 2007.
4. Toskala E, Kennedy DW. Asthma risk factors. Int Forum Allergy Rhinol. 2015;5 Suppl 1(Suppl 1):S11-S16. https://doi.org/10.1002/alr.21557
5. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health. 2012;12:204. https://doi.org/10.1186/1471-2458-12-204
6. Menezes AM, Wehrmeister FC, Horta B, Szwarcwald CL, Vieira ML, Malta DC. Prevalence of asthma medical diagnosis among Brazilian adults: National Health Survey, 2013. Rev Bras Epidemiol. 2015;18 Suppl 2:204-213. https://doi.org/10.1590/1980-5497201500060018
7. Fuseini H, Newcomb DC. Mechanisms Driving Gender Differences in Asthma. Curr Allergy Asthma Rep. 2017;17(3):19. https://doi.org/10.1007/s11882-017-0686-1
8. Robinson CL, Baumann LM, Gilman RH, Romero K, Combe JM, Cabrera L, et al. The Peru Urban versus Rural Asthma (PURA) Study: methods and baseline quality control data from a cross-sectional investigation into the prevalence, severity, genetics, immunology and environmental factors affecting asthma in adolescence in Peru. BMJ Open. 2012;2(1):e000421. https://doi.org/10.1136/bmjopen-2011-000421
9. Su X, Ren Y, Li M, Zhao X, Kong L, Kang J. Prevalence of Comorbidities in Asthma and Nonasthma Patients: A Meta-analysis. Medicine (Baltimore). 2016;95(22):e3459. https://doi.org/10.1097/MD.0000000000003459
10. Peters JB, Rijssenbeek-Nouwens LH, Bron AO, Fieten KB, Weersink EJ, Bel EH, et al. Health status measurement in patients with severe asthma. Respir Med. 2014;108(2):278-286. https://doi.org/10.1016/j.rmed.2013.11.012

J Bras Pneumol. 2020;46(4):e20200218
https://dx.doi.org/10.36416/1806-3756/e20200218

Should all COVID-19 patients be approached in the same way?

Caio Julio Cesar dos Santos Fernandes[1,2,3]

TO THE EDITOR:

Since the first reports of coronavirus disease (COVID-19) in Wuhan, China, in 2019, it has become clear that hypoxemic respiratory failure is the most severe clinical manifestation of COVID-19.[1] A high incidence of cases of severe acute respiratory syndrome (SARS) or acute respiratory distress syndrome (ARDS) in a short period of time among patients exposed to a wet market in Wuhan raised the possibility of a highly contagious infectious disease caused by a new coronavirus, which was later designated SARS coronavirus 2 (SARS-CoV-2).[2]

Given that COVID-19 causes severe respiratory failure, is highly transmissible, and results in a high number of deaths from respiratory disease, different therapeutic modalities have been employed. Identification of the etiologic agent of COVID-19 and of pathophysiological mechanisms of COVID-19–related lung parenchymal injury led to two different therapeutic approaches: treatments aimed at reducing viral load and replication (remdesivir and plasma from patients who recovered from COVID-19); and those aimed at reducing the pulmonary inflammatory response to SARS-CoV-2 (including chloroquine, corticosteroids, and tocilizumab [an anti-IL-6 receptor antibody]).[3] However, the efficacy of these treatments has yet to be established in controlled clinical trials.

A third therapeutic approach has recently been proposed, namely, treatment of SARS-CoV-2–induced pulmonary vascular disease. Autopsy studies have shown the presence of endotheliitis[4] and thrombosis in the pulmonary microvasculature.[5] Elevated D-dimer levels have been correlated with poor prognosis in patients with COVID-19,[6] indicating the relevance of vascular disease in the clinical course of COVID-19. Gattinoni et al.[7] showed that, despite the severity of hypoxemia, lung compliance is relatively preserved in cases of COVID-19–induced ARDS. However, unlike what has been reported in other causes of ARDS, pulmonary shunt fraction is surprisingly high, suggesting that vascular disease plays a role in the severity of COVID-19. In this scenario, it is tempting to consider the possibility of treating vascular disease in patients with COVID-19. In a retrospective study conducted in China, heparin was reported to play a potential role in the treatment of vascular disease in patients with COVID-19.[8] However, this treatment approach has yet to be evaluated in prospective controlled studies.

COVID-19 arrived in Brazil in mid-March 2020, and clinical experience demonstrated a wide variety of pulmonary manifestations.[9,10] With regard to inclusion in randomized clinical trials and clinical management, it might be inappropriate to treat vascular disease in patients with predominantly parenchymal involvement. Patient selection for inclusion in prospective studies, clinical support, and specific treatment modalities can be essential to achieve the expected result. Figure 1 shows chest CT scans of two patients. Patient A presented with severe hypoxemia but no lung parenchymal changes that might account for it, as well as presenting with markedly elevated D-dimer levels, all of which were suggestive of concomitant vascular disease as the underlying cause of hypoxia. Should this patient have received treatment aimed at reducing the lung parenchymal inflammatory process despite the fact that the underlying condition appeared to be pulmonary vascular disease? Patient management included hospitalization, ventilatory support, and prophylactic heparin. In contrast, patient B presented with extensive lung parenchymal changes, without hypoxemia or elevated D-dimer levels, and was therefore managed at home. Should patients without evident vascular disease receive anticoagulation therapy? Both patients responded well to treatment at 10 days and are clinically well at this writing. The aforementioned cases suggest that COVID-19 has varying phenotypes (i.e., parenchymal and vascular), and this has an impact on the clinical management of the disease. However, there is currently no evidence for a phenotype-based approach to COVID-19 treatment.

Given that several pathophysiological pathways are involved in the development of COVID-19, indiscriminate treatment of COVID-19 patients can lead to negative results in clinical studies and unsatisfactory individual clinical outcomes. Proper identification of the pathophysiological mechanism of lung injury in patients with COVID-19 might prove essential to appropriate clinical management and the interpretation of the results of clinical trials currently underway. However, it should be born in mind that definitive conclusions on the efficacy and safety of COVID-19 therapeutic strategies other than ventilatory support await results of ongoing prospective clinical trials.

1. Grupo de Circulação Pulmonar, Departamento de Cardiopneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Instituto do Câncer do Estado de São Paulo, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
3. Hospital Sírio-Libanês, São Paulo (SP) Brasil.

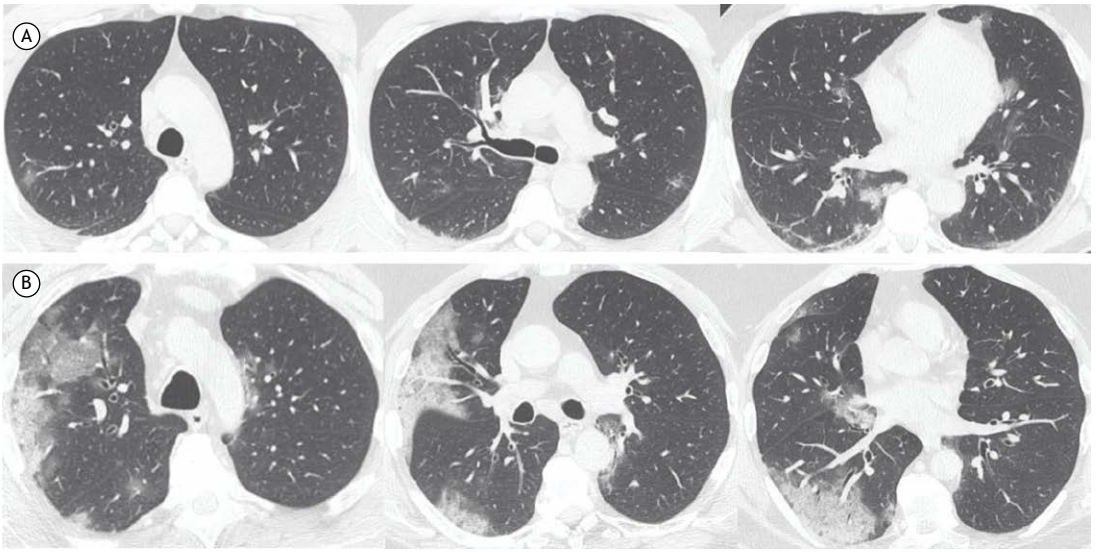


Figure 1. Chest CT scans of two patients with COVID-19, both of whom had an approximately 10-day history of respiratory symptoms. In A, a 48-year-old male patient with no comorbidities and an SpO_2 of 89% on room air, as well as a D-dimer level of 2,600 ng/mL. In B, a 62-year-old male patient with hypertension and diabetes, as well as an SpO_2 of 95% on room air and a D-dimer level of 420 ng/mL.

REFERENCES

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China [published online ahead of print, 2020 Feb 7]. JAMA. 2020;323(11):1061-1069. https://doi.org/10.1001/jama.2020.1585
2. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019 [published online ahead of print, 2020 Apr 1]. Nature. 2020;10.1038/s41586-020-2196-x. https://doi.org/10.1038/s41586-020-2196-x
3. Md Insiat Islam Rabby. Current Drugs with Potential for Treatment of COVID-19: A Literature Review. J Pharm Pharm Sci. 2020;23(1):58-64. https://doi.org/10.18433/jpps31002
4. Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G. Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis [published online ahead of print, 2020 Apr 26]. Clin Chim Acta. 2020;507:167-173. https://doi.org/10.1016/j.cca.2020.04.027
5. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, Ferraz da Silva LF, Pierre de Oliveira E, Nascimento Saldiva PH, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19 [published online ahead of print, 2020 Apr 15]. J Thromb Haemost. 2020;10.1111/jth.14844. https://doi.org/10.1111/jth.14844
6. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19 [published online ahead of print, 2020 Apr 19]. J Thromb Haemost. 2020;10.1111/jth.14859. https://doi.org/10.1111/jth.14859
7. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2020;201(10):1299-1300. https://doi.org/10.1164/rccm.202003-0817LE
8. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-1099. https://doi.org/10.1111/jth.14817
9. Araujo-Filho JAB, Sawamura MVY, Costa AN, Cerri GG, Nomura CH. COVID-19 pneumonia: what is the role of imaging in diagnosis?. J Bras Pneumol. 2020;46(2):e20200114. https://doi.org/10.36416/1806-3756/e20200114
10. Chate RC, Fonseca EKUN, Passos RBD, Teles GBDS, Shoji H, Szarf G. Presentation of pulmonary infection on CT in COVID-19: initial experience in Brazil. J Bras Pneumol. 2020;46(2):e20200121. https://doi.org/10.36416/1806-3756/e20200121

J Bras Pneumol. 2020;46(4):e20190335
https://dx.doi.org/10.36416/1806-3756/e20190335

Pulmonary endometriosis: an unusual cause of hemoptysis

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

TO THE EDITOR:

A 29-year-old woman was referred to our hospital with a 5-month history of cough and monthly episodes of hemoptysis lasting 2-3 days. The hemoptysis was associated with her menstrual cycle. Her medical history was significant in that it included two induced abortions. Physical examination and laboratory test findings were unremarkable. Chest CT performed during the menstrual period showed two small cavitary nodules, containing ground-glass opacities, one in each of the lower lobes (Figures 1A and 1B). Another chest CT, acquired two weeks later (between menses), demonstrated that those abnormalities had resolved, except for a small thin-walled cavity in the right lower lobe (Figures 1C and 1D). Fiberoptic bronchoscopy performed during menstruation showed fresh blood at the entrance of the right lower lobe bronchus. The diagnosis of pulmonary endometriosis was suspected. The patient underwent video-assisted thoracoscopic surgery with resection of both nodules. Histopathological examination revealed uterine endometrial cells with stromal components (findings typical of endometriosis). The postoperative course was uneventful. At this writing, the patient has been asymptomatic for more than 18 months after surgery, without adjuvant pharmacological treatment.

Endometriosis is characterized by the presence of endometrial tissue at sites other than the uterine cavity. This condition most frequently affects women of reproductive age with a history of pelvic surgery, childbirth, or surgical procedures involving the uterine cavity.[1-3] Thoracic endometriosis, involving the pleura and pulmonary parenchyma, can occur, manifesting as the well-recognized clinical entities of catamenial pneumothorax, catamenial hemothorax, and catamenial hemoptysis, as well as nodules in the pleura or lung. Although the CT findings of thoracic endometriosis are relatively nonspecific, CT continues to be the first-line imaging method, because it can be used to rule out other diagnoses and map lesions for surgery. Examination by CT is more sensitive during menses, because lesions may vary in size or even disappear during other phases of the menstrual cycle. The images acquired by CT can also show pneumothorax, hydrothorax, or hydropneumothorax. Recurrent spontaneous pneumothoraces occur between 24 h before and 72 h after the onset of menses. The right hemithorax is involved in more than 90% of all forms of thoracic endometriosis.[4]

Studies have shown that magnetic resonance imaging (MRI) plays an important role in the evaluation of patients with thoracic endometriosis, given that it is better able than is CT to characterize hemorrhagic tissues and to detect endometriotic nodules. In addition, MRI is quite useful in detecting hemoglobin degradation products at the level of the diaphragm or the pleural cavity, which, in the context of endometriosis, is of great value. Endometriotic nodules exhibit distinctive blood components that may appear hyperintense on T1- and T2-weighted images, in some cases being accompanied by hemorrhagic pleural effusion, which can also show a hyperintense signal on T1-weighted images. Endometriotic nodules are commonly hyperintense when they are located on the pleural surface, although their signal intensity can differ between T1- and T2-weighted images.[4-6] One of the most rapidly evolving techniques in the MRI field is diffusion weighted imaging (DWI). In some cases, the restricted diffusion seen on DWI could be useful for the detection of small endometriomas, which show variable degrees of restricted diffusion, depending on the age of the lesion.[4,5] Therefore, MRI is a viable option for the characterization of pleural endometriotic nodules and hemorrhagic pleural effusion.[4-6]

Pleural endometriosis is more common than is pulmonary endometriosis.[1-3,7,8] In most cases, pulmonary endometriosis is thought to result from embolization of endometrial tissue to the lung parenchyma. Rupture of the capillaries or alveoli within the lesion during menstruation can result in hemoptysis or pneumothorax. In addition, blood invades the interstitium of the lung and spreads to the surrounding area. Absorption of the hemorrhagic lesions then occurs between menstruations.[1-3,8] The diagnosis of pulmonary endometriosis is established on the basis of recurrent hemoptysis that is synchronized with the menstrual cycle, together with persistent, pathologically confirmed foci of endometriosis. Symptoms manifest during menstruation and then disappear.[1,2,7,8] On CT, pulmonary endometriosis may be characterized by small areas of consolidation or ground-glass attenuation, nodular lesions, or thin-walled cavities, the appearance of which change over the course of the menstrual cycle. These findings can be presumed to represent pulmonary hemorrhage. The size and severity of the lesions during menstruation differ significantly from those in the period between menses.[1,3,8] Histopathological findings include uterine endometrial cells with features of proliferative or secretory endometrium.[8] Treatments include hormonal therapy and surgical resection. Surgical resection is considered to be the most effective treatment, although it is generally considered only when hormonal therapy fails.[1,3,7] The successful management of pulmonary endometriosis requires accurate diagnosis and lesion

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.

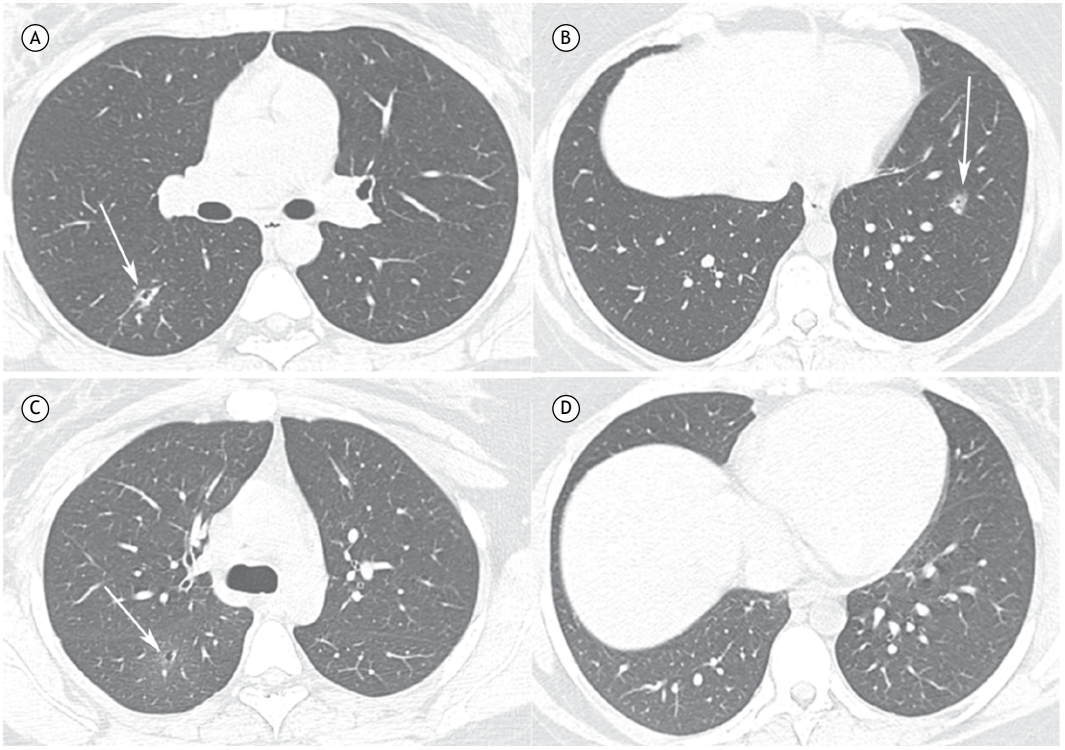


Figure 1. In A and B, chest CT scans acquired during the menstrual period, showing thickening of the nodule wall and the presence of another nodule with a similar appearance in the left lower lobe (arrows). The nodule in the left lower lobe was not evident in the image acquired between menses (in D). In C and D, chest CT scans acquired two weeks after menstruation, showing a small cavitary nodule located in the apical segment of the right lower lobe (arrow in C).

localization. The acquisition of CT scans during and two weeks after menstruation can help confirm the diagnosis and can facilitate the localization of parenchymal pulmonary endometriosis.

REFERENCES

1. Chung SY, Kim SJ, Kim TH, Ryu WG, Park SJ, Lee DY, et al. Computed tomography findings of pathologically confirmed pulmonary parenchymal endometriosis. J Comput Assist Tomogr. 2005;29(6):815-818. https://doi.org/10.1097/01.rct.0000176014.37051.c7
2. Tong SS, Yin XY, Hu SS, Cui Y, Li HT. Case report of pulmonary endometriosis and review of the literature. J Int Med Res. 2019;47(4):1766-1770. https://doi.org/10.1177/0300060518800868
3. Suwatanapongched T, Boonsarngsuk V, Amornputtisathaporn N, Leelachaikul P. Thoracic endometriosis with catamenial haemoptysis and pneumothorax: computed tomography findings and long-term follow-up after danazol treatment. Singapore Med J. 2015;56(7):e120-e123. https://doi.org/10.11622/smedj.2015115
4. de Paula MC, Escuissato DL, Belém LC, Zanetti G, Souza Jr AS, Hochhegger B, et al. Focal pleural tumorlike conditions: nodules and masses beyond mesotheliomas and metastasis. Respir Med. 2015;109(10):1235-1243. https://doi.org/10.1016/j.rmed.2015.06.004
5. Marchiori E, Zanetti G, Rodrigues RS, Souza LS, Souza Jr AS, Francisco FA, et al. Pleural endometriosis: findings on magnetic resonance imaging. J Bras Pneumol. 2012;38(6):797-802. https://doi.org/10.1590/S1806-37132012000600017
6. Pessôa FM, de Melo AS, Souza AS Jr, de Souza LS, Hochhegger B, Zanetti G, et al. Applications of Magnetic Resonance Imaging of the Thorax in Pleural Diseases: A State-of-the-Art Review. Lung. 2016;194(4):501-509. https://doi.org/10.1007/s00408-016-9909-9
7. Fang HY, Jan CI, Chen CK, Chen WT. Catamenial pneumothorax due to bilateral pulmonary endometriosis. Respir Care. 2012;57(7):1182-1185. https://doi.org/10.4187/respcare.01256
8. Fujimoto K, Kasai H, Suga M, Sugiura T, Terada J, Suzuki H, et al. Pulmonary Endometriosis which Probably Occurred through Hematogenous Metastasis after Artificial Abortion. Intern Med. 2017;56(11):1405-1408. https://doi.org/10.2169/internalmedicine.56.8265

J Bras Pneumol. 2020;46(4):e20200023
https://dx.doi.org/10.36416/1806-3756/e20200023

A summary of the proceedings of a meeting on the treatment of latent tuberculosis infection in target populations in Brazil

Valeria Rolla[1], Anete Trajman[2,3], Masae Kawamura[4], Solange Cavalcante[1,5], Elizabeth Soares[5], Filipe de Barros Perini[6], Anna Cristina Calçada Carvalho[7], Julio Croda[8,9], Jose Roberto Lapa e Silva[3]; LTBI Brazilian discussion group*

TO THE EDITOR:

An overview of the diagnosis and treatment of latent tuberculosis infection (LTBI) was provided during a meeting of tuberculosis experts in the city of Rio de Janeiro, Brazil, on July 18, 2018. The experts discussed the tools for LTBI diagnosis and the evolving policies on the preferred method of testing, either interferon-gamma release assay (IGRA) or the tuberculin skin test (TST), the latter being the standard method for LTBI diagnosis in Brazil. Current Brazilian guidelines recommend treatment of all contacts of pulmonary tuberculosis cases in whom LTBI is detected on the basis of a positive TST or IGRA, regardless of age, after active tuberculosis has been ruled out.[1] Although IGRAs are commercially available in Brazil, they have not been incorporated into the *Sistema Nacional de Saúde* (SUS, Brazilian Unified Health Care System).

In 2015 and 2018, the World Health Organization (WHO) issued policies on the management of LTBI that moved from disallowing the use of IGRAs for LTBI diagnosis in low- and medium-income countries to stating that IGRAs are interchangeable with TST for the diagnosis of LTBI.[2]

Tuberculin proteins overlap with proteins present in the BCG vaccine, resulting in TST having poor specificity, estimated at 59% among BCG-vaccinated persons.[3] QuantiFERON-TB Gold Plus (QFT-Plus), a 4th generation IGRA, has an additional CD8+ T cell tube, manufacturing improvements, and flexible blood draw options. Recent data show improved sensitivity of QFT-Plus in active culture-proven tuberculosis when compared with the prior version, known as the QuantiFERON-TB Gold-in-Tube assay.[4] Studies have demonstrated a correlation of CD8 responses with active tuberculosis and recent exposure to the pathogen.[4]

In the meeting of tuberculosis experts, the pros and cons of the use of IGRAs were discussed. The advantages of QFT assays over TST include higher specificity, which reduces the number of people misdiagnosed with LTBI and consequently the number needed to treat. In addition, IGRAs do not require a second patient visit to obtain results. Furthermore, unlike TST, QFT assays do not induce immune boosting if an individual is retested. Moreover, the QFT result is objective and is unaffected by previous BCG vaccination. Finally, quality control of test results is more easily achieved with the QFT assays.[3] However, the drawback of IGRAs is their higher price, lower cost-effectiveness in Brazil compared with TST,[5] and the need for a laboratory network to run tests for the public sector.

Despite the advantages provided by QFT assays, there was consensus among the meeting participants that QFT assays and TST are both fairly good tests for LTBI detection, despite their limitations. Although TST specificity is lower in BCG vaccinated-populations,[6] especially among individuals who are revaccinated after the first year of life, BCG vaccination may have a less pronounced impact in Brazil, because since nearly all children in the country are vaccinated only once, in the first month of life. Therefore, a positive TST (or IGRA) in a contact of a patient with pulmonary tuberculosis or in people living with HIV/AIDS (PLWHA) should be considered LTBI with high confidence and should be treated as such, when applicable. The superior predictive value of IGRAs is controversial, meta-analyses having presented conflicting findings. In children, TST have also been useful for diagnosing active tuberculosis as part of a scoring system. Above all, the benefit derived from treating LTBI in PLWHA, based on a positive TST, has been demonstrated in a number of trials.[7] However, there are few data regarding the use of IGRAs for selecting patients that will benefit from LTBI treatment.

The WHO recommends that treatment for LTBI be offered to individuals in some high-risk groups, such as children under 5 years of age and PLWHA, without testing or regardless of a test result, in order to avoid missing opportunities.[2] The main health care system hurdles, policy barriers, and challenges for the wider use of LTBI treatment include the lack of robust recommendations, the shortage of diagnostic tests/drugs, the need for

1. Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
2. McGill University, Montreal, Quebec, Canada.
3. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
4. Medical and Scientific Affairs, QIAGEN Inc., Hilden, Germany.
5. Secretaria Municipal da Saúde, Prefeitura do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
6. Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis, Ministério da Saúde, Brasília (DF) Brasil.
7. Laboratório de Inovações em Terapias, Ensino e Bioprodutos, Instituto Oswaldo Cruz, Rio de Janeiro (RJ) Brasil.
8. Fundação Oswaldo Cruz Mato Grosso do Sul, Campo Grande (MS) Brasil.
9. Universidade Federal de Mato Grosso do Sul, Campo Grande (MS) Brasil.
*LTBI Brazilian discussion group: Carolina Arana Stanis Schmaltz, Flavia Marinho Sant'Anna, Mayara Bastos, Adriano Gomes, Betina Durovni, Valeria Saraceni, Elisangela Silva, Fernanda Carvalho de Queiroz Mello, Marcelo Cordeiro dos Santos, Marcia Pinto, Marisa Santos, Fernando Augusto Dias e Sanches, and Sandra Maria do Valle Leone de Oliveira

a more robust surveillance/reporting system, and insufficient funding.

At the meeting, data on tuberculosis/HIV coinfection were presented by a representative from the Brazilian National Ministry of Health, who pointed out that tuberculosis continues to be the leading cause of death from an infectious agent among PLWHA in Brazil. Of the approximately 70,000 new tuberculosis cases reported annually, approximately 9.5% occur in PLWHA. Despite the increase in the proportion of new tuberculosis cases tested for HIV infection in recent years (76.3% in 2016), comprehensive HIV testing is still a challenge. Brazilian guidelines, published in June of 2018,[1] recommend that all HIV patients with a CD4+ cell count < 350 cells/mm^3 be treated for LTBI, assuming that active tuberculosis has been excluded, without the need for a TST or IGRA.

Prison inmates are plausible candidates for tuberculosis screening because they are "institutional amplifiers" of tuberculosis. Genotypic evidence supports transmission linkage between tuberculosis cases in prisons and the general population.[8]

The following is a summary of the main points discussed at the meeting of tuberculosis experts in Rio de Janeiro:

1. A network of the close contacts of each pulmonary tuberculosis case should be registered so that the contacts can be screened and treated for LTBI.
2. Each health care facility should use local data to identify risk groups to target and to create a cascade of LTBI diagnosis and treatment.
3. All new policy initiatives and variables for each step of the LTBI diagnosis and treatment cascade should be monitored in order to evaluate program performance and progress.
4. The results of tests, including TST, and chest X-ray findings should not be allowed to create a barrier to access to preventive therapy for the most vulnerable populations, such as PLWHA and children under 5 years of age.
5. The CD4+ cell count should not be allowed to create a barrier to access to LTBI treatment for PLWHA.
6. The QFT assays could play an important role in the event of continued shortages of TST, as an alternative to TST in some settings, and for target populations, such as PLWHA. There is a need for a laboratory network to promote future incorporation of QFT assays into the routine at public health care facilities and an update of the cost-effectiveness analyses, as well as for economic analyses in other target populations.
7. Children will benefit from shorter course rifampin regimens for LTBI. A 4-month course of rifampin is safer than is treatment with isoniazid alone or with any other regimen[9,10] and has been included as an option in Brazilian national guidelines.
8. Providing inmates with treatment for LTBI at the time of their release from prison could be a priority innovation approach to reduce the impact of tuberculosis transmission in the community.

REFERENCES

1. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Programa Nacional de Controle da Tuberculose. Manual de Recomendações para o Controle da Tuberculose no Brasil. 2nd ed. Brasília: Ministério da Saúde; 2018.
2. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization; 2018. PMID: 30277688
3. Trajman A, Steffen RE, Menzies D. Interferon-Gamma Release Assays versus Tuberculin Skin Testing for the Diagnosis of Latent Tuberculosis Infection: An Overview of the Evidence. Pulm Med. 2013;2013:601737. https://doi.org/10.1155/2013/601737
4. Sotgiu G, Saderi L, Petruccioli E, Aliberti S, Piana A, Petrone L, et al. QuantiFERON TB Gold Plus for the diagnosis of tuberculosis: a systematic review and meta-analysis. J Infect. 2019;79(5):444-453. https://doi.org/10.1016/j.jinf.2019.08.018
5. Steffen RE, Caetano R, Pinto M, Chaves D, Ferrari R, Bastos M, et al. Cost-effectiveness of Quantiferon®-TB Gold-in-Tube versus tuberculin skin testing for contact screening and treatment of latent tuberculosis infection in Brazil. PLoS One. 2013;8(4):e59546.https://doi.org/10.1371/journal.pone.0059546
6. Zwerling A, Behr MA, Verma A, Brewer TF, Menzies D, Pai M. The BCG World Atlas: a database of global BCG vaccination policies and practices. PLoS Med. 2011;8(3):e1001012. https://doi.org/10.1371/journal.pmed.1001012
7. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev. 2010;2010(1):CD000171. https://doi.org/10.1002/14651858.CD000171.pub3
8. Mabud TS, de Lourdes Delgado Alves M, Ko AI, Basu S, Walter KS, Cohen T, et al. Evaluating strategies for control of tuberculosis in prisons and prevention of spillover into communities: An observational and modeling study from Brazil [published correction appears in PLoS Med. 2019 Mar 1;16(3):e1002764]. PLoS Med. 2019;16(1):e1002737. https://doi.org/10.1371/journal.pmed.1002737
9. Diallo T, Adjobimey M, Ruslami R, Trajman A, Sow O, Obeng Baah J, et al. Safety and Side Effects of Rifampin versus Isoniazid in Children. N Engl J Med. 2018;379(5):454-463. https://doi.org/10.1056/NEJMoa1714284
10. Stagg HR, Zenner D, Harris RJ, Muñoz L, Lipman MC, Abubakar I. Treatment of latent tuberculosis infection: a network meta-analysis. Ann Intern Med. 2014;161(6):419-428. https://doi.org/10.7326/M14-1019

J Bras Pneumol. 2020;46(4):e20200168
https://dx.doi.org/10.36416/1806-3756/e20200168

COVID-19 pneumonia: a risk factor for pulmonary thromboembolism?

Dany Jasinowodolinski[1], Mariana Marins Filisbino[1], Bruno Guedes Baldi[2,3]

In December of 2019, a new virus was discovered in Wuhan, China. It was characterized as a coronavirus and is responsible for the COVID-19 pandemic. A small number of those affected by the virus develop acute respiratory distress syndrome and other complications, of which the most recently reported is acute pulmonary thromboembolism (PTE).[1] Although the mechanism by which this viral infection increases the risk of acute PTE has yet to be fully understood, it might be related to the endothelial damage caused by the viral infection.[1]

The aim of the present report is to show the possible causal relationship between COVID-19 pneumonia and acute PTE. An obese 40-year-old man was initially diagnosed with mild COVID-19. Seven days after the

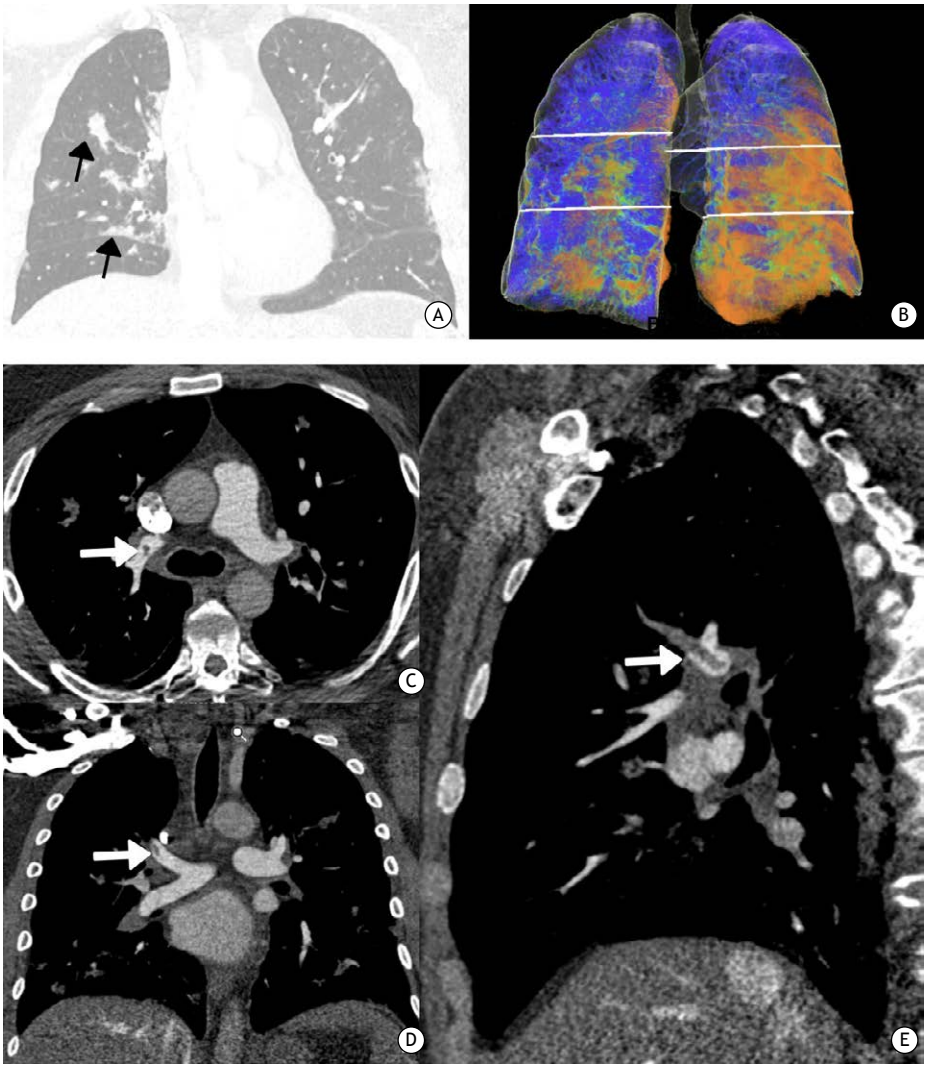


Figure 1. A CT scan of the chest showing foci of consolidation (in A) one week after an initial scan had shown only opacities and ground-glass attenuation, consistent with the usual evolution of COVID-19 pneumonia. A posterior projection of the lungs using three-dimensional reconstruction (in B) shows the extent of lung parenchyma involvement (37.7%), predominantly in the posterior region. CT angiography of the chest showing a central filling defect—white arrows in C (axial reconstruction), D (coronal reconstruction), and E (sagittal reconstruction)—in the branch of the right pulmonary artery to the upper lobe, consistent with acute pulmonary thromboembolism.

1. Departamento de Radiologia, Hospital do Coração, São Paulo (SP), Brasil.
2. Serviço de Pneumologia, Hospital do Coração, São Paulo (SP), Brasil.
3. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo – HC-FMUSP – São Paulo (SP), Brasil.

onset of the symptoms, he presented with worsening dyspnea and an increase in D-dimer levels (from 700 ng/mL to 7,000 ng/mL). At hospital admission, CT angiography of the chest showed a typical pattern of viral pneumonia[2] and PTE (Figure 1). There was no hypoxemia. Doppler ultrasound of the lower extremities was negative for deep vein thrombosis, and an echocardiogram was unremarkable. In the case of COVID-19 pneumonia reported here, the absence of major risk factors for venous thrombosis supports the hypothesis that the viral pneumonia was the triggering factor for acute PTE.[3]

AUTHOR CONTRIBUTIONS

DJ: study design, writing, and final review of the manuscript. MMF and BGB: writing and final review of the manuscript.

REFERENCES

1. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? [published online ahead of print, 2020 Mar 30]. Eur Heart J. 2020;ehaa254. https://doi.org/10.1093/eurheartj/ehaa254.
2. Lei J, Li J, Li X. CT imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia. Radiology. 2020;295(1):18. Available from: https://doi.org/10.1148/radiol.2020200236.
3. Xie Y, Wang X, Yang P, Zhang S. COVID-19 Complicated by Acute Pulmonary Embolism. Radiol Cardiothoracic Imaging. 2020;2(2):e200067. https://doi.org/10.1148/ryct.2020200067.

EDITAL DE SELEÇÃO

Brasília, 26 de junho de 2020

No período entre 01 de julho e 15 de setembro de 2020 estarão abertas as inscrições para candidatos ao cargo de Vice-Editor do Jornal Brasileiro de Pneumologia, com atuação no biênio 2021-2022. O Vice-Editor eleito assumirá a posição de Editor-Chefe em 2023.

Os interessados ao posto deverão ter experiência prévia como editor de periódicos de circulação internacional e enviar à administração da SBPT, em Brasília, suas propostas de gestão e Curriculum Vitae na plataforma Lattes. As propostas dos candidatos deverão abranger os campos administrativo, científico e orçamentário, e deverão ser apresentadas em relação ao período de dois anos como Vice-Editor e aos quatro anos previstos para o futuro mandato como Editor-Chefe.

Os candidatos deverão conhecer as normas relativas à seleção do Vice-Editor e o funcionamento do Jornal Brasileiro de Pneumologia, descritas em seu regulamento, que pode ser obtido por meio de contato com a secretaria do JBP em Brasília.

Dr. José Miguel Chatkin
Presidente da SBPT

Dr. Bruno Guedes Baldi
Editor-Chefe Jornal Brasileiro de Pneumologia

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

Congresso Brasileiro de Pneumologia e Tisiologia

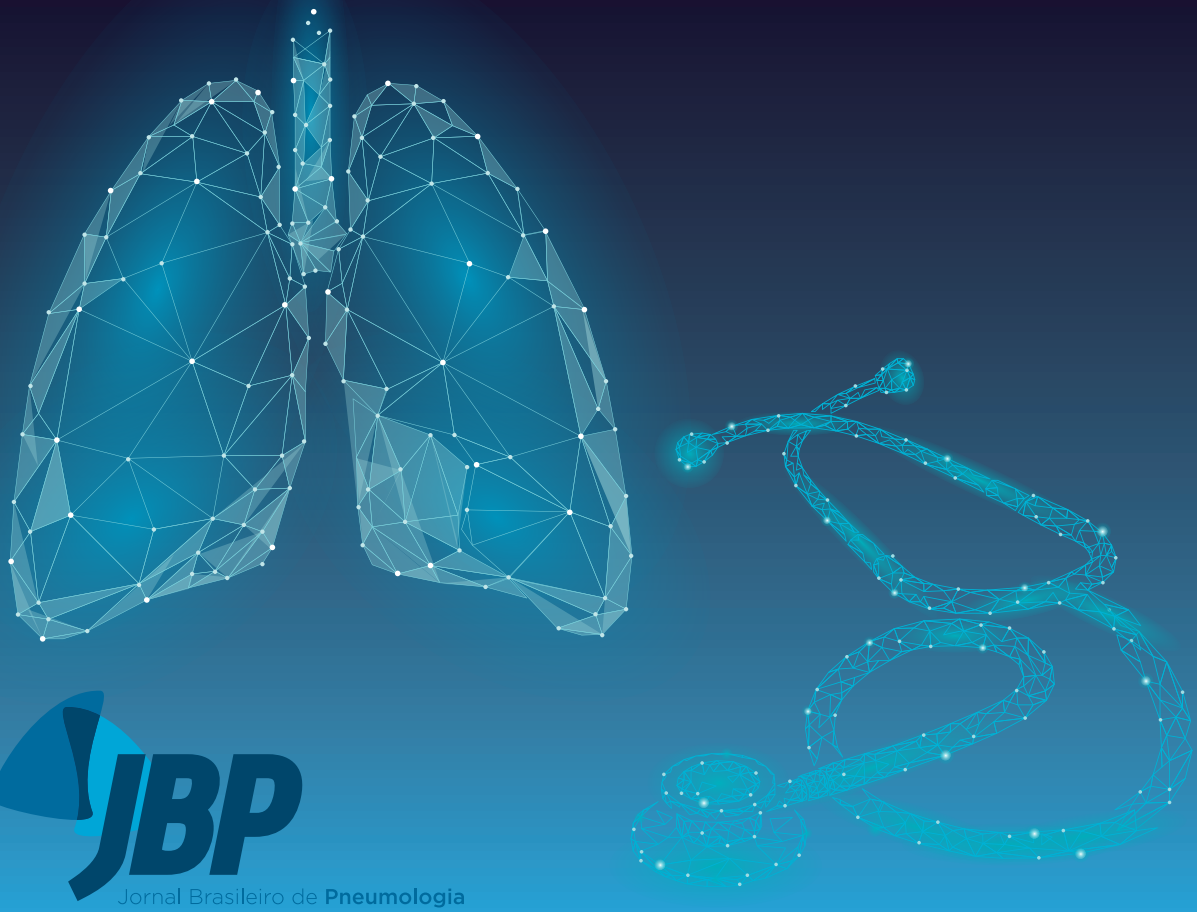
SBPT Virtual 10 a 12 | Outubro | 2020

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



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 ·