ISSN (ON-LINE): 1806-3756

JBP
Jornal Brasileiro de **Pneumologia**

PUBLICAÇÃO OFICIAL DA SOCIEDADE BRASILEIRA DE PNEUMOLOGIA E TISIOLOGIA

Volume 50, Number 3
May | June
2024

Volume 50, Number 3 May | June 2024

HIGHLIGHT

Benzbromarone as adjuvant therapy for cystic fibrosis lung disease: a pilot clinical trial

Respiratory syncytial virus infection in children during SARS-CoV-2 pandemic at a referral center in Rio de Janeiro, Brazil

Impact of COVID-19 on diagnosis of tuberculosis and tuberculosis infection in South America, Asia, and Africa

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 (ON-LINE): 1806-3756

Continuous and Bimonthly Publication, J Bras Pneumol. v. 50, n. 3, May/June 2024

ISSN (ON-LINE): 1806-3756

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 08000 616218. Website: www.sbpt.org.br.
E-mail: sbpt@sbpt.org.br

The Brazilian Journal of Pulmonology (ISSN 1806-3756) 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 08000 616218.
Editorial Manager: Luana Maria Bernardes Campos.
E-mail: jbp@jbp.org.br | jbp@sbpt.org.br
Distribution: Free to members of the BTS and libraries

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 (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 50, n. 3, May/June 2024

Contents

ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 50, n. 3, May/June 2024

Contents

J Bras Pneumol. 2024;50(3):e20240218
https://dx.doi.org/10.36416/1806-3756/e20240218

Assessing alternative treatment targets in patients with cystic fibrosis

Rodrigo Cavallazzi[1], Marcia Pizzichini[2]

Cystic fibrosis is an autosomal recessive genetic disease that involves multiple organ systems. The cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7 encodes the CFTR protein, an ion channel responsible for transporting chloride ions from inside the cells to the airway lumen. The presence of two pathogenic variants of the CFTR leads to malfunction of the channel with consequent viscous secretions mainly affecting the gut and lungs. There are over 2000 mutations in the CFTR gene,[1] with 700 of these being disease-causing variants.[2] The most common variant is the *F508del*,[3] which leads to phenylalanine deletion at position 508 and consequent misfolding and degradation of the CFTR protein.[2] The frequency of *F508del* variant in people with cystic fibrosis varies globally. For example, it is present in 85% of the population with cystic fibrosis in areas with predominant European ancestry[3] and 38% in a cohort from South India.[4] In Brazil, the *F508del* variant is found in 52.8% of individuals with cystic fibrosis, with 24.5% being homozygous for the *F508del* variant and 28.8% being heterozygous.[5]

An estimate based on data from 5 Brazilian states from the South and Southeast showed an incidence of cystic fibrosis homozygotes of 1 in 20,202 (95% CI 8,651–47,179). The incidence ranged from 1 in 1,587 (95% CI 504–5005) in Rio Grande do Sul to 1 in 32,258 (95% CI 3,281–318,549) in Sao Paulo.[6] In Brazil, the median age of individuals with cystic fibrosis is 10.8 years,[5] contrasting with 21.9 years in the United States,[3] with adults comprising 25% of the population affected.[5] Among Brazilian individuals with cystic fibrosis, the racial distribution is as follows: white (69%), mixed-race (24%), black (6%), Asian (1%), and Indigenous (1%). However, it is important to note that these data are not based on self-declared race.[5]

The diagnosis of cystic fibrosis is established when there is clinical suspicion (e.g. a positive newborn screening test or clinical symptoms or family history) plus a positive sweat chloride test (≥60 mmol/L) or two cystic fibrosis-causing mutations when the sweat chloride test is in the intermediate range (30 – 59 mmol/L).[7] All patients with a diagnosis of cystic fibrosis should undergo genetic testing.[8] Where newborn screening for cystic fibrosis is widely implemented, most cases are detected early in the asymptomatic phase by screening.[3] Clinically, patients with cystic fibrosis can present in a variety of ways. Approximately 15% of the patients present with meconium ileus as neonates.[9] In those aged ≥ 1 year upon diagnosis, almost half of the patients have respiratory symptoms. Other common presenting manifestations include nasal polyps and sinus disease, steatorrhea, infertility, malnutrition, failure to thrive, and digital clubbing. Over time, these patients develop bronchiectasis, obstructive lung disease, and recurrent respiratory infections, mainly by *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[3] Most deaths are due to respiratory or cardiorespiratory failure.[3]

The survival of patients with cystic fibrosis has been steadily improving. In the United States, the predicted survival age for individuals with cystic fibrosis is currently estimated at 68.2 years.[3] In Brazil, analysis based on death certificate reports has shown a notable increase in the median age of individuals who died from cystic fibrosis over time,[10] which is likely attributable to advances in cystic fibrosis management and the establishment of cystic fibrosis centers.[11] However, substantial regional healthcare disparities exist in the diagnosis and management of cystic fibrosis patients in Brazil[12] Continued improvement in patient outcomes require addressing these disparities, ensuring universal and effective access to newborn screening, reliable sweat tests,[12] and the expansion of multidisciplinary cystic fibrosis centers.[11]

A revolution in the treatment of patients with cystic fibrosis has been the introduction of the CFTR modulators. These medications act as potentiators, by improving the function of the CFTR, or as correctors, by increasing the amount of CFTR in the airway epithelia. CFTR modulators improve respiratory symptoms, lung function, and nutritional status; reduce the frequency of exacerbations; and lower sweat chloride concentraton.[2] In late 2020, ivacaftor was included into the *Sistema Único de Saúde* (Brazil's public health care system) for patients aged 6 years and with gating mutations.[13] In September 2023, the Brazilian Ministry of Health announced the inclusion of elexacaftor-tezacaftor-ivacaftor for patients aged 6 years and older with at least one *F508del* mutation in the *CFTR* gene. This decision is expected to benefit an estimated 1,700 eligible patients.[14]

Despite significant advancements obtained by newborn screening, diagnostic tests, treatment of complications, multidisciplinary care, cystic fibrosis centers, and CFTR modulators, cystic fibrosis continues to be a disease with a challenging prognosis. Alternative treatment targets have the potential to further improve the outcomes of these patients. One of them is TMEM16A, a Ca2+-activated chloride channel present in airway epithelial and smooth cells. Basic research has shown that TMEM16A mediates mucus secretion and can be upregulated by cytokines in human airway epithelial cells. Additionally, inhibitors of TMEM16A, such as

1. Division of Pulmonary, Critical Care, and Sleep Disorders. Department of Medicine. University of Louisville, Louisville, KY
2. Programa de Pós Graduação em Ciências Médicas Universidade Federal de Santa Catarina (UFSC), Florianópolis,SC

ISSN 1806-3756

niclosamide, and benzbromarone, lead to decreased airway mucus production although this effect could also be due to inhibition of other proteins.[16] Both inhibitors and activators of TMEM16A may prove to have a role in the treatment of inflammatory airway diseases, including cystic fibrosis. An intriguing finding is that is that cells expressing F508 del have impaired expression of TMEM16A by its regulator, CLCA1. This indicates an interdependence between TMEM16A and CFTR.[16] This also brings the possibility that the effect of inhibitors and activators of TMEM16A may be influenced by CFTR modulators.

In this edition of the *Jornal Brasileiro de Pneumologia*, Friedrich et al.[15] conducted a single center, single arm pilot trial assessing the safety of benzbromarone in children > 6 years with confirmed cystic fibrosis. In addition to the standard treatment for cystic fibrosis, which at the time did not include CFTR modulators presumably due to their unavailability, patients were administered 100 mg of oral benzbromarone once daily for a duration of 90 days. The primary outcome was the safety of benzbromarone in these patients. One patient developed a 3 kg weight loss, which improved after the medication was discontinued. One patient experienced a pulmonary exacerbation during the study period. One patient chose to withdraw from the study before its completion. The FEV_1 in percentage of predicted increased by 8% although the difference did not quite reach statistical difference.

This proof-of-concept study explores an alternative treatment approach for patients with cystic fibrosis, based on robust foundational research.[16] The tested medication, the uricosuric agent benzbromarone, is cost-effective and has been used for a different condition for decades. However, the study's small sample size precludes definitive conclusions regarding the medication's safety in pediatric patients with cystic fibrosis. Future studies, ideally multicenter and placebo-controlled with safety outcomes adjudication, are needed to establish benzbromarone's safety in this population. Nevertheless, this study marks an initial step toward understanding the medication's effects and safety in pediatric patients with cystic fibrosis, for which the authors deserve commendation.

REFERENCES

1. Brasil. Ministério da Saúde. Comissão Nacional de Incorporação de Tecnologias no SUS (CONITEC). Portaria Conjunta SAES/SECTICS Nº 5, de 30 de abril de 2024. Aprova o Protocolo Clínico e Diretrizes Terapêuticas da Fibrose Cística. [updated 2024 Apr 4] Protocolo clínico e diretrizes terapêuticas da fibrose cística. [Adobe Acrobat document, 47p.] Available from: https://www.gov.br/conitec/pt-br/midias/protocolos/20211230_portal-portaria-conjunta-no-25_pcdt_fibrose-cistica.pdf/view
2. Ong T, Ramsey BW. Cystic Fibrosis: A Review. JAMA. 2023;329(21):1859-1871. https://doi.org/10.1001/jama.2023.8120
3. Cystic Fibrosis Foundation. 2022 Annual Data Report. Cystic Fibrosis Foundation Patient Registry; 2023. Available from: https://www.cff.org/medical- professionals/patient-registry
4. Varkki SD, Aaron R, Chapla A, Danda S, Medhi P, Rani NJ. CFTR mutations and phenotypic correlations in people with cystic fibrosis: a retrospective study from a single centre in south India. Lancet Region Health Southeast Asia. 2024;27.100434. https://doi.org/10.1016/j.lansea.2024.100434
5. Grupo Brasileiro de Estudos de Fibrose Cística. Relatório anual de 2021. 2021. Registro brasileiro de fibrose cística ano 2021. Available from: http://gbefc.org.br/ingles/site/pagina.php?idpai=128&id=15
6. Raskin S, Pereira-Ferrari L, Reis FC, Abreu F, Marostica P, Rozov T, et al. Incidence of cystic fibrosis in five different states of Brazil as determined by screening of p.F508del, mutation at the CFTR gene in newborns and patients. J Cyst Fibros. 2008;7(1):15-22. https://doi.org/10.1016/j.jcf.2007.03.006
7. Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr. Feb 2017;181s:S4-S15.e1. https://doi.org/10.1016/j.jpeds.2016.09.064
8. Athanazio RA, Silva Filho LVRF, Vergara AA, Ribeiro AF, Riedi CA, Procianoy EDFA, 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
9. Marson FA, Hortencio TD, Aguiar KC, Ribeiro JD; CYFIUC Group. Demographic, clinical, and laboratory parameters of cystic fibrosis during the last two decades: a comparative analysis. BMC Pulm Med. 2015;15:3. https://doi.org/10.1186/1471-2466-15-3
10. Santo AH, Silva-Filho LVRFD. Cystic fibrosis-related mortality trends in Brazil for the 1999-2017 period: a multiple-cause-of-death study. J Bras Pneumol. 2021;47(2):e20200166. https://doi.org/10.36416/1806-3756/e20200166
11. endrusculo FM, Donadio MVF, Pinto LA. Cystic fibrosis in Brazil: achievements in survival. J Bras Pneumol. 2021;47(2):e20210140. https://doi.org/10.36416/1806-3756/e20210140
12. da Silva Filho LVRF, Maróstica PJC, Athanazio RA, Reis FJC, Damaceno N, Paes AT, et al. Extensive CFTR sequencing through NGS in Brazilian individuals with cystic fibrosis: unravelling regional discrepancies in the country. J Cyst Fibros. 2021;20(3):473-484. https://doi.org/10.1016/j.jcf.2020.08.007
13. Athanazio RA, Tanni SE, Ferreira J, Dalcin PTR, Fuccio MB, Esposito C, et al. Brazilian guidelines for the pharmacological treatment of the pulmonary symptoms of cystic fibrosis. Official document of the Sociedade Brasileira de Pneumologia e Tisiologia (SBPT, Brazilian Thoracic Association). J Bras Pneumol. 2023;49(2):e20230040. https://doi.org/10.36416/1806-3756/e20230040
14. Brasil. Ministério da Saúde. Brasília: gov.br; c2024 [updated 2023 Sep 14; cited 2024 Jun 20]. Ministério da Saúde incorpora novo medicamento para fibrose cística no SUS. Available from: https://www.gov.br/saude/pt-br/assuntos/noticias/2023/setembro/ministerio-da-saude-incorpora-novo-medicamento-para-fibrose-cistica-no-sus
15. Friedrich F, Petry LM, Garcia LCE, Pieta MP, Meneses ADS, Bittencourt LB, et al. Benzbromarone as adjuvant therapy for cystic fibrosis lung disease: a pilot clinical trial. J Bras Pneumol. 2024;50(3):e20230292. https://doi.org/10.36416/1806-3756/e20230292
16. Cabrita I, Benedetto R, Wanitchakool P, Lerias J, Centeio R, Ousingsawat J, et al. TMEM16A Mediates Mucus Production in Human Airway Epithelial Cells. Am J Respir Cell Mol Biol. 2021;64(1):50-58. https://doi.org/10.1165/rcmb.2019-0442OC

Calcifications in multiple lymph node chains

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

A 46-year-old female patient with no smoking history, complaining of dry cough and tiredness, was admitted. Her laboratory test results were unremarkable. Chest CT showed reticular opacities with architectural distortion predominating in the middle thirds of the lungs, in addition to lymph node calcifications affecting multiple mediastinal and hilar chains (Figure 1).

Lymph node calcifications are most often sequelae of granulomatous infections, especially tuberculosis and histoplasmosis. Other less common causes are sarcoidosis, silicosis, amyloidosis, and calcifications secondary to lymphoma treatment (radiotherapy or chemotherapy).

However, the characteristics of lymph node calcifications in the patient were very specific. The calcifications involved multiple lymph node chains. When the presence of calcifications affecting multiple lymph node chains is observed, two diseases are paramount for differential diagnoses: silicosis and sarcoidosis. Differentiation by imaging can be very difficult since both diseases can present with small nodules, conglomerate masses, and areas of emphysema, in addition to having a fibrosing evolution. In this situation, clinical and occupational history, such as previous contact with silica dust, is essential, since patients with silicosis, in general, carried out professional activities related to exposure. Our patient had no past or current history of exposure to silica, which allowed us to rule out the hypothesis of silicosis.

Sarcoidosis is a systemic inflammatory disease of unknown etiology, characterized by the formation of noncaseating epithelioid cell granulomas. Involvement of the lungs and mediastinal and hilar lymph nodes is more common, being observed in approximately 90% of patients, and is responsible for most of the morbidity and mortality associated with the disease. However, it can also involve any organ in the body; skin, eyes, heart, and liver are the most common ones. Pulmonary symptoms are variable. Patients may be asymptomatic and the disease may be identified on chest images obtained for unrelated reasons. However, patients more commonly present with nonspecific symptoms, such as cough, fatigue, and exertional dyspnea.[1,2]

On CT, the most typical findings of pulmonary involvement are small nodules with perilymphatic distribution, bilateral perihilar parenchymal opacities, and fibrotic changes. Hilar and/or mediastinal lymph node disease is also a common finding. Atypical manifestations, such as alveolar or mass-like opacities, honeycombing, miliary opacities, mosaic attenuation, and tracheobronchial involvement, may also be observed. Pleural effusion is rare in sarcoidosis.[1,2] The final diagnosis was sarcoidosis.

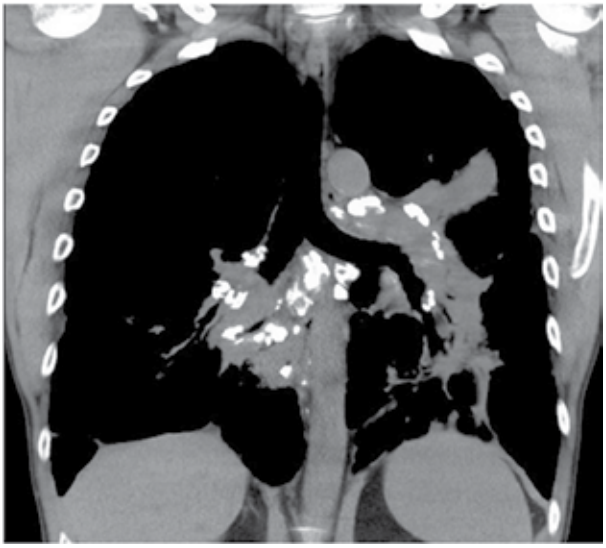

Figure 1. Coronal reconstruction of a chest CT scan with a mediastinum window setting showing calcifications affecting lymph nodes in several mediastinal and hilar chains. Also note evidence of fibrotic distortion in the perihilar regions.

REFERENCES

1. Hamzeh N. Sarcoidosis. Med Clin North Am. 2011;95(6):1223-1234. https://doi.org/10.1016/j.mcna.2011.08.004
2. Criado E, Sánchez M, Ramírez J, Arguis P, de Caralt TM, Perea RJ, et al. Pulmonary sarcoidosis: typical and atypical manifestations at high-resolution CT with pathologic correlation. Radiographics. 2010;30(6):1567-1586. https://doi.org/10.1148/rg.306105512

1. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
2. University of Florida, Gainesville (FL) USA.

◄ Voltar ao sumário

Using data from patient registries to answer important research questions

Samia Rached[1,2], Cecilia M Patino[1,3], Juliana Ferreira[1,2]

PRACTICAL SCENARIO

A group of pediatricians and pulmonologists from the largest referral centers for cystic fibrosis (CF) in Brazil has questioned whether there are genetic, clinical, and treatment distinctions among the different regions of the country. They choose to create a patient registry to compile the characteristics of CF patients in the various regions of Brazil. A few years later, some of these investigators used data from the registry to study the most common types of mutations leading to CF in Brazil and regional differences regarding accessibility to genetic testing.[1]

WHAT ARE PATIENT REGISTRIES?

A patient registry is an organized data system in which data is systematically collected over time for a population with a specific disease, condition, or outcome.

Patient registries include real world data, potentially providing a realistic image of the target population's characteristics, treatments, and outcomes. Data are collected periodically and in a timeline that can be used to study the natural course of diseases and changes in the patterns of care over time. Reports of aggregate data are created and made widely available to the public and medical community. Patient registries are especially helpful in evaluating rare diseases because they typically include data from patients at different medical centers and in several regions of a country or continent. Comparing data from different regions may reveal disparities in the severity of disease at the time of diagnosis, the treatments most often used, and short and long-term outcomes, which could inform the development of diagnosis and treatment guidelines, as well as public health policy to improve health equity and patient outcomes. Registries may also be useful for monitoring the real world impact and safety of new treatments, because they include data from high-risk patients, who are usually excluded from randomized controlled trials.[2]

REGISTRY-BASED STUDIES

Although registries are created mostly to inform clinical management, the accumulated data can be used in order to answer research questions. A registry-based study is an observational method to answer a research question using data from patient registries. Researchers can answer research questions using a patient registry to quickly access data provided by hundreds, or even thousands, of similar patients. In our practical scenario example, the researchers found that only 67% of patients in the Brazilian registry had access to genotyping tests, and that access to newborn screening and age at diagnosis were mediators of the effect that region had on a positive genotyping result.[1] Multiple studies may be performed by using a single patient registry. Although studies using patient registries are typically retrospective in nature, they have the advantage of including very broad study populations, thus providing results that are more frequently generalizable to the target population than are those of highly controlled randomized clinical trials. The differences between a patient registry and a registry-based study are shown in Table 1.

CHALLENGES OF PATIENT REGISTRIES

Developing and implementing a registry is not an easy task. It requires human and financial resources to design and implement the project. Case finding and data collection are time consuming and demand adequate training and motivation of stakeholders, to ensure participation and the collection of reliable data. Those can

Table 1. Differences between a patient registry and a registry-based study.

Aspect	Patient registry	Registry-based study
Nature	Data collection system, mostly to increase awareness and inform public policy	Designed to answer a focused research question, applicable to the target population of the registry
Follow-up	Long-term, open-ended	Defined by the study objectives
Patient enrolment	All patients within the purpose of the registry (all patients with that condition in the specified area)	Defined by the study objectives and target population
Data collection	Wide range	Restricted to variables needed by the research question
Analysis plan	Routine periodic data analysis	Planned in the study protocol
Data quality	Applied routinely to all data and processes	Study-specific data quality management potentially needed

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

◄ Voltar ao sumário
ISSN 1806-3756

be barriers, and financial and nonfinancial incentives or credits may be used. Sustainability of the project, with continued funding and data collection, also needs to be considered. Registries also need appropriate ethical and legal analysis, including participant consent and strategies to ensure data confidentiality and security. Technological developments may facilitate the design and maintenance of a reliable registry, as well as its use for research and quality improvement projects.[2]

KEY MESSAGES

1. Patient registries are a useful source of real-world patient data. Registry-based studies use these databases to answer research questions.
2. Developing a patient registry requires human and financial resources. To acquire reliable data, it is essential to have a prepared and motivated team.

REFERENCES

1. da Silva Filho LVRF, Maróstica PJC, Athanazio RA, Reis FJC, Damaceno N, Paes AT, et al. Extensive CFTR sequencing through NGS in Brazilian individuals with cystic fibrosis: unravelling regional discrepancies in the country. J Cyst Fibros. 2021;20(3):473-484. https://doi.org/10.1016/j.jcf.2020.08.007
2. Eldh AC, Wallin L, Fredriksson M, Vengberg S, Winblad U, Halford C, et al. Factors facilitating a national quality registry to aid clinical quality improvement: findings of a national survey. BMJ Open. 2016;6(11):e011562. https://doi.org/10.1136/bmjopen-2016-011562

The role of the pulmonary function laboratory to assist in disease management: connective tissue diseases

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

BACKGROUND

The respiratory system is variably affected by the systemic consequences of connective tissue diseases (CTDs). These abnormalities contribute to morbidity and mortality, being ascribed to direct autoimmune effects, drug toxicity, and/or opportunist infections. Pulmonary function tests (PFTs) might help recognize respiratory involvement, constituting an important auxiliary tool for CTD management.[1]

OVERVIEW

A 22-year-old woman with systemic lupus erythematosus under treatment with methotrexate and hydroxychloroquine reported worsening dyspnea over 10 months [currently modified Medical Research Council (mMRC) score = 4/4]. Chest CT showed minor atelectatic bands only. A severe and proportional reduction in FEV_1 [32% of the predicted values (pred)] and FVC (28% pred) coexisted with moderately severe decrement in TLC (50% pred), supranormal K_{CO}, and reduced maximal inspiratory pressures. Given the absence of any other cause for extraparenchymal restriction, she was diagnosed with shrinking lung syndrome. Pulse therapy with cyclophosphamide was associated with partial recovery of lung function (FEV_1 and FVC ≈40% pred) and marked clinical improvement (mMRC = 2) four months later (Case #1). A 63-year-old ex-smoker (30 pack-years) woman with undifferentiated systematic rheumatic disease reported nonproductive cough and progressive exertional dyspnea (mMRC = 2) over 6 months, associated with a nonspecific interstitial pneumonia pattern on HRCT. Serial spirometry showed a 10% relative decline in FVC from 2.29 L (67% pred) to 2.06 L (61% pred), fulfilling a functional criterion for progressive pulmonary fibrosis.[2] Oral azathioprine was related to improvement in both FEV_1 and FVC (≈78% pred) and dyspnea (mMRC = 1).

Although respiratory involvement is thought to occur at later stages of CTDs, they may be the initial presentation ("lung dominant"). Conversely, some patients may remain asymptomatic for a long time despite impaired PFTs or abnormalities in chest imaging. Interstitial lung disease (ILD) and pulmonary hypertension are the most common respiratory complications. A spectrum of other manifestations, however, may occur including airway disease (bronchiectasis, bronchiolitis), other pulmonary vascular disease (pulmonary embolism, chronic thromboembolic pulmonary hypertension), pleurisy, and respiratory muscle weakness.[3]

A restrictive ventilatory defect is the typical presentation of ILD (Case #2) but may also occur in the presence of respiratory muscle weakness (Case #1) and pleural space disease. The two last complications are typically associated with a supranormal K_{CO} ("extraparenchymal" restriction), provided there is no anemia or another cause for an out-of-proportion decrease in DL_{CO} relative to lung volume.[4,5] Conversely, an isolated reduction in hemoglobin-corrected DL_{CO}, in turn, may signal incipient ILD or some sort of pulmonary vascular involvement.[5] Each CTD has predominant patterns of respiratory involvement with routine pulmonary function assessment recommended accordingly. The conjunction of PFT findings suggests the type of respiratory complication (Chart 1). In most diseases, serial measurements of FVC and (if possible) DL_{CO} at least yearly are used in order to evaluate progression in CTD-ILD.[1-3]

CLINICAL MESSAGE

Respiratory symptoms are a frequent feature of CTDs. Proper diagnosis of the underlying causes might be challenging, notably in patients with multiple comorbidities (e.g., COPD, asthma, heart failure) and obesity. The pulmonologist should be familiar with the pattern of abnormalities expected in the most frequent diseases (Chart 1), interpreting testing results and considering concurrent clinical, laboratory, and imaging findings.

AUTHOR CONTRIBUTIONS

All authors equally contributed to this manuscript.

CONFLICTS OF INTEREST

None declared.

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.

◄ Voltar ao sumário
ISSN 1806-3756

	Respiratory involvement	PFTs recommendation	Most frequent PFTs findings
Scleroderma spectrum	• Some degree of pulmonary involvement is present in more than 80% of patients • Main manifestations are ILD and pulmonary vascular disease, leading to PAH • Other pulmonary complications include thromboembolic disease, pleural disease, aspiration pneumonitis, airway disease, and lung cancer • More than one of these processes may be presentin each patient	• All patients should have complete PFTs (spirometry, plethysmography, and DLco) performed at the initial presentation • ↓DLco (< 65% pred) without significant lung volume reduction or a decrease in DLco ≥20%/year suggests PH, particularly in a patient with long-standing limited cutaneous sclerosis • A ratio of FVC/DLco (in % pred) > 1.6 also suggests PH	• The combination of ↓ TLC and JHb-corrected DLco suggests ILD • An absolute decline in FVC > 5% pred and/or DLco > 10% pred within 1 year of follow-up suggests CTD-ILD progression • ↓ Hb-corrected DLco with normal lung volumes can be seen in pulmonary vascular disease or early ILD • ↓ TLC with preserved DLco (usually accompanied by high Kco) suggests respiratory muscle weakness, pleural disease and/or abnormalities of thoracic cage mobility • Flow-volume loops can help identify upper airway obstruction when blunted peak inspiratory flow is present • The combination of airflow limitation (↓FEV1/FVC), normal or ↓ DLco, and HRCT with expiratory air trapping (mosaic or diffuse), bronchial wall thickening, and centrilobular nodules may establish a "clinical" diagnosis of bronchiolitis obliterans • Both obstructive and restrictive patterns have been noted in follicular bronchiolitis, although restriction is more common • A ↑ DLco suggests pulmonary hemorrhage • Sitting and supine FVC decline (>10%), ↓ maximum voluntary ventilation, and ↓ maximal inspiratory and expiratory pressures are helpful to confirm and monitor respiratory muscle weakness • A six-minute walk test is useful for detecting exercise-induced oxygen desaturation
Rheumatoid arthritis	• ILD and pleural disease are the most common abnormalities • The leading cause of upper airway obstruction is cricoarytenoid arthritis; less common causes include rheumatoid nodules on the vocal cord or vasculitis in recurrent laryngeal or vagus nerves • Lower airway involvement includes bronchiolitis obliterans, follicular bronchiolitis, and bronchiectasis • ↑risk of pulmonary embolism • Abnormalities of thoracic cage mobilitylikely due to pleurisy, myopathy, and thoracic rigidity	• The role of surveillance for lung disease in patients with rheumatoid arthritis is unclear Respiratory symptoms or abnormalities in respiratory examination should trigger the evaluation with a chest radiograph • Additional studies are utilized (PFTs, HRCT) based on the findings of the clinical evaluation, chest radiograph and the degree of clinical suspicion for associated pleuropulmonary disease	
SLE	• Most patients show involvement of the lung, pulmonary vasculature, pleura, and/or diaphragm at some point during thecourse of the disease • Respiratory manifestations include pleuritis (with or without effusion), pneumonitis, ILD, PH, shrinking lung syndrome, and alveolar hemorrhage • The risk of thromboembolic involvement is increased in those with antiphospholipid antibodies or with lupus anticoagulant	• Full PFTs are obtained to assess the pattern and severity of respiratory impairment. • Distinguishing between diffuse alveolar hemorrhage and acute lupus pneumonitis is difficult. DLco could help differentiate these entities (↑ DLco is suggestive of alveolar hemorrhage), but the patients are usually too ill to undergo the testing in practice	
Sjogren's syndrome	• Approximately 10-20% show airwaysand/or pulmonary interstitial involvement indicated by symptoms, abnormal PFTs, and/or chest radiograph • Involvement of exocrine glands may affect the upper respiratory tract • Bronchiolitis is the main small airway lesion, including follicular, chronic, and obliterative forms • A valve effect phenomenon may ensueand result in lung cysts or bullae. Theymaycoexist with bronchiectasis, micronodules, ground-glass opacity, and/or air-trapping	• Baseline complete PFTs and chest radiograph may be considered to evaluate for the presence of underlying pulmonary manifestations • In patients with chronic respiratory symptoms, crackles on chest examination, or an abnormal chest radiograph, full PFTs and HRCT are useful to evaluate/grade pulmonary involvement • In a patient with respiratory symptoms, the interval for repeat HRCT and PFTs must be determined individually according to the nature and severity of functional impairment	
Idiopathic Inflammatory myositis	• ILD is a major cause of morbidity and mortality, affecting 30-40% of patients • Respiratory muscle weakness maybe sub clinical, more frequently seen inpatients with severe skeletal muscle weakness. Hypercapnic respiratory failure has been reported, rarely as the presenting manifestation • Spontaneous pneumomediastinum, pulmonary hypertension (Group 3 from ILD), and venous thromboembolism are other complications	• PFTs help distinguish the cause of dyspnea (e.g., ILD versus respiratory muscle weakness) and assess the severity of respiratory impairment • Hypercapnia due to respiratory muscle weakness should be considered in the presence of complaints of daytime sleepiness, reduced maximal respiratory pressures (<30% pred), and FVC < 55% pred	

Chart 1. Most relevant respiratory involvement and overall recommendations for pulmonary function testing (PFT) in different connective tissue diseases. Key PFT findings consistent with each respiratory complication are described in the third column. ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; % pred: percentage of predicted values; PH: pulmonary hypertension; SLE: systemic lupus erythematosus; Hb: hemoglobin; and Kco: carbon monoxide transfer coefficient of the lung.

REFERENCES

1. Ciancio N, Pavone M, Torrisi SE, Vancheri A, Sambataro D, Palmucci S, et al. Contribution of pulmonary function tests (PFTs) to the diagnosis and follow up of connective tissue diseases. Multidiscip Respir Med. 2019;14:17. https://doi.org/10.1186/s40248-019-0179-2
2. Neder JA, Berton DC, O'Donnell DE. The role of the pulmonary function laboratory to assist in disease management: interstitial lung disease. J Bras Pneumol. 2023;49(5):e20230312. https://doi.org/10.36416/1806-3756/e20230312
3. Mathai SC, Danoff SK. Management of interstitial lung disease associated with connective tissue disease. BMJ. 2016;352:h6819. https://doi.org/10.1136/bmj.h6819
4. D'Cruz J, Neder-Serafini I, Zapotichny A, Neder JA. Exposing the Roots of Restriction: When the Transfer Coefficient Makes the Difference. Ann Am Thorac Soc. 2024;21(2):343-350. https://doi.org/10.1513/AnnalsATS.202305-484CC
5. Neder JA, Berton DC, Muller PT, O'Donnell DE. Incorporating Lung Diffusing Capacity for Carbon Monoxide in Clinical Decision Making in Chest Medicine. Clin Chest Med. 2019 Jun;40(2):285-305. doi: 10.1016/j.ccm.2019.02.005.

Pediatric obstructive sleep apnea: diagnosis and management

Luiza Fernandes Xavier[1], Paula Barros de Barros[1], Sofia Prates da Cunha de Azevedo[1], Leonardo Araujo Pinto[2,3], Magali Santos Lumertz[2,3]

INTRODUCTION

Obstructive sleep apnea (OSA) is a respiratory disorder characterized by a reduction in or cessation of airflow in the airways during sleep. It is known to be present in 1-5% of the pediatric population.[1,2] Therefore, OSA is now common in childhood, especially given the significant increase in childhood obesity, which constitutes a significant risk factor for this pathology.[1,2] Another main risk factor is adenotonsillar hypertrophy.[1,2] Consequently, in the pediatric population, OSA is more common in children between two and six years of age.[2] In addition, prematurity, craniofacial anomalies, neuromuscular diseases, genetic syndromes (such as Down, Prader-Willi, and Crouzon syndromes), asthma, and allergic rhinitis are considered risk factors for the development of pediatric OSA.[1,3,4]

OSA is within the broad classification of obstructive sleep disordered breathing (SDB), which also includes primary snoring, upper airway resistance syndrome, and obstructive hypoventilation.[1] In addition, OSA is associated with neurocognitive impairment, behavioral problems, failure to thrive, hypertension, and cardiac dysfunction, as well as potentially having systemic repercussions, such as the chronic induction of inflammation, thus contributing to the development of metabolic syndrome and to decreased quality of life.[1,2]

DIAGNOSIS

In children, the first step for the clinician is to ask if the child/adolescent snores. An affirmative answer should prompt a more focused evaluation.[2] Clinical and polysomnography (PSG) criteria that are not attributable to other disorders are necessary for the diagnosis of OSA (Figure 1).[5]

According to the American Academy of Sleep Medicine (AASM), the clinical diagnostic criteria for pediatric OSA include the presence of one or more of the following symptoms[5]: snoring; labored, paradoxical, or obstructed breathing during sleep or drowsiness; hyperactivity; behavioral problems; and learning disabilities or other cognitive problems. Other possible clinical findings of pediatric OSA include night sweats, nocturnal enuresis (especially secondary), headaches on awakening, mouth breathing (during sleep or while awake), tonsillar hypertrophy, adenoidal facies, micrognathia/retrognathia, and a high-arched palate.[2]

The AASM has also established PSG criteria for pediatric OSA,[5] which include an obstructive apnea-hypopnea

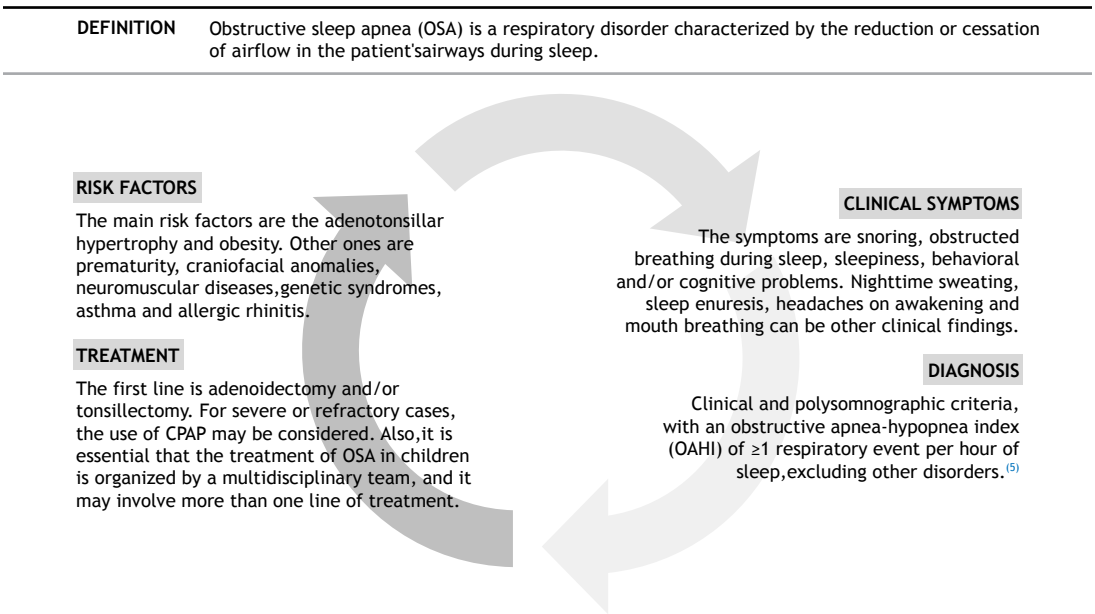

Figure 1. Pediatric Obstructive Sleep Apnea (OSA).

1. Centro Infant, Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.
2. Programa de Pós-Graduação em Medicina – Pediatria, Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.
3. Serviço de Pediatria, Hospital Moinhos de Vento, Porto Alegre (RS) Brasil.

ISSN 1806-3756

index (AHI) ≥ 1 event/hour of sleep, with or without a pattern of obstructive hypoventilation—defined as hypercapnia during ≥ 25% of the total sleep time, together with snoring, flattening of the inspiratory nasal pressure waveform, or paradoxical thoracoabdominal motion. Assessment of the severity of respiratory events according to the PSG findings, even if based on practice and limited consensus, can also help define the management approach. If the respiratory events index, most commonly the AHI, is less than 5 events/hour, OSA is considered mild,[1,2] whereas an AHI of 5.0-9.9 indicates moderate OSA and an AHI ≥ 10 indicates severe OSA.[1]

MANAGEMENT

The treatment of OSA in children is approached comprehensively, considering their unique needs and their developing physical characteristics. Frequently, it includes more than one option of intervention. Lifestyle modifications, such as promoting weight loss in cases of obesity and establishing consistent sleep routines to ensure a conducive rest environment, are essential considerations for initial therapy. In addition, it might be necessary to treat underlying conditions such as allergies and nasal congestion that contribute to airway obstruction during sleep.[3]

If a patient with pediatric OSA has adenotonsillar hypertrophy and has no contraindication to surgery, surgical removal of the tonsils and adenoids (adenoidectomy and/or tonsillectomy) is the first line of treatment.[1,2] Other specific types of surgery, such as craniofacial surgery (e.g., mandibular distraction osteogenesis), have been proposed in children with syndromic craniofacial abnormalities.[1] For severe or refractory cases, the use of CPAP may be considered in order to maintain open airways during sleep. The use of nasal corticosteroids, montelukast, or both can be an option in mild cases, as can rapid maxillary expansion and orthodontic appliances in patients with maxillary constriction, retrognathia, or malocclusion.[1,2] It is also essential that the treatment of OSA in children be coordinated by a multidisciplinary team, including pediatricians, otolaryngologists, pulmonologists, and other healthcare professionals, especially when this form of SDB is diagnosed in an infant.[4] Regular monitoring is necessary in order to assess the efficacy of treatment and adjust it as needed, thus ensuring adequate sleep, promoting healthy growth, and improving the overall well-being of the child.[2]

PREVENTION AND PROGNOSIS

Clinicians need to be aware of the possibility of OSA symptoms in children and adolescents. The potential consequences of untreated pediatric OSA include neurobehavioral deficits, metabolic alterations, cardiovascular disease (elevated blood pressure, ventricular dysfunction, or pulmonary hypertension), and exacerbation of comorbidities (e.g. asthma), as well as growth impairment.[1,2,6] To mitigate the adverse effects of this pathology, preventive measures such as addressing modifiable risk factors can be employed. There are some ways to minimize the risk of SDB: avoiding smoking in the home, treating asthma or allergic rhinitis, assisting with weight reduction (if the child is overweight or obese), and performing surgery for enlarged tonsils and adenoids on the children for whom surgical intervention is indicated.[2,3,5]

AUTHOR CONTRIBUTIONS

LFX, PBB, and SPCA contributed to the literature review and drafting of the manuscript. LAP and MSL contributed to writing, reviewing, and editing the manuscript.

CONFLICTS OF INTEREST

None declared.

FINANCIAL SUPPORT

This study received financial support from the *Pontifícia Universidade Católica do Rio Grande do Sul* Young Investigator Grants (BPA/PUCRS 2023-24). Leonardo A. Pinto is the recipient of a Research Productivity Grant from the Brazilian Conselho Nacional de *Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development; Grant no. 309074/2022-3).

REFERENCES

1. Kaditis AG, Alonso Alvarez ML, Boudewyns A, Alexopoulos EI, Ersu R, Joosten K, et al. Obstructive sleep disordered breathing in 2- to 18-year-old children: diagnosis and management. Eur Respir J. 2016;47(1):69-94. https://doi.org/10.1183/13993003.00385-2015
2. Marcus CL, Brooks LJ, Draper KA, Gozal D, Halbower AC, Jones J, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics. 2012;130(3):e714-e755. https://doi.org/10.1542/peds.2012-1672
3. D'Elia C, Gozal D, Bruni O, Goudouris E, Meira E Cruz M. Allergic rhinitis and sleep disorders in children - coexistence and reciprocal interactions. J Pediatr (Rio J). 2022;98(5):444-454. https://doi.org/10.1016/j.jped.2021.11.010
4. Qubty WF, Mrelashvili A, Kotagal S, Lloyd RM. Comorbidities in infants with obstructive sleep apnea. J Clin Sleep Med. 2014;10(11):1213-1216. https://doi.org/10.5664/jcsm.4204
5. American Academy of Sleep Medicine. International Classification of Sleep Disorders, 3rd ed, text revision (ICSD-3-TR). Darien (IL): American Academy of Sleep Medicine; 2023.
6. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Bethesda: GINA; 2024.

J Bras Pneumol. 2024;50(3):e20230292
https://dx.doi.org/10.36416/1806-3756/e20230292

Benzbromarone as adjuvant therapy for cystic fibrosis lung disease: a pilot clinical trial

Frederico Friedrich[1], Lucas Montiel Petry[1], Laura de Castro e Garcia[1], Marina Puerari Pieta[1], Amanda da Silva Meneses[1], Luana Braga Bittencourt[1], Luiza Fernandes Xavier[1], Marcos Otávio Brum Antunes[1], Lucas Kich Grun[1,2], Magali Lumertz[1], Karl Kunzelmann[3], Leonardo Araujo Pinto[1]

1. Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul – PUCRS – Porto Alegre (RS) Brasil.
2. Laboratório de Imunobiologia, Pontifícia Universidade Católica do Rio Grande do Sul – PUCRS – Porto Alegre (RS) Brasil.
3. Physiological Institute, University of Regensburg, Regensburg, Germany.

Submitted: 6 September 2023.
Accepted: 21 December 2023.

Study carried out at the Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul – PUCRS – Porto Alegre (RS) Brasil.

ABSTRACT

Objective: Cystic fibrosis (CF) affects multiple organs, the most severe consequences being observed in the lungs. Despite significant progress in developing CF transmembrane conductance regulator-specific treatments for CF lung disease, exploring alternative CF-targeted medications seems reasonable. We sought to evaluate the potential beneficial effects of oral benzbromarone as an adjuvant therapy in CF patients with reduced lung function. **Methods:** This was a prospective open-label pilot study of oral benzbromarone (100 mg/day) administered once daily for 90 days. Patients were followed at a tertiary referral center in southern Brazil. Safety was assessed by the number of reported adverse events. Secondary objectives included percent predicted FEV_1 (FEV_1%) and pulmonary exacerbations. **Results:** Ten patients were enrolled. Benzbromarone was found to be safe, with no serious drug-related adverse events. Eight patients completed the study; the median relative change in FEV_1% tended to increase during the treatment, showing an 8% increase from baseline at the final visit. However, a nonparametric test showed that the change was not significant ($p = 0.06$). Of a total of ten patients, only one experienced at least one pulmonary exacerbation during the study. **Conclusions:** Oral benzbromarone appears to be safe, and improved FEV_1% has been observed in patients with CF. Further assessment in larger trials is warranted to elucidate whether oral benzbromarone can be a potential adjuvant therapy for CF.

Keywords: Cystic fibrosis/therapy; Mucociliary clearance; respiratory tract diseases.

INTRODUCTION

Cystic fibrosis (CF) is a severe autosomal recessive genetic disease that is most commonly observed in White populations.[1] CF affects multiple systems, impacting the function of nearly all body organs by altering the activity of exocrine glands, resulting in reduced function of the CF transmembrane conductance regulator (CFTR) protein.[2] In some countries, the estimated incidence of CF ranges from approximately 1 per 3,000 live births to 1 per 6,000 live births.[3] In Brazil, the incidence of CF is approximately 1 per 7,576 live births.[4]

Airway inflammation caused by mucus hypersecretion is the primary contributor to CF morbidity and mortality, with approximately 90% of patients succumbing to the progression of lung disease.[1] Despite significant progress in developing CFTR-specific treatments for CF lung disease, exploring alternative drug targets in CF appears justified. Several experimental studies have emphasized the role of TMEM16A in mucus production and secretion.[5-8] TMEM16A is an alternative calcium-activated chloride channel contributing to mucus hypersecretion and bronchoconstriction.[9] Benzbromarone is a drug that has been shown to inhibit TMEM16A activity in animal models.[8,10,11] Recent evidence suggests that inhibiting TMEM16A function may offer therapeutic benefits, potentially reducing mucus production and impacting the severity of CF lung disease.[12]

Oral benzbromarone is a potent uricosuric agent indicated for the treatment of chronic gout.[13] It has been approved for use in Brazil by the Brazilian Health Regulatory Agency and has been commercially available since the 1970s.[14] Given its low cost, easy accessibility, and ability to control the activity of CF-related ion channels, benzbromarone is an intriguing alternative for the treatment of CF irrespective of the presence of disease-causing mutations.

On the basis of experimental models,[5,6,9-11] we conducted a pilot clinical trial to evaluate the potential beneficial effects of oral benzbromarone (100 mg/day) as an adjuvant therapy in CF patients with reduced lung function.

METHODS

Study design, participants, and setting

We conducted an open prospective pilot trial involving ten CF patients at a tertiary referral center in southern

Correspondence to:
Frederico Friedrich. Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul, Avenida Ipiranga, 6690, CEP 90610-000, Porto Alegre, RS, Brasil.
Fax: 55 51 3320-3312. Tel.: 55 51 3320-3000. E-mail: frederico.friedrich@pucrs.br
Financial support: This study received financial support from the Brazilian *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Office for the Advancement of Higher Education; Funding Code 001).

ISSN 1806-3756

Brazil. The study was conducted in accordance with the amended Declaration of Helsinki, with approval from local institutional review boards (Protocol no. 3.927.092; CAEE no. 29576220.0.0000.5336). Written informed consent was obtained from all patients and their parents. The trial is registered in Brazil under identifier number RBR-5wvg53s (available at https://ensaiosclinicos.gov.br/rg/RBR-5wvg53s).

Children > 6 years of age were included if they had a confirmed diagnosis of CF based on the following criteria: a positive sweat chloride test (> 60 mEq/L) and identification of two pathogenic variants in the *CFTR* gene. Additionally, participants had to have a percent predicted FEV_1 (FEV_1%) of < 90% in order to be classified as having reduced lung function. Key exclusion criteria included pregnancy, initiation of new therapy, use of CFTR modulators, and experiencing a pulmonary exacerbation within four weeks before the study initiation.

The primary outcome was the safety of oral benzbromarone, as assessed by pulmonary exacerbations, vital signs, physical examination, hematological markers, coagulation markers, and drug-related adverse events.[15] Liver function was also assessed,[14] and if any adverse effects were observed, the drug was discontinued until clarification.

Spirometry tests (FEV_1%) were performed at screening, at baseline (day 1), before the first day of treatment with oral benzbromarone, and during follow-up (at 30, 60, and 90 days). Changes in FEV_1% were assessed by comparing FEV_1% values obtained on day 1 with those obtained at the final study visit. Spirometry was performed with a KoKo spirometer (KoKo PFT, Longmont, CO, USA), in accordance with the guidelines of the American Thoracic Society and European Respiratory Society.[16] The results were presented as absolute values and percentages of the predicted values.[17] The number of pulmonary exacerbations was evaluated during follow-up (at 30, 60, and 90 days).

Intervention

All patients received standard CF treatment, including chest physiotherapy, dietary supplementation, fat-soluble vitamins, pancreatic enzyme replacement therapy for pancreatic insufficiency, and antibiotics for CF respiratory exacerbations. Furthermore, patients were instructed to take 100 mg of oral benzbromarone once daily for 90 days. The dose was determined on the basis of the established use of benzbromarone in the treatment of chronic gout. This dose has been shown to be safe and effective in adults with gout, making it a reasonable starting point for exploration in the CF population.

Statistical analysis

Given that previous studies have identified a 10% increase in FEV_1 with the use of ivacaftor, we opted for a more conservative increase. We adopted a significance level of 0.05, a power of 80%, and a standard deviation of 10.0 with the objective of detecting a minimum expected difference of 5% in the values of the variable of interest (FEV_1). The calculated sample size was 32 individuals. The inclusion of lung function measurements allowed a more comprehensive assessment, aligned with clinical relevance, although safety remained the primary focus. Sample size parameters were chosen to detect a 5% difference, balancing potential clinical impact with safety evaluation. Results were expressed by descriptive statistics (median and interquartile range). Comparisons were made with the paired Wilcoxon test. Statistical analysis was performed with the R computing environment (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Eighty-three patients with a confirmed diagnosis of CF were evaluated at our center. Of those, ten were eligible for inclusion in the study (Figure 1). Baseline demographics are summarized in Table 1 (unadjusted analysis). Eight patients completed the treatment with oral benzbromarone (adjusted analysis).

The primary endpoint of this pilot study was the safety of oral benzbromarone in CF patients. No serious drug-related adverse events were reported. Two participants were excluded from the final analysis. The only adverse event identified was weight loss (a loss of 3 kg in one patient), which was not considered severe, because the patient did not use the medication as recommended. Oral benzbromarone was discontinued, and the patient was started on standard treatment, after which the weight loss resolved. The patient continued to be followed at our center. Additionally, one patient chose to withdraw consent and discontinue the treatment with oral benzbromarone. Throughout the study period, no changes were found in patient vital signs or laboratory test results (data not shown).

The median relative change in FEV_1% tended to increase during benzbromarone treatment, showing an 8% increase from baseline at the final visit (at 90 days; Figure 2). However, we observed no significant difference in the increase in FEV_1% ($p = 0.06$). Furthermore, only one patient experienced one episode of pulmonary exacerbation during the study period. The patient was treated and did not require hospital admission.

DISCUSSION

This prospective open-label pilot study was the first clinical trial to assess the use of oral benzbromarone as an adjuvant for treating CF. Oral benzbromarone was found to be safe, with no reports of serious adverse events. Although the study was not powered to achieve statistical significance in secondary outcomes, increases in the overall mean values of FEV_1% were observed during the 90 days of treatment.

Our findings are consistent with those of a recent preclinical animal study, suggesting that inhibiting

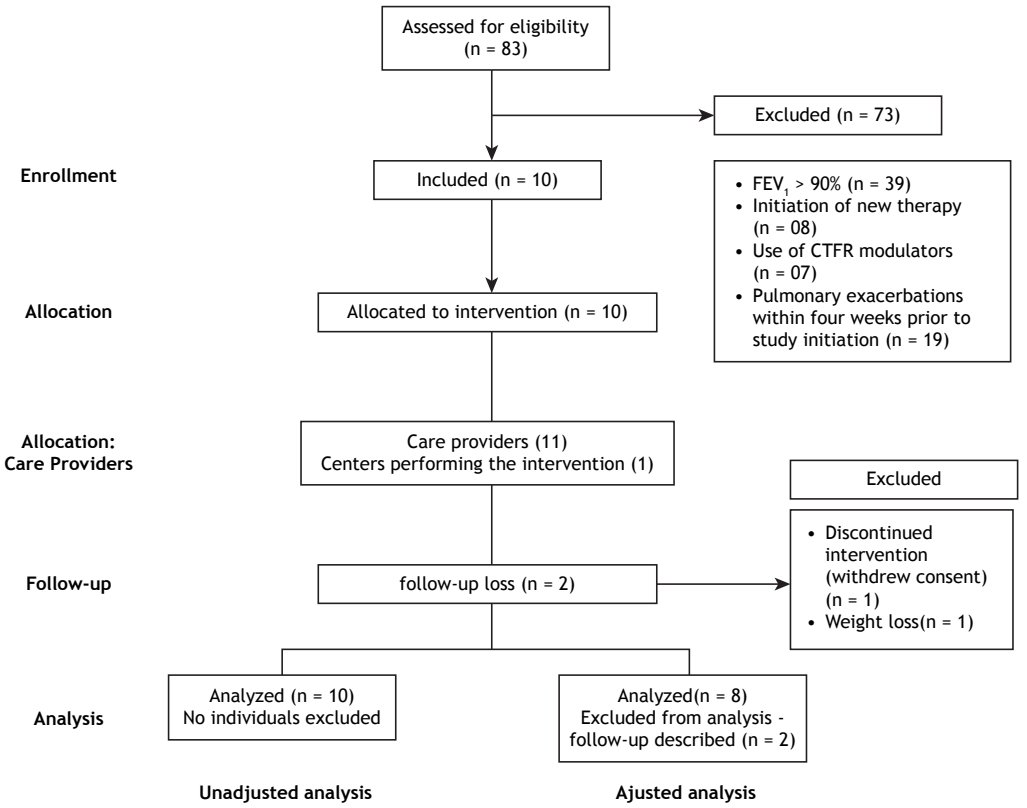

Figure 1. Flow chart of screening and follow-up.

Table 1. Demographic characteristics of the participants at baseline.[a]

Characteristic	Result
N (female:male)	10 (4:6)
Age, years	10 (9-16)
Weight, kg	40 (33-47)
Height, cm	141 (139-151)
Meconium ileus at diagnosis/birth	3 (30%)
CFTR genotype	
Heterozygous for F508del	7 (70%)
Homozygous for F508del	3 (30%)
Chronic colonization of the airways	
Staphylococcus aureus	8 (80%)
Pseudomonas aeruginosa	2 (20%)
Pulmonary function	
FEV_1 (% predicted)	84 (53-88)

[a]Data presented as n (%) or median (IQR), except where otherwise indicated.

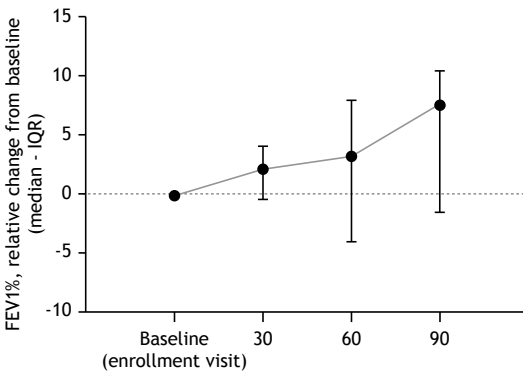

Figure 2. The effect of oral benzbromarone on lung function was assessed by measuring median changes in FEV_1% from baseline (enrollment visit) on spirometry in eight patients at 30, 60, and 90 days. The paired Wilcoxon test showed no significant change in FEV_1% (p = 0.06).

an alternative chloride channel may be an attractive therapeutic strategy in CF.[5,8,11] Importantly, because TMEM16A expression and function are independent of disease-causing mutations in the *CFTR* gene, this therapeutic approach is predicted to be suitable for all patients with CF irrespective of their genotype.[18] The counterintuitive idea of using inhibitors of TMEM16A channels is based on their role in mucus production and secretion, as recently evidenced.[11] This proposal is grounded in reports that nonselective regulators of TMEM16A function may affect airway smooth muscle and mucin release from goblet cells.[10,19,20] Therefore, potent and safe TMEM16A inhibitors should be further examined in preclinical and clinical studies for use in CF lung disease and other inflammatory airway diseases.

Studies have indicated that airway calcium-activated chloride channels, such as TMEM16A and ETX001,

hold potential therapeutic benefits for CF treatment.[19] However, the numerous physiological attributes associated with the former, such as improved lung function through mucociliary clearance, especially in the main airways, may enhance therapeutic action by increasing the channel activity.[11]

This regulation encompasses airway smooth muscle contraction and airway hyperresponsiveness, along with goblet cell formation and exocytosis.[10] In fact, TMEM16A expression has been identified in airway smooth muscle, and TMEM16A blockers, such as benzbromarone and niclosamide, have been shown to attenuate smooth muscle contraction in human and murine airways. Additionally, benzbromarone has been shown to impair mucin release from epithelial cells of human airways, suggesting a role in the mechanism of exocytosis.[20-22]

Several limitations of our clinical trial should be acknowledged. The primary limitation is the small sample size, which constrained the statistical power to detect differences, with 80% of the sample consisting of individuals < 18 years of age. Consequently, the results should be interpreted with caution. A critical limitation of this study is the absence of a control group. Given the small sample size and variability observed in FEV_1 measurements, the lack of a control group makes it challenging to conclusively attribute lung function improvement to the intervention. A control group would have provided a baseline for comparison and a more robust assessment of the impact of the intervention. Additionally, the fact that this was an open study conducted at a single center introduces the possibility of bias. To mitigate this, the study team reviewed all data twice, and, in case of discrepancies, a third review was considered. Furthermore, all information was recorded on electronic medical records.

Another critical point is the small number of adverse events observed in our study. This may be attributed to the low number of participants and the short duration of treatment. It is also of note that we collected no information regarding mucus production in the study participants. This information could contribute to a better understanding of the biological response mechanisms of the proposed therapeutic option.

Oral benzbromarone appears to be safe, and improved FEV_1% has been observed in patients with CF. Importantly, because TMEM16A expression and function are independent of disease-causing mutations in the *CFTR* gene, this adjuvant therapeutic option is predicted to be suitable for all patients with CF. This study represents the first evaluation of the use of oral benzbromarone in patients with CF. Further assessment in larger trials is warranted to elucidate whether oral benzbromarone can be a potential adjuvant therapy for CF.

ACKNOWLEDGMENTS

We are grateful to all the staff and departmental heads at our tertiary referral center for cystic fibrosis for supporting our study.

AUTHOR CONTRIBUTIONS

FF participated in the conception and design of the study; in the acquisition, analysis, and interpretation of data; and in the writing and critical review of the article. LMP, LCG, MPP, ASM, LBB, LFX, MOBA, LKG, ML, KK, and LAP participated in the design of the study; in the analysis and interpretation of data; and in the writing and critical review of the article. All authors approved the final version to be published.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Elborn JS. Cystic fibrosis. Lancet. 2016;388(10059):2519-2531. https://doi.org/10.1016/S0140-6736(16)00576-6
2. Sanders DB, Fink AK. Background and Epidemiology. Pediatr Clin North Am. 2016;63(4):567-584. https://doi.org/10.1016/j.pcl.2016.04.001
3. Scotet V, L'Hostis C, Férec C. The Changing Epidemiology of Cystic Fibrosis: Incidence, Survival and Impact of the CFTR Gene Discovery. Genes (Basel). 2020;11(6):589. https://doi.org/10.3390/genes11060589
4. Raskin S, Pereira-Ferrari L, Reis FC, Abreu F, Marostica P, Rozov T, et al. Incidence of cystic fibrosis in five different states of Brazil as determined by screening of p.F508del, mutation at the CFTR gene in newborns and patients. J Cyst Fibros. 2008;7(1):15-22. https://doi.org/10.1016/j.jcf.2007.03.006
5. Sondo E, Caci E, Galietta LJ. The TMEM16A chloride channel as an alternative therapeutic target in cystic fibrosis. Int J Biochem Cell Biol. 2014;52:73-76. https://doi.org/10.1016/j.biocel.2014.03.022
6. Benedetto R, Ousingsawat J, Cabrita I, Pinto M, Lérias JR, Wanitchakool P, et al. Plasma membrane-localized TMEM16 proteins are indispensable for expression of CFTR. J Mol Med (Berl). 2019;97(5):711-722. https://doi.org/10.1007/s00109-019-01770-4
7. Benedetto R, Ousingsawat J, Wanitchakool P, Zhang Y, Holtzman MJ, Amaral M, et al. Epithelial Chloride Transport by CFTR Requires TMEM16A. Sci Rep. 2017;7(1):12397. https://doi.org/10.1038/s41598-017-10910-0
8. Centeio R, Cabrita I, Benedetto R, Talbi K, Ousingsawat J, Schreiber R, et al. Pharmacological Inhibition and Activation of the Ca2+ Activated Cl- Channel TMEM16A. Int J Mol Sci. 2020;21(7):2557. https://doi.org/10.3390/ijms21072557
9. Yang YD, Cho H, Koo JY, Tak MH, Cho Y, Shim WS, et al. TMEM16A confers receptor-activated calcium-dependent chloride conductance. Nature. 2008;455(7217):1210-1215. https://doi.org/10.1038/nature07313
10. Huang F, Zhang H, Wu M, Yang H, Kudo M, Peters CJ, et al. Calcium-activated chloride channel TMEM16A modulates mucin secretion and airway smooth muscle contraction. Proc Natl Acad Sci U S A. 2012;109(40):16354-16359. https://doi.org/10.1073/pnas.1214596109
11. Kunzelmann K, Ousingsawat J, Cabrita I, Doušová T, Bähr A, Janda M, et al. TMEM16A in Cystic Fibrosis: Activating or Inhibiting?. Front Pharmacol. 2019;10:3. https://doi.org/10.3389/fphar.2019.00003
12. Cabrita I, Benedetto R, Schreiber R, Kunzelmann K. Niclosamide repurposed for the treatment of inflammatory airway disease.

JCI Insight. 2019;4(15):e128414. https://doi.org/10.1172/jci.insight.128414

13. Azevedo VF, Kos IA, Vargas-Santos AB, da Rocha Castelar Pinheiro G, Dos Santos Paiva E. Benzbromarone in the treatment of gout. Adv Rheumatol. 2019;59(1):37. https://doi.org/10.1186/s42358-019-0080-x
14. Lee MH, Graham GG, Williams KM, Day RO. A benefit-risk assessment of benzbromarone in the treatment of gout. Was its withdrawal from the market in the best interest of patients?. Drug Saf. 2008;31(8):643-665. https://doi.org/10.2165/00002018-200831080-00002
15. Heel RC, Brogden RN, Speight TM, Avery GS. Benzbromarone: a review of its pharmacological properties and therapeutic use in gout and hyperuricaemia. Drugs. 1977;14(5):349-366. https://doi.org/10.2165/00003495-197714050-00002
16. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70-e88. https://doi.org/10.1164/rccm.201908-1590ST
17. Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. J Bras Pneumol. 2007;33(4):397-406. https://doi.org/10.1590/S1806-37132007000400008
18. Mall MA, Danahay H, Boucher RC. Emerging Concepts and Therapies for Mucoobstructive Lung Disease. Ann Am Thorac Soc. 2018;15(Suppl 3):S216-S226. https://doi.org/10.1513/AnnalsATS.201806-368AW
19. Danahay HL, Lilley S, Fox R, Charlton H, Sabater J, Button B, et al. TMEM16A Potentiation: A Novel Therapeutic Approach for the Treatment of Cystic Fibrosis. Am J Respir Crit Care Med. 2020;201(8):946-954. https://doi.org/10.1164/rccm.201908-1641OC
20. Miner K, Labitzke K, Liu B, Wang P, Henckels K, Gaida K, et al. Drug Repurposing: The Anthelmintics Niclosamide and Nitazoxanide Are Potent TMEM16A Antagonists That Fully Bronchodilate Airways. Front Pharmacol. 2019;10:51. https://doi.org/10.3389/fphar.2019.00051
21. Gallos G, Remy KE, Danielsson J, Funayama H, Fu XW, Chang HY, et al. Functional expression of the TMEM16 family of calcium-activated chloride channels in airway smooth muscle. Am J Physiol Lung Cell Mol Physiol. 2013;305(9):L625-L634. https://doi.org/10.1152/ajplung.00068.2013
22. Huang F, Rock JR, Harfe BD, Cheng T, Huang X, Jan YN, et al. Studies on expression and function of the TMEM16A calcium-activated chloride channel. Proc Natl Acad Sci U S A. 2009;106(50):21413-21418. https://doi.org/10.1073/pnas.0911935106

J Bras Pneumol. 2024;50(3):e20230353
https://dx.doi.org/10.36416/1806-3756/e20230353

EBUS-TBNA in mediastinal staging of non-small cell lung cancer: comparison with pathological staging

Sara Braga[1], Rita Costa[2], Adriana Magalhães[3], Gabriela Fernandes[3]

1. Serviço de Pneumologia, Hospital Sousa Martins – Unidade Local de Saúde da Guarda E.P.E., Guarda, Portugal.
2. Serviço de Cirurgia Torácica, Centro Hospitalar Universitário de São João E.P.E., Porto, Portugal.
3. Serviço de Pneumologia, Centro Hospitalar Universitário de São João E.P.E., Porto, Portugal.

Submitted: 9 November 2023.
Accepted: 4 June 2024.

Study carried out at the Centro Hospitalar Universitário de São João E.P.E., Porto, Portugal.

ABSTRACT

Objective: Although EBUS-TBNA combined with EUS-FNA or EUS-B-FNA stands as the primary approach for mediastinal staging in lung cancer, guidelines recommend mediastinoscopy confirmation if a lymph node identified on chest CT or showing increased PET scan uptake yields negativity on these techniques. This study aimed to assess the staging precision of EBUS/EUS. **Methods:** We conducted a retrospective study comparing the clinical staging of non-small cell lung cancer patients undergoing EBUS/EUS with their post-surgery pathological staging. We analyzed the influence of histology, location, tumor size, and the time lapse between EBUS and surgery. Patients with N0/N1 staging on EBUS/EUS, undergoing surgery, and with at least one station approached in both procedures were selected. Post-surgery, patients were categorized into N0/N1 and N2 groups. **Results:** Among the included patients (n = 47), pathological upstaging to N2 occurred in 6 (12.8%). Of these, 4 (66.7%) had a single N2 station, and 2 (33.3%) had multiple N2 stations. The adenopathy most frequently associated with upstaging was station 7. None of the analyzed variables demonstrated a statistically significant difference in the occurrence of upstaging. PET scan indicated increased uptake in only one of these adenopathies, and only one was visualized on chest CT. **Conclusions:** Upstaging proved independent of the studied variables, and only 2 patients with negative EBUS/EUS would warrant referral for mediastinoscopy. Exploring other noninvasive methods with even greater sensitivity for detecting micrometastatic lymph node disease is crucial.

Keywords: Carcinoma, non-small cell lung; Neoplasm staging; Endoscopic ultrasound-guided fine needle aspiration.

INTRODUCTION

Lung cancer stands as the malignancy with the highest global mortality rate, and its incidence shows a continual rise.[1] Accurate staging is pivotal for prognostic assessment and crafting suitable treatment plans, crucially determining whether the tumor is anatomically amenable to curative surgical resection.

In the absence of distant metastasis, curative treatment hinges on the extent of tumor involvement (T) and the level of thoracic lymph node engagement. Generally, for patients with N0 (no lymph node involvement) and N1 (metastasis in ipsilateral pulmonary or hilar lymph nodes) disease, along with a resectable primary tumor, surgery emerges as the preferred option, provided that the patient demonstrates satisfactory cardiopulmonary function and absence of high risk comorbidities. If contralateral mediastinal/hilar lymph nodes or supraclavicular nodes (N3) are involved, surgery is not typically pursued. However, in cases of ipsilateral mediastinal or subcarinal lymph nodes (N2) involvement, surgery may be considered as part of a multimodality treatment approach. The decision depends on factors such as the number, size, and location of the affected lymph nodes, determined through a multidisciplinary team consensus.[2,3]

EBUS-TBNA has evolved into an indispensable technique for lung cancer staging, emerging as the primary choice for approaching mediastinal lymph nodes.[4,5] The combined utilization of EBUS-TBNA and EUS-FNA or transesophageal bronchoscopic ultrasound-guided fine needle aspiration (EUS-B-FNA) is strongly recommended over relying solely on EBUS.[5] EUS serves as a valuable complement to EBUS, synergistically enhancing the diagnostic yield of this staging approach.[5-7] Expanding beyond the stations accessed by EBUS alone (stations 2, 3, 4, 7, 10, 11), EUS extends accessibility to additional stations, including 2L, 4L, 5, 7, 8, and 9.[5-7] This collaborative use of both techniques is progressively supplanting surgical approaches in lung cancer staging.[5-7]

For several years, mediastinoscopy held the prestigious status of the gold standard for mediastinal staging in lung cancer. However, contemporary guidelines relegate it to a minor role,[2] a shift attributed not only to the rise of minimally invasive approaches but also to the limited access provided by mediastinoscopy to lymph node stations 2, 4, and 7.[8] Beyond the conventional cervical mediastinoscopy, initially described in 1959,[9] alternative techniques for invasive staging have emerged, including video-assisted mediastinoscopy (VAM), video-assisted

Correspondence to:
Sara Braga. Serviço de Pneumologia, Hospital Sousa Martins – Unidade Local de Saúde da Guarda E.P.E., Avenida Rainha Dona Amélia, 19, 6300-749, Guarda, Portugal.
Tel.: 35 1271200200. E-mail: sara_bmachado@hotmail.com
Financial support: None.

◄ Voltar ao sumário
ISSN 1806-3756

mediastinoscopic lymphadenectomy (VAMLA), and transcervical extended mediastinal lymphadenectomy (TEMLA). VAMLA employs a mediastinoscope affixed to a camera and a blade, expanding the dissection space for systematic lymph node dissection, particularly targeting stations 2R, 2L, 4R, 4L, and 7 to enhance sensitivity.[10,11] On the other hand, TEMLA represents the most extensive transcervical mediastinal dissection technique, incorporating sternal elevation and video mediastinoscopy. It provides access to a broader array of lymph node stations, including 1, 2R, 2L, 3a, 4R, 4L, 5, 6, 7, and 8. However, it is important to note that TEMLA carries a heightened risk of complications and mortality, a contrast to the comparatively lower risks associated with EBUS and EUS.[10,11] However, as per the guidelines, if a mediastinal lymph node exhibits heightened uptake on PET or is detected on chest CT but yields a negative result on EBUS/EUS, the recommended course of action is surgical confirmation through mediastinoscopy.[2,12]

We conducted a retrospective analysis to assess the staging precision of EBUS/EUS. The primary objective was to compare the clinical staging of non-small cell lung cancer (NSCLC) patients who underwent EBUS-TBNA/EUS-B-FNA with their pathological post-surgical staging. The secondary objectives encompassed the evaluation of the impact of selected variables, such as histology, tumor location, size, and the time elapsed between EBUS and surgery on post-surgical staging. Additionally, the study aimed to compare the concordance between CT/PET results, EBUS/EUS findings, and the subsequent pathological staging after surgery.

METHODS

This retrospective study was conducted at a tertiary hospital, spanning between January of 2019 and December of 2021.

Population

Following the diagnosis and histological confirmation of NSCLC, all patients underwent a PET scan to evaluate the extent of the disease. In cases without distant metastases, patients with a primary tumor exceeding a large axis of > 3 cm, enlarged lymph nodes surpassing a short axis of > 1 cm on chest CT, adenopathies exhibiting increased uptake on PET scan, and those with centrally located primary tumors were chosen for lymph node staging through EBUS/EUS.

Patients with a mediastinal staging of N0 or N1 on EBUS/EUS, who underwent surgery, and had at least one biopsied station (with representative lymph node material) approached in both procedures were included in the study. Patients undergoing neoadjuvant therapy were excluded from the analysis.

Subsequently, the selected patients were categorized based on post-surgical pathological results into two groups: N0/N1 and N2. The 8th international staging system TNM was utilized for classification.

EBUS-TBNA/EUS-B-FNA

EBUS-TBNA/EUS-B-FNA procedures were conducted under either intravenous general anesthesia or intravenous sedation, coupled with local anesthesia using 2% lidocaine.

Both techniques were performed with a flexible ultrasound bronchoscope (BF-UC180F; Olympus, Japan or BF-UC190F; Olympus, Japan) equipped with a convex ultrasound transducer (7.5 MHz). Image manipulation was facilitated through a dedicated ultrasound processor (EVIS EXERA III [CLV-190]; Olympus, Japan) and color power Doppler mode was used when necessary. The punctures during the procedure were executed using a 22-gauge needle (NA-201SX-4022; Olympus, Japan). All examinations were carried out by bronchoscopists well-versed in this procedure, boasting more than five years of experience.

Upon introducing the bronchoscope through a mouthpiece in the tracheobronchial tree, lymph node mapping was initiated. Following the identification of adenopathies, sample collection commenced, starting from the contralateral nodes and progressing from N3 to N1.

EUS-B was employed for CT/PET positive adenopathies that proved challenging or inaccessible via EBUS. During EUS-B, the bronchoscope was introduced into the esophagus, identifying and evaluating lymph node stations from the lowest (9) to the highest (2L), as previously described.[13] In cases in which more than one adenopathy was punctured, the procedure extended from station N3 to N1. A minimum of three needle passes were executed for each station.

Rapid on-site evaluation was not conducted. The aspirated samples were deposited in a container with a preservation solution, facilitating the subsequent preparation of a cytoblock for further cytological examination.

Surgery

Surgeries were conducted utilizing the uniportal VATS technique, following the established standard procedure as previously described.[14] This technique was performed under general anesthesia, employing selective ventilation with a double-lumen tube. The radical lymphadenectomy encompassed the N1 hilar nodes of the respective lung (stations 10 and 11). For N2 stations, radical lymphadenectomy targeted stations 7, 8, and 9 on both sides; stations 2, 3, and 4 on the right side; and stations 5 and 6 on the left side.

Statistical analysis

Data presentation included absolute and relative frequencies for categorical variables, while mean and standard deviation or median and range were applied for continuous variables.

The statistical analysis employed included the chi-square test and the Fisher's exact test for independent samples, results being considered statistically significant

if $p < 0.05$. Statistical analyses were carried out using IBM SPSS Statistics software package, version 26 (IBM Corporation, Armonk, NY, USA).

RESULTS

Our initial sample consisted of 75 patients who underwent surgery following endosonographic mediastinal staging. Of these, 47 were considered for inclusion in the study, while 28 were excluded. Exclusion criteria comprised the administration of neoadjuvant therapy (n = 11), cases in which lymph nodes were biopsied on EBUS/EUS without subsequent surgical approach (n = 16), and presence of N2 stage on EBUS/EUS (n = 1; Figure 1).

Among the 47 patients included, 41 (87.2%) were male, with ages ranging from 47 to 85 years (median = 69 years; Table 1). Concerning tumor histology, 34 (72.3%) and 13 (27.7%) were diagnosed with adenocarcinoma and squamous cell carcinoma, respectively. Regarding tumor location, 29 tumors (61.7%) were situated in the right lung, most of which (n = 29; 61.7%) being located in the upper lobes. Among these patients, 6 (12.8%) had tumors in a central location (within the inner two-thirds of the lung), and 41 (87.2%) had them in peripheral locations. Tumor size varied from 9 to 66 mm (median = 29 mm).

As for noninvasive staging methods, regarding the presence of adenopathies on CT (with a size greater than 10 mm in the short axis), 31 patients (66%) were staged as N0/N1, while 16 (34%) were classified as N2/N3. Regarding the presence of adenopathies with increased uptake on PET scan, 22 (46.8%) of the patients were staged as N0/N1, and 25 (53.2%) of the patients were categorized as N2/N3.

In the context of EBUS-TBNA and EUS-FNA, a total of 378 punctures were performed, with a mean of 9.0 ± 3.2 punctures per patient (ranging from a minimum of 3 to a maximum of 16). The median number of punctures per lymph node station was 3. The mean size of the biopsied lymph node was 8.5 mm, spanning from 4.5 mm to 15 mm. The most frequently biopsied lymph node was station 7 (n = 39), followed by station 4R (n = 31) and 4L (n = 20). There were no complications during the EBUS/EUS performance.

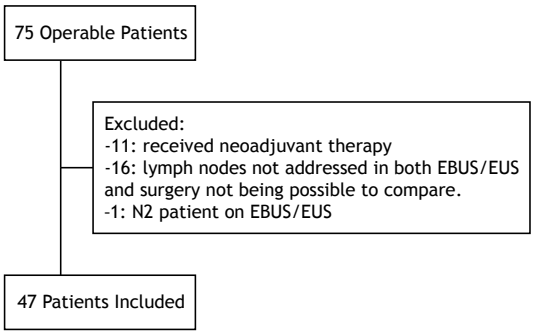

Figure 1. Selection of the patients included in the study.

Concerning surgery outcomes, the time interval between EBUS and surgery varied from 30 days to 280 days (median = 68). The patient with the lengthiest gap between the two procedures underwent transthoracic needle biopsy (TNB), which did not yield a diagnosis. Subsequently, EBUS/EUS was performed while awaiting the TNB result, and it turned out to be negative. Only later was the patient able to undergo a repeat TNB, confirming the diagnosis of neoplasia, followed by surgery. There was one intraoperative complication involving major bleeding that necessitated conversion to thoracotomy. No other major complications were observed.

Among the patients included, pathological staging revealed N0/N1 in 41 patients and N2 in 6 patients. Consequently, upstaging to N2 occurred in 6 (12.8%) of these patients. Of the upstaged patients, 4 (66.7%) had only one N2 station, while 2 (33.3%) had multiple N2 stations (in both cases, 4R and 7). The adenopathy most frequently associated with upstaging was station 7 (in 4 patients), followed by adenopathy 4R (in 3 patients; Table 2). The average size of tumors in upstaged patients was 28.2 mm.

All upstaged patients had adenocarcinoma, with no statistically significant difference regarding this variable. As for the lung side and lobe involved, there was no statistically significant difference regarding upstaging. Upstaging occurred in 3 (10.3%) of the patients whose tumor was located on the right side and in 3 (16.7%) of the patients whose tumor was located on the left side. Regarding the lobe involved, upstaging occurred in 4 (13.8%) of the patients whose tumor was located in the upper lobe, in 2 (12.5%) patients whose tumor was located in the lower lobe, and in none of the

Table 1. Descriptive analysis of the variables under study.

Variables	n (%)
Gender	
Male	41 (87.2)
Female	6 (12.8)
Histology	
Adenocarcinoma	34 (72.3)
Squamous cell carcinoma	13 (27.7)
Pulmonary side of the tumor	
Right	29 (61.7)
Left	18 (38.3)
Pulmonary lobe of the tumor	
Upper lobe	29 (61.7)
Lower lobe	16 (34.0)
Upper and lower lobes	1 (2.1)
Upper and middle lobes	1 (2.1)
Location of the tumor	
Central	6 (12.8)
Peripheral	41 (87.2)
Age, years: median = 69 [range, 47-85]; mean = 67.66 ± 9.30.	
Tumor size, mm: median = 29 [range, 9-66]; mean = 29.81 ± 13.30.	

patients with involvement of more than one lobe (Table 3). Of the patients with a peripheral tumor location, 6 (14.6%) had upstaging, while among those with a central tumor location (n = 6), none had upstaging, with no statistically significant difference regarding this variable. Regarding both the time between EBUS and surgery and tumor size, there was no statistically significant difference regarding upstaging.

Among upstaged patients, only 1 (16.7%) had increased uptake of the respective station on PET scan, and only 1 (16.7%) had the respective adenopathy visualized on chest CT.

Concerning staging based on imaging methods, in comparison with post-surgical staging, CT upstaging occurred in 5 (10.6%) of the patients, and downstaging occurred in 15 (31.9%) of the patients. As for PET scan, upstaging occurred in 4 (8.5%) of the patients, and downstaging occurred in 23 (48.9%) of the patients.

DISCUSSION

Among the 47 patients with NSCLC included in the study, upstaging to N2 occurred in 6 (12.8%). The rates of upstaging to N2 can vary across different studies. For instance, Zirafa et al.[15] conducted a comparison between lobectomy performed via open surgery and robotic surgery, reporting upstaging to N2 in 9.4% of patients with robotic lobectomy and 2.8% of patients with open lobectomy. Nachira et al.[16] observed upstaging to N2 in 4.3% of cases with open surgery and in 13% using uniportal VATS. In that study,[16] as in ours, no independent risk factor for upstaging was identified.

The decision to perform surgical resection in cases of known stage IIIA/B-N2 disease remains a subject of debate due to the heterogeneous nature of this group. Consequently, all such patients are presented at a multidisciplinary team meeting, where a thorough risk/benefit discussion takes place. The selection of treatment depends not only on imaging factors, such as the location, size, and number of lymph node stations involved,[12,17,18] but also on the patient's comorbidities and lung function.[19] A retrospective study conducted by Mainguene et al.[17] revealed that the histological type also plays a role in influencing treatment decisions. Adenocarcinoma, for instance, tends to be more commonly associated with surgical treatment, unlike squamous cell carcinoma, which is often linked to heavy smokers exhibiting greater functional limitations, a more central presentation, and more extensive lymph node involvement. In addition to these considerations, patient preference also plays a significant role in the treatment selection process.[18] The heterogeneity of this stage, coupled with the absence of a universal definition of resectability, complicates decision-making in multidisciplinary meetings. Mainguene et al.[17], who examined the reproducibility of multidisciplinary decisions in IIIA/B-N2 disease, a 70% agreement was observed, with a kappa coefficient of 0.43. The 9th international TNM staging

Table 2. Characteristics of the upstaged patients.

Case	Station	Histology	Size (mm)	Location	Side	Lobe	PET positivity	CT positivity
1	7	Adenocarcinoma	38	Peripheral	Left	Lower	No	No
2	5	Adenocarcinoma	13	Peripheral	Left	Upper	No	No
3	4R	Adenocarcinoma	15	Peripheral	Right	Upper	Yes	No
4	4R/7	Adenocarcinoma	25	Peripheral	Right	Upper	No/No	No/No
5	7	Adenocarcinoma	29	Peripheral	Left	Lower	No	No
6	4R/7	Adenocarcinoma	49	Peripheral	Right	Upper	No	Yes/No

Table 3. Association between the variables studied and upstaging.

Variable		Upstaging		p
		Yes	No	
Histology	Adenocarcinoma	6	28	0.1
	Squamous cell carcinoma	0	13	
Pulmonary side where the tumor is located	Right	3	26	0.7
	Left	3	15	
Pulmonary lobe where the tumor is located	Upper	4	25	0.96
	Lower	2	14	
	Upper and lower	0	1	
	Upper and middle	0	1	
Location of the tumor	Central	0	6	0.4
	Peripheral	6	35	
Time between EBUS and surgery, months	< 3	3	29	0.37
	≥ 3	3	12	
Tumor size, cm	< 3	5	19	0.1
	≥ 3	1	22	

system classifies N2 stages into N2a (single station) and N2b (multiple stations), emphasizing the distinct prognosis associated with these categories. While this classification may contribute to informed treatment decisions, it also necessitates enhanced precision from radiologists, pathologists, and practitioners involved in performing mediastinal staging techniques.[20]

In potentially resectable stage IIIA/B-N2 cases (excluding T4), patients undergo neoadjuvant chemotherapy with or without radiotherapy. Following reassessment and absence of disease progression, these patients may be considered for surgical resection. For cases deemed nonresectable, the proposed course of action involves definitive chemoradiotherapy.[2,12] Regarding the 6 patients with post-surgical upstaging, 4 with only one N2 station had these lymph node metastases been detected before surgery, and their cases would likely have been discussed in a multidisciplinary team meeting, potentially opening the possibility of surgical resection.

Concerning PET scan staging, upstaging was observed in 4 patients (8.5%), while downstaging occurred in 23 (48.9%) of the patients. Recent studies have highlighted the high sensitivity of this test in detecting neoplastic disease but have also emphasized its low specificity.[21] Interestingly, PET scan demonstrated increased uptake in only one of the adenopathies associated with pathological upstaging, and only one of these adenopathies was visualized on chest CT. In essence, most cases in which upstaging occurred were likely instances of micrometastatic disease, involving small clusters of tumor cells that went undetected in both imaging and endoscopic examinations.[22] Consequently, these cases may not have been suitable for referral to mediastinoscopy either.

The approach by EBUS-TBNA and EUS-B-FNA represents a minimally invasive and safe method, offering access to a greater number of lymph node stations when compared with mediastinoscopy. Yasufuku et al.[23] demonstrated a combined sensitivity and negative predictive value of EBUS-TBNA and mediastinoscopy at 92% and 96%, respectively, supporting the notion that mediastinoscopy may not provide significant advantages after a negative EBUS. Liberman et al.[24] concluded that the utilization of a combined EBUS/EUS procedure surpasses mediastinoscopy in the preoperative staging of NSCLC and should be considered the new gold standard in mediastinal staging, eliminating the need for confirmation by surgical staging in the case of negative EBUS/EUS results. A systematic review and meta-analysis[25] have yielded the conclusion that both EBUS-TBNA and mediastinoscopy demonstrate comparable results in the mediastinal staging of NSCLC. Additionally, the study suggests that EBUS-TBNA can serve as a viable replacement for mediastinoscopy in patients with potentially resectable NSCLC. The authors assert that the complication rate associated with mediastinoscopy appears to be higher than that of EBUS-TBNA.[25] In a study conducted by Ge et al.,[26] a comparison between VAM and EBUS-TBNA for mediastinal staging resulted in the finding that both procedures similarly exhibit high diagnostic accuracy. However, the VAM group displayed a higher incidence of complications and fewer false negatives compared with the EBUS-TBNA group. Decaluwé et al.[27] conducted a study where VAMLA emerged as the preferred technique for pre-resection mediastinal nodal staging in patients with cN1 NSCLC, as opposed to endosonography, owing to its high sensitivity. While VAMLA and TEMLA demonstrate high accuracy and reduced false negatives concerning potential micrometastases, the available data on their results and safety remain limited.

Recently, molecular biology techniques such as PCR and immunohistochemistry have been explored and applied in the detection of lymph node micrometastasis in NSCLC.[22] The emergence of these new techniques holds significant importance for accurate staging, and, consequently, treatment strategies, as well as enabling a better prognostic assessment of patients with NSCLC. This detection could lead, for instance, in some cases, to neoadjuvant/adjuvant therapy, and, in others, to a multidisciplinary decision on nonsurgical treatment, thus not subjecting patients to unnecessary treatment, although more research is needed in this area.

This study has several limitations. Being retrospective, it restricts access to and analysis of certain variables and clinical characteristics. Furthermore, the small sample size could introduce potential bias into the study results and may impact the interpretation of statistical significance of certain variables. Additionally, there might be a selection bias, as patients who underwent neoadjuvant treatment were excluded, and those without at least one adenopathy approached in both procedures were also excluded. This exclusion criterion might have contributed to an underestimation of the upstaging value, although they align with findings from other studies. To address these limitations, future research efforts should consider conducting a prospective, multicenter study with a larger and more diverse sample of patients. That study should include participants who underwent neoadjuvant treatment, providing a more comprehensive understanding of the complexities associated with the staging of NSCLC. Furthermore, our study did not make a direct comparison with mediastinoscopy, which would also be interesting in a future study in which other techniques such as VAMLA, TEMLA, and their respective accuracy and complications could be evaluated.

In conclusion, our study showed N2 upstaging in 12.8% of the sample, a result consistent with other studies. The upstaging in this study was determined to be independent of the variables under investigation. Only two patients, both with negative lymph nodes on EBUS/EUS that showed positivity on either PET or CT would potentially be candidates for referral to mediastinoscopy.

This study not only presents findings corroborated by previous studies but also delves into contentious aspects surrounding these findings. We address the challenges associated with staging and treatment selection in stages

IIIA/B-N2 and the inherent variability in multidisciplinary decision-making processes, exploring the potential benefits offered by the latest 9th international TNM staging system in effectively categorizing stage N2. Moreover, the article delves into the significance of PET in mediastinal staging and emphasizes the criticality of detecting micrometastatic disease. It also discusses the pivotal role played by advanced techniques such as EBUS/EUS, VAMLA, and TEMLA, and the importance of exploring other noninvasive methods with even greater sensitivity in achieving this goal.

AUTHOR CONTRIBUTIONS

SB, GF, and AM: concept and design; SB and RC: data acquisition and analysis; and interpretation of results. All of the authors wrote, reviewed, and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Oliver AL. Lung Cancer: Epidemiology and Screening. Surg Clin North Am. 2022;102(3):335-344. https://doi.org/10.1016/j.suc.2021.12.001
2. Aisner DL, Akerley W, Bauman JR, et al. NCCN Guidelines Version 5.2022. Non-Small Cell Lung Cancer Continue NCCN Guidelines Panel Disclosures 2022. Plymouth Meeting (PA): National Comprehensive Cancer Network; 2022.
3. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The Eighth Edition Lung Cancer Stage Classification. Chest. 2017;151(1):193-203. https://doi.org/10.1016/j.chest.2016.10.010
4. Nardecchia E, Cattoni M, Dominioni L. Endobronchial ultrasound-transbronchial needle aspiration for mediastinal staging of non-small cell lung cancer: variability of results and perspectives. J Thorac Dis. 2017;9(Suppl 5):S418-S424. https://doi.org/10.21037/jtd.2017.04.12
5. Vilmann P, Clementsen PF, Colella S, Siemsen M, De Leyn P, Dumonceau JM, et al. Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS) [published correction appears in Endoscopy. 2015 Jun;47(6):c1. Vasquez-Sequeiros, Enrique [corrected to Vazquez-Sequeiros, Enrique]]. Endoscopy. 2015;47(6):545-559. https://doi.org/10.1055/s-0034-1392040
6. Rintoul RC, Skwarski KM, Murchison JT, Wallace WA, Walker WS, Penman ID. Endobronchial and endoscopic ultrasound-guided real-time fine-needle aspiration for mediastinal staging. Eur Respir J. 2005;25(3):416-421. https://doi.org/10.1183/09031936.05.00095404
7. Jenssen C, Annema JT, Clementsen P, Cui XW, Borst MM, Dietrich CF. Ultrasound techniques in the evaluation of the mediastinum, part 2: mediastinal lymph node anatomy and diagnostic reach of ultrasound techniques, clinical work up of neoplastic and inflammatory mediastinal lymphadenopathy using ultrasound techniques and how to learn mediastinal endosonography. J Thorac Dis. 2015;7(10):E439-E458.
8. Sehgal IS, Dhooria S, Aggarwal AN, Behera D, Agarwal R. Endosonography Versus Mediastinoscopy in Mediastinal Staging of Lung Cancer: Systematic Review and Meta-Analysis. Ann Thorac Surg. 2016;102(5):1747-1755. https://doi.org/10.1016/j.athoracsur.2016.05.110
9. CARLENS E. Mediastinoscopy: a method for inspection and tissue biopsy in the superior mediastinum. Dis Chest. 1959;36:343-352. https://doi.org/10.1378/chest.36.4.343
10. Witte B, Wolf M, Huertgen M, Toomes H. Video-assisted mediastinoscopic surgery: clinical feasibility and accuracy of mediastinal lymph node staging. Ann Thorac Surg. 2006;82(5):1821-1827. https://doi.org/10.1016/j.athoracsur.2006.05.042
11. Yendamuri S, Demmy TL. Is VAMLA/TEMLA the new standard of preresection staging of non-small cell lung cancer?. J Thorac Cardiovasc Surg. 2012;144(3):S14-S17. https://doi.org/10.1016/j.jtcvs.2012.03.038
12. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv1-iv21. https://doi.org/10.1093/annonc/mdx222
13. Bugalho A, de Santis M, Slubowski A, Rozman A, Eberhardt R. Trans-esophageal endobronchial ultrasound-guided needle aspiration (EUS-B-NA): A road map for the chest physician. Pulmonology. 2017 Dec 11:S2173-5115(17)30162-8.
14. Gonzalez-Rivas D, Sihoe ADL. Important Technical Details During Uniportal Video-Assisted Thoracoscopic Major Resections. Thorac Surg Clin. 2017;27(4):357-372. https://doi.org/10.1016/j.thorsurg.2017.06.004
15. Zirafa C, Aprile V, Ricciardi S, Romano G, Davini F, Cavaliere I, et al. Nodal upstaging evaluation in NSCLC patients treated by robotic lobectomy. Surg Endosc. 2019;33(1):153-158. https://doi.org/10.1007/s00464-018-6288-8
16. Nachira D, Congedo MT, Tabacco D, Sassorossi C, Calabrese G, Ismail M, et al. Surgical Effectiveness of Uniportal-VATS Lobectomy Compared to Open Surgery in Early-Stage Lung Cancer. Front Surg. 2022;9:840070. https://doi.org/10.3389/fsurg.2022.840070
17. Mainguene J, Basse C, Girard P, Beaucaire-Danel S, Cao K, Brian E, et al Surgical or medical strategy for locally-advanced, stage IIIA/B-N2 non-small cell lung cancer: Reproducibility of decision-making at a multidisciplinary tumor board. Lung Cancer. 2022;163:51-58. https://doi.org/10.1016/j.lungcan.2021.12.004
18. Glatzer M, Leskow P, Caparrotti F, Elicin O, Furrer M, Gambazzi F, et al. Stage III N2 non-small cell lung cancer treatment: decision-making among surgeons and radiation oncologists. Transl Lung Cancer Res. 2021;10(4):1960-1968. https://doi.org/10.21037/tlcr-20-1210
19. Jiang G, Zhang L, Zhu Y, Chen C, Zhou X, Liu J, et al. Clinical consensus on preoperative pulmonary function assessment in patients undergoing pulmonary resection (first edition). Curr Chall Thorac Surg. 2019;1:7. https://doi.org/10.21037/ccts.2019.06.01
20. Huang J, Osarogiagbon RU, Giroux DJ, Nishimura KK, Bille A, Cardillo G, et al. The International Association for the Study of Lung Cancer Staging Project for Lung Cancer: Proposals for the Revision of the N Descriptors in the Forthcoming Ninth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2024;19(5):766-785. https://doi.org/10.1016/j.jtho.2023.10.012
21. Erer OF, Anar C, Erol S, Özkan S. The utility of EBUS-TBNA in mediastinal or hilar lymph node evaluation in extrapulmonary malignancy. Turk J Med Sci. 2016;46(1):112-119. https://doi.org/10.3906/sag-1407-113
22. Sun J, Wu S, Jin Z, et al. Lymph node micrometastasis in non-small cell lung cancer. Biomed Pharmacother. 2022;149:112817. https://doi.org/10.1016/j.biopha.2022.112817
23. Yasufuku K, Pierre A, Darling G, de Perrot M, Waddell T, Johnston M, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. J Thorac Cardiovasc Surg. 2011;142(6):1393-400.e1. https://doi.org/10.1016/j.jtcvs.2011.08.037
24. Liberman M, Sampalis J, Duranceau A, Thiffault V, Hadjeres R, Ferraro P. Endosonographic mediastinal lymph node staging of lung cancer. Chest. 2014;146(2):389-397. https://doi.org/10.1378/chest.13-2349
25. Figueiredo VR, Cardoso PFG, Jacomelli M, Santos LM, Minata M, Terra RM. EBUS-TBNA versus surgical mediastinoscopy for mediastinal lymph node staging in potentially operable non-small cell lung cancer: a systematic review and meta-analysis [published correction appears in J Bras Pneumol. 2021 Feb 08;47(1):e20190221errata]. J Bras Pneumol. 2020;46(6):e20190221. https://doi.org/10.36416/1806-3756/e20190221
26. Ge X, Guan W, Han F, Guo X, Jin Z. Comparison of Endobronchial Ultrasound-Guided Fine Needle Aspiration and Video-Assisted Mediastinoscopy for Mediastinal Staging of Lung Cancer. Lung. 2015;193(5):757-766. https://doi.org/10.1007/s00408-015-9761-3
27. Decaluwé H, Dooms C. Invasive mediastinal staging by endosonography or video-assisted mediastinoscopy in PET-CT clinical N1 non-small cell lung cancer. Mediastinum. 2020;4:6. https://doi.org/10.21037/med.2019.12.01

J Bras Pneumol. 2024;50(3):e20240072
https://dx.doi.org/10.36416/1806-3756/e20240072

ORIGINAL ARTICLE

Respiratory syncytial virus infection in children during SARS-CoV-2 pandemic at a referral center in Rio de Janeiro, Brazil

Giuliana Pucarelli Lebreiro[1], Marianna Tavares Venceslau[1], Maria Angélica Arpon Marandino Guimarães[1], Thalita Fernandes Abreu[2], Yarina Rangel[2], Ana Cristina Cisne Frota[2], Cristina Barroso Hofer[1]

1. Departamento de Doenças Infecciosas e Parasitárias, Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ) Brasil.
2. Instituto de Puericultura e Pediatria Martagão Gesteira, Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ) Brasil.

Submitted: 30 March 2024.
Accepted: 13 May 2024.

Study carried out at the Instituto de Puericultura e Pediatria Martagão Gesteira, Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ) Brasil.

ABSTRACT

Objective: In order to study the scenario of respiratory infections in pediatrics after the emergence of SARS-CoV-2 in Brazil, this study aimed to compare characteristics of children admitted for SARS or upper airway infection caused by either RSV or SARS-CoV-2. **Methods:** This was a cross-sectional study involving children up to 48 months of age admitted to a tertiary pediatric hospital with a diagnosis of SARS or upper airway infection between April of 2020 and April of 2021. Respiratory secretion samples were collected 2-5 days after hospitalization, and antigen/PCR tests for viral etiologies were performed. In this analysis, patients with laboratorial diagnosis of SARS-CoV-2 and/or RSV were selected, and their clinical and epidemiological characteristics were compared using logistic regression. **Results:** Our sample initially comprised 369 participants. SARS-CoV-2 and RSV infections were confirmed in 55 (15%) and 59 children (16%), respectively. Mean age was 12 months (0-48 months), and 47 were female. The following characteristics were significantly more frequent in patients with RSV when compared with those with COVID-19: younger age (OR = 0.94; 95% CI: 0.90-0.98); lower frequency of fever (OR = 0.18; 95% CI: 0.05-0.66); and more frequent upper airway symptoms: cough (OR = 7.36; 95% CI: 1.04-52.25); and tachypnea (OR = 6.06; 95% CI: 1.31-28.0). **Conclusions:** Children with RSV-related SARS were younger, had lower frequency of fever at admission, but had a higher frequency of signs of upper airway infection and lower systemic inflammation when compared with children hospitalized for COVID-19 during the first year of the pandemic.

Keywords: SARS-CoV-2; Respiratory syncytial virus infections; Pediatrics; Brazil.

INTRODUCTION

Respiratory syncytial virus (RSV) is the most common lower respiratory infection etiology during the first years of life. Approximately 60% of infants are infected with RSV during their first six months of age, and 80% at their first birthday.[1]

The main clinical manifestations of RSV infection are mild and comprise fever, cough, and nasal discharge. However, around 20% of these will develop more critical disease, with lower respiratory tract manifestations such as tachypnea, lower oxygen saturation, and poor feeding. Some of these infants will require hospital admission to provide respiratory support.[2]

After 2019, a new etiologic agent was described causing respiratory disease in humans. Infection with SARS-CoV-2 is more severe in adults, showing higher mortality and case-fatality rates. This agent was also described as an important respiratory infection in children with several clinical manifestations, including bronchiolitis.[3,4]

Several authors described that the SARS-CoV-2 pandemic changed the epidemiological scenario of RSV infection in the pediatric population. A lower number of hospital admissions and differences on RSV seasonality were found.[2,5,6]

The clinical manifestations of RSV during the pandemic were also described as different from those in previous years, mainly because more patients were admitted with symptoms in the higher respiratory tract instead of in the lower respiratory tract.[5,7]

Since different approaches are recommended for different respiratory viruses, the etiology of respiratory tract infections must be determined. Molecular or antigen-based tests, with high sensitivity and specificity, are used; however, their costs are still a barrier in developing countries, where clinical and basic laboratory tests are the main diagnosis tools available.

In this study, we aimed to describe the main signs and symptoms in children with RSV infection admitted to a tertiary university-based hospital in the city of Rio de

Correspondence to:
Cristina Barroso Hofer. Instituto de Puericultura e Pediatria Martagão Gesteira, Universidade Federal do Rio de Janeiro, Rua Bruno Lobo, 50, Ilha do Fundão, Rio de Janeiro, RJ, Brasil.
Tel.: 55 22 99206-3853. E-mail: cbhofer@hucff.ufrj.br
Financial support: Cristina Barroso Hofer received financial support from the Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development; Grant no. 307488/2021-7) and from the *Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro* (FAPERJ, Foundation for the Support of Research in the State of Rio de Janeiro; Grants no. E26/200,843/2021 and E26/202.021/2016;. CNE and COVID group A, respectively).

◄ Voltar ao sumário
ISSN 1806-3756

Janeiro, Brazil, during the first year of the SARS-CoV-2 pandemic and compare the clinical manifestations of RSV and SARS-CoV-2 infections in children up to 48 months of age.

METHODS

Study design and participants

This was a nested cross-sectional study, and data were originated from a prospective cohort study of children and adolescents hospitalized at a tertiary pediatric hospital: *Instituto de Puericultura e Pediatria Martagão Gesteira* (IPPMG) of the Federal University of Rio de Janeiro, which is a referral center for rheumatology, immunology, infectious diseases, and onco-hematology care in the city of Rio de Janeiro, Brazil. The children and adolescents who had suspected COVID-19 diagnosis between April 14, 2020 and April 30, 2021 were enrolled.[3]

All patients under 48 months of age admitted at our institution with upper airway infection (with or without fever) and/or SARS were eligible for inclusion. Exclusion criteria were being older than 48 months at admission or RT-PCR for SARS-CoV-2 results being unavailable.

Data collection

Following enrollment, all parents or legal guardians of the participants completed an initial questionnaire, and the participants were followed during hospitalization for data collection.

The variables collected included age, gender, race, socioeconomic status, previous contact with a suspected or confirmed COVID-19 case, contact with indoor smoking, underlying medical conditions, signs and symptoms, oxygen requirement, admission to critical care, presence of other viral coinfections, and laboratory test results.

Ethical aspects

Parents/guardians of participants provided written informed consent before participation. The study was reviewed and approved by the IPPMG Research Ethics Committee (no. 30786020.4.0000.5264). All clinical specimens were obtained in accordance with ethical guidelines.

Definitions

A participant was considered as infected with SARS-CoV-2 when RT-PCR for SARS-CoV-2 was positive or undetermined from any clinical sample (nasopharyngeal or oropharyngeal swab, bronchoalveolar lavage, stool, or cerebrospinal fluid) and if serological results were positive (IgM and IgG or IgG) 30 days after the onset of symptoms. We consider reagent IgG as a confirmatory laboratory criterion only in unvaccinated individuals, with no previous laboratory diagnosis for COVID-19 and who presented compatible signs and symptoms within the first six months of the study (and the first six months of the pandemic). Patients with positive RT-PCR for SARS-CoV-2 and positive serological tests were compared with those with positive RSV tests. The date of symptom onset was defined as the day when the first symptom or sign occurred.

Sample collection and viral detection

The specimens collected varied according to the patient's symptoms. Nasopharyngeal and nasal swabs specimens were collected with synthetic fiber swabs; each swab was inserted into a separate sterile tube containing 2 mL of phosphate buffered saline. In intubated or tracheostomized patients, tracheal aspirate specimens were obtained the same way. Specimens were immediately processed at the Virology Laboratory or stored at 4°C until processing. Nucleic acid extraction was performed manually with the Bio Gene Viral DNA/RNA extraction kit (Bioclin, Belo Horizonte, Brazil). SARS-CoV-2 RNA was detected using both the CDC 2019-nCoV RT-PCR Diagnostic Panel and Bio-Manguinhos SARS-CoV-2 Molecular Kit using the 7500 Real-Time PCR System (Applied Biosystems, Waltham, MA, USA). The Charité/Berlin protocol was used, and samples were considered SARS-CoV-2 positive when both E and RdRP target genes were detected, and if the CT value was not higher than 37.

Additional diagnostic tests were performed for children aged 0-3 months (multiplex respiratory PCR panel; FilmArray; BioFire Diagnostics, Salt Lake City, UT, USA) and those aged 3-48 months (Influenza and RSV PCR tests). SARS-CoV-2 serology was performed using a chemiluminescence immunoassay (Kit MAGLUMI 2019-nCOV IgG/IgM CLIA; Snibe, Shenzhen, China). All assays were performed according to manufacturer instructions. Tests were performed according to hospital unit availability for testing. For this study, we selected participants who had a confirmed diagnosis of either COVID-19 or RSV (i.e., cases of coinfection were not included in this analysis).

Statistical analyses

The data collected was compiled using Microsoft Access for Windows 10, version 2019. All variable distributions were studied. Categorical variables were described as absolute and relative frequencies; continuous variable distributions were studied graphically and were described as means and standard deviations. Bivariate analysis was performed using the Fisher's exact test (categorical variables) or the Mann-Whitney test (continuous variables). Independent variables with $p < 0.2$ were included in a multivariate analysis model, using backward stepwise logistic regression. Variables with < 5% of frequency were not added into the multivariate analysis model. Since this study took place in a tertiary hospital, it was common that patients with comorbidities were admitted to the emergency room, and these comorbidities might have had a role in the pathogenicity of the respiratory infections in study; therefore, we forced this variable (presence or not of a comorbidity) into the final model. The main dependent variable was a diagnosis of

SARS-CoV-2 or RSV infection. Models with and without interactions were tested using the −2 log-likelihood test. The fitness of the model was evaluated using the Hosmer-Lemeshow test. Alternative hypotheses were accepted if the comparison p-value was ≤ 0.05. All data were analyzed using the Stata software, version 15 (Stata Corp LP, College Station, TX, USA).

RESULTS

In this analysis, among 369 patients eligible for the study, we detected 114 patients infected with either SARS-CoV-2 (n = 59; 52%) or RSV (n = 55; 48%) during the first year of the COVID-19 pandemic. The mean age was 12 months (range: 0-48 months).

The time distribution of RSV cases during the first year of the SARS-CoV-2 pandemic was different from their normal distribution. Most of the cases (75%) occurred between Brazilian late spring and summer (between October of 2020 and January of 2021), whereas they regularly occur between late autumn and winter (from May to August).

RSV patients were younger than were patients with SARS-CoV-2 infection. No differences were found regarding gender or other sociodemographic variables between the groups. RSV patients presented with respiratory distress manifestations, while patients with SARS-CoV-2 presented with more systemic and inflammatory manifestations (fever at admission and higher inflammatory markers, such as protein C reactive or white blood cells; Table 1).

When we consider the multivariate analysis, none of the laboratory testing variables was significant. Children infected with RSV tended to be younger and presented with a phenotype of respiratory distress at admission, whereas those infected with SARS-CoV-2 tended to present with a systemic disease (fever or higher inflammatory enzymes; Table 2).

None of the participants died. Admissions to the ICU in the SARS-CoV-2 and RSV groups were 6/55 (11%) and 13/59 (22%), respectively (p = 0.11). The mean length of hospital stay was seven days in both groups (p = 0.77).

Table 1. Comparison of clinical manifestations and laboratory test results between patients infected with RSV or SARS-CoV-2 (bivariate analysis).[a]

Variable	RSV N = 59 (52%)	SARS-CoV-2 N = 55 (48%)	p*
Age, months	7.9	20.1	< 0.01
Gender, female	26 (44.1)	21 (40.3)	0.42
Family income[b]	1.6	1,3	0.07
Tobacco exposure at household	21(37.5)	14 (28)	0.31
Fever at admission	32 (54)	41 (75)	0.01
Cough	57 (97)	35 (64)	< 0.01
Rhinorrhea	43 (75)	26 (49)	< 0.01
Tachypnea	54 (93)	29 (53)	< 0.01
Dyspnea	49 (88)	25 (48)	< 0.01
SpO_2 < 95%	30 (53)	13 (23)	< 0.01
Rash	2 (3.5)	5 (9.4)	0.26
Abdominal pain	24 (24.9)	10 (18.9)	< 0.01
Diarrhea	14 (24.6)	18 (32.7)	0.35
Vomiting	18 (32.1)	23 (41.8)	0,33
Chronic disease	19 (33.9)	32 (61.5)	< 0.01
Hemoglobin, g/dL	11.0	10.7	0.39
White blood cells, cells/mm^3	10,956	12,845	0.20
Lymphocytes, cells/mm^3	5202	4092	0.02
Platelets, count/mm^3	356,707	350,816	0.83
Protein C reactive mg/dL	16.0	54.1	< 0.01

[a]Values expressed as mean or n (%). [b]Brazilian minimum salary = US$300 *Variables with p < 0.05 were included in the initial multivariate analysis.

Table 2. Comparison of clinical manifestations between patients infected with RSV or SARS-CoV-2 (multivariate analysis).

Variable	OR	95% CI	p
Age, months	0.94	0.90-0.98	< 0.01
Fever at admission	0.18	0.05-0.66	< 0.01
Rhinorrhea	2.33	0.64- 8.46	0.19
Tachypnea	6.06	1.31-28.01	0.02
Chronic disease	0.52	0.17-1.63	0.26
Cough	7.36	1.04-52.25	0.04

DISCUSSION

This prospective, nested cross-sectional study compared clinical and laboratory data of children aged 0-4 years infected with either RSV or SARS-CoV-2 during the first year of the COVID-19 pandemic. The time distribution of RSV cases was studied during this period.

During the study year, there was a time shift of RSV cases, from winter to summer. The main clinical manifestations of RSV cases were as a respiratory disease in younger children, while SARS-CoV-2 infection was more frequent in older children, who presented with high fever.

The distribution of the RSV cases during the first year of the SARS-CoV-2 pandemic was different from that observed in the southeast region of Brazil in previous years, during which most cases occurred during autumn and winter (May to August). In 2020/2021, most of the cases were in the summer. This phenomenon was also observed in other countries in the southern hemisphere, such as Australia and Thailand.[5,6] We believe that the prolonged social isolation that occurred in our country in the first months of the pandemic was responsible for the deviation of the curve of RSV cases during summer.

Although SARS-CoV-2 is a new respiratory disease etiology, its phenotype is different from the RSV-related

bronchiolitis in children up to four years of age, even when controlling for chronic diseases.

A Thai study that compared RSV cases before and during pandemic found that the cases that required hospitalization during the pandemic were less severe when compared with those before the pandemic.[5] Although it was not the main aim of this study, we found no differences regarding the description of RSV phenotype.

In an Australian surveillance study of the RSV cases during the first year of the pandemic,[6] the authors observed that RSV patients were older than in previous years (on average, 18 months). In our series of RSV cases, the children were younger (mean age, 8 months) and even younger than the children with SARS-CoV-2 infection.

A study also comparing SARS-CoV-2 and RSV cases in children up to two years of age in Italy described the same results as ours; children with the former infection had more fever, but the latter etiologic agent was more severe, although the authors did not adjust their findings for age and/or chronic diseases, as we did in our study.[8]

Pediatricians are used to diagnosing RSV infections based on the clinical manifestations of this infection in young populations[1,2]; however, after the introduction of a new agent in the differential diagnosis of respiratory diseases in children, it is important to understand the differences between these major agents. Some studies carried out in high-income countries made comparisons using small sample sizes,[6-8] leaving an information gap regarding children in middle- and low-income countries such as Brazil.[9]

An important limitation in our study was that the data derived from the first year of the COVID-19 pandemic; since then, several SARS-CoV-2 variants have circulated in Brazil, and some of these presented with different clinical manifestations when compared with others. Comparisons between clinical manifestations and variants over time in children demonstrated that some manifestations were more frequent for each variant, but disease severity was the same.[10]

In this study, we were able to demonstrate that the seasonality of RSV infection during the first year of the SARS-CoV-2 pandemic shifted from winter to summer, as described in other countries in the southern hemisphere.

The clinical phenotypes of the two different etiologies are different, and the differences pointed out in this study are important for pediatricians working at emergency departments in middle- and lower-income countries, where diagnosis tests and therapies are limited.

AUTHOR CONTRIBUTIONS

GPL: conceptualization; data curation; project administration; and writing (review & editing). MTV: conceptualization; data curation; formal analysis; and writing (review & editing). MAAMG: conceptualization; formal analysis; methodology; and project administration; and writing (review & editing) (supporting role). TFA: project administration; and writing (review & editing) (supporting role). YR: drafting, editing, and reviewing of the manuscript (supporting role). ACCF: conceptualization; data curation; investigation; and writing (review & editing). CBH: conceptualization; data curation; formal analysis; funding acquisition; methodology; supervision; and drafting of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Bardsley M, Morbey RA, Hughes HE, Beck CR, Watson CH, Zhao H, et al. Epidemiology of respiratory syncytial virus in children younger than 5 years in England during the COVID-19 pandemic, measured by laboratory, clinical, and syndromic surveillance: a retrospective observational study. Lancet Infect Dis. 2023;23(1):56-66. https://doi.org/10.1016/S1473-3099(22)00525-4
2. Jiang MY, Duan YP, Tong XL, Huang QR, Jia MM, Yang WZ, et al. Clinical manifestations of respiratory syncytial virus infection and the risk of wheezing and recurrent wheezing illness: a systematic review and meta-analysis. World J Pediatr. 2023;19(11):1030-1040. https://doi.org/10.1007/s12519-023-00743-5
3. National Institutes of Health [homepage on the Internet]. Bethesda: NIH; c2023 [updated 2023 Jul 21; cited 2023 Feb 15]. COVID-19 Treatment Guidelines: Therapeutic Management of Hospitalized Children With COVID-19, Available from: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-children/hospitalized-children-therapeutic-management/
4. Pucarelli-Lebreiro G, Venceslau MT, Cordeiro CC, Maciel FQ, Anachoreta TD, de Abreu TF, et al. Clinical Manifestations and Complications of Children With COVID-19 Compared to Other Respiratory Viral Infections: A Cohort Inpatient Study From Rio de Janeiro, Brazil. Front Pediatr. 2022;10:934648. https://doi.org/10.3389/fped.2022.934648
5. Chaiut W, Sapbamrer R, Dacha S, Sudjaritruk T, Parwati I, Sumarpo A, et al Characteristics of Respiratory Syncytial Virus Infection in Hospitalized Children Before and During the COVID-19 Pandemic in Thailand. J Prev Med Public Health. 2023;56(3):212-220. https://doi.org/10.3961/jpmph.23.019
6. Foley DA, Yeoh DK, Minney-Smith CA, Martin AC, Mace AO, Sikazwe CT, et al. The Interseasonal Resurgence of Respiratory Syncytial Virus in Australian Children Following the Reduction of Coronavirus Disease 2019-Related Public Health Measures. Clin Infect Dis. 2021;73(9):e2829-e2830. https://doi.org/10.1093/cid/ciaa1906
7. Ozeki S, Kawada JI, Yamashita D, Yasufuku C, Akano T, Kato M, et al. Impact of the Coronavirus Disease 2019 Pandemic on the Clinical Features of Pediatric Respiratory Syncytial Virus Infection in Japan. Open Forum Infect Dis. 2022;9(11):ofac562. https://doi.org/10.1093/ofid/ofac562
8. Pruccoli G, Castagno E, Raffaldi I, Denina M, Barisone E, Baroero L ,et al. The Importance of RSV Epidemiological Surveillance: A Multicenter Observational Study of RSV Infection during the COVID-19 Pandemic. Viruses. 2023;15(2):280. https://doi.org/10.3390/v15020280
9. Freitas AR, Donalisio MR. Respiratory syncytial virus seasonality in Brazil: implications for the immunisation policy for at-risk populations. Mem Inst Oswaldo Cruz. 2016;111(5):294-301. https://doi.org/10.1590/0074-02760150341
10. Sumner MW, Xie J, Zemek R, Winston K, Freire G, Burstein B, et al. Comparison of Symptoms Associated With SARS-CoV-2 Variants Among Children in Canada. JAMA Netw Open. 2023;6(3):e232328. https://doi.org/10.1001/jamanetworkopen.2023.2328

J Bras Pneumol. 2024;50(3):e20240156
https://dx.doi.org/10.36416/1806-3756/e20240156

SPECIAL ARTICLE

Brazilian Thoracic Society recommendations for the diagnosis and monitoring of asbestos-exposed individuals

Ubiratan Paula Santos[1], Eduardo Algranti[2], Eduardo Mello De Capitani[3], Gustavo Faibischew Prado[4], Ana Paula Scalia Carneiro[5], Sílvia Carla Sousa Rodrigues[6], Jefferson Benedito Pires de Freitas[1,7], Rodrigo Caruso Chate[8,9], Rafael Futoshi Mizutani[1], Hermano Albuquerque de Castro[10], Marcos Abdo Arbex[11], Patrícia Canto Ribeiro[12], Carlos Nunes Tietboehl Filho[13], Maria Vera Cruz de Oliveira Castellano[6], Guilherme Ward Leite[1], Gustavo Corrêa de Almeida[14];
Committee on Environmental and Occupational Diseases

1. Grupo de Doenças Respiratórias Ocupacionais, Ambientais e de Cessação de Tabagismo, Divisão de Pneumologia, Instituto do Coracao – InCor – Hospital das Clinicas, Faculdade de Medicina, Universidade de Sao Paulo – FMUSP – Sao Paulo (SP) Brasil.
2. Fundação Jorge Duprat Figueiredo de Segurança e Medicina do Trabalho – FUNDACENTRO – São Paulo (SP) Brasil.
3. Disciplina de Pneumologia e Centro de informação e Assistência Toxicológica – CIATox – Departamento de Clínica Médica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas – UNICAMP – Campinas (SP) Brasil.
4. Hospital Alemão Oswaldo Cruz, São Paulo (SP) Brasil.
5. Ambulatório de Pneumologia Ocupacional do SEST, Hospital das Clínicas, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
6. Serviço de Pneumologia, Hospital do Servidor Público Estadual Francisco Morato Oliveira (HSPE-FMO)/Instituto de Assistência Médica ao Servidor Público Estadual – IAMSPE – de São Paulo, São Paulo (SP) Brasil.
7. Departamento de Saúde Coletiva, Faculdade de Ciências Médicas da Santa Casa de São Paulo – FCMSCSP – São Paulo (SP) Brasil.
8. Serviço de Radiologia, Instituto do Coracao – InCor – Hospital das Clinicas, Faculdade de Medicina, Universidade de Sao Paulo – FMUSP – Sao Paulo (SP) Brasil.
9. Hospital Israelita Albert Einstein, São Paulo (SP) Brasil.
10. Fundação Oswaldo Cruz – Fiocruz – Rio de Janeiro (RJ) Brasil.
11. Área Temática Pneumologia, Faculdade de Medicina, Universidade de Araraquara, Araraquara (SP) Brasil.
12. Atenção à saúde da Vice-Presidência de Ambiente Atenção e Promoção da Saúde, Fundação Oswaldo Cruz – Fiocruz – Rio de Janeiro (RJ) Brasil.
13. Secretaria da Saúde do Estado do Rio Grande do Sul, Porto Alegre (RS) Brasil.
14. Hospital de Base, Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto (SP) Brasil.

Submitted: 2 June 2024.
Accepted: 5 June 2024.

ABSTRACT

Asbestos was largely used in Brazil. It is a mineral that induces pleural and pulmonary fibrosis, and it is a potent carcinogen. Our objective was to develop recommendations for the performance of adequate imaging tests for screening asbestos-related diseases. We searched peer-reviewed publications, national and international technical documents, and specialists' opinions on the theme. Based on that, the major recommendations are: Individuals exposed to asbestos at the workplace for ≥ 1 year or those with a history of environmental exposure for at least 5 years, all of those with a latency period > 20 years from the date of initial exposure, should initially undego HRCT of the chest for investigation. Individuals with pleural disease and/or asbestosis should be considered for regular lung cancer monitoring. Risk calculators should be adopted for lung cancer screening, with a risk estimate of 1.5%.

Keywords: Asbestosis/diagnosis; Asbestosis/prevention & control; Environmental exposure; Occupational exposure.

INTRODUCTION

Asbestos is a general term that refers to a heterogeneous group of natural minerals that occur in the form of fibers (length to diameter ratio ≥3:1), mostly composed of hydrated magnesium silicates and a variable content of other cations such as iron, aluminum, and sodium.[1]

Asbestos has been employed in different production sectors of the manufacturing industry due to its physical and chemical properties of heat resistance, even in high temperatures, low density, flexibility, mechanical and chemical resistance, and also because of its low cost.

Inhaled fibers can cause a spectrum of diseases, including lung cancer; malignant mesothelioma of the pleura, peritoneum, pericardium, and tunica vaginalis; laryngeal and ovarian cancers; nonmalignant pleural diseases; asbestosis; and airflow obstruction.[2,3] Less consistent evidence has shown that they are associated with a higher incidence of retroperitoneal fibrosis.[3] Asbestos exposure is the main risk factor for occupational cancer globally and a significant cause of disease and disability.[4]

The incidence and prevalence of those diseases are intimately related to occupational and environmental exposure to asbestos, such as workers in asbestos mining and processing, as well as workers in industries of manufactured goods such as asbestos-cement, automotive parts, textile products, thermal insulation materials, and others. Relatives of exposed workers and people living in communities surrounding mining and industrial areas also face risk of exposure.[5,6]

There are no serological markers nor other types of markers for the early diagnosis of the diseases related to asbestos exposure mentioned above. For pleuropulmonary

Correspondence to:
Ubiratan de Paula Santos. Avenida Dr. Enéas Carvalho de Aguiar, 44, Bloco II, 5º Andar, CEP 05403-000, São Paulo, SP, Brasil.
Tel.: 55 11 2661-5801. E-mail: pneubiratan@incor.usp.br
Financial support: None.

◄ Voltar ao sumário
ISSN 1806-3756

diseases, the object of the present document, chest imaging is the detection method used globally.

In Brazil, despite efforts to restrict asbestos production and use, the number of reported cases of asbestos-related diseases is still much lower than the estimates,[7,8] which strengthens the need to develop structured programs for the screening of these diseases featuring the incorporation of more sensitive imaging methods such as chest CT.[9-13]

OBJECTIVE

To develop recommendations for the screening of pleuropulmonary diseases related to asbestos exposure through the performance of imaging tests.

METHODS

A narrative review of the literature of diagnostic imaging of nonmalignant asbestos-related diseases and lung cancer screening in asbestos-exposed individuals was elaborated. The literature used in the development of this document encompassed peer-reviewed publications and documents from national and international institutions. Based on this narrative review, a panel of specialists composed of pulmonologists and a radiologist with expertise in the field proposed recommendations for the diagnosis and monitoring of asbestos-exposed individuals.

EPIDEMIOLOGY

Asbestos exposure is one of the main occupational risk factors for respiratory diseases and has the greatest impact on morbidity and mortality. Global estimates for 2019 reveal that 239.3 thousand deaths and 4.189 million disability-adjusted life-years derive from asbestos exposure.[4] The greatest impact is associated with lung cancer, in which asbestos accounts for approximately 10% of global deaths, not to mention thousands of cases of mesothelioma of serous membranes diagnosed on an annual basis.[4,14] Global estimates for the same year suggest that lung cancer has the highest incidence (2.26 million) and the highest mortality (2.04 million) among cancers.[4,15]

In Brazil, a cross-sectional study involving former asbestos-cement workers who had been employed predominantly in the 1960s and 1970s found a high prevalence of nonmalignant asbestos-related diseases and a progressive reduction in prevalence among those employed in the 1980s,[16] a predictable trend due to pressures for asbestos ban, which caused a slow reduction in asbestos use. Data from other countries[17] and global data[14] have indicated a slower reduction in mortality, varying between countries and with a greater predicted impact from 2030 onwards. An ecological study suggested greater mortality due to lung cancer in men and women, from mesothelioma in men, and from ovarian cancer in women in a cluster of municipalities that housed asbestos-cement factories and/or asbestos mining in Brazil,[18] corroborating another study that found evidence of an important underreporting of cases of asbestos-related diseases in the country.[19]

It is important to bear in mind that smoking is the main risk factor for lung cancer, followed by asbestos exposure and air pollution,[4,15] and it is well established that exposure to asbestos and tobacco smoke presents a positive synergism, that is, the associated risk of both exposures is higher than the sum of the respective risks for lung cancer incidence.[20,21] The prevalence of the sum of smokers and former smokers in Brazil and globally exceeds 40% of the population older than 18 years, being higher in the male sex,[22,23] that is, a large number of adult workers may have been exposed to the two risk factors: asbestos and smoking.

Studies indicate that occupational asbestos exposure is associated with a relative risk for lung cancer incidence that is 2 to 10 times higher compared with the general population, and has a dose-response relationship with fiber concentration in the work environment and cumulative exposure,[24] not to mention the synergistic effect with other carcinogens, such as those present in tobacco smoke.[20]

IMAGING METHODS

Chest radiography is the exam required by the Brazilian legislation on occupational safety and medicine[25] for the periodical monitoring of workers exposed to mineral dust. Periodical chest radiographs have the advantages of standardized interpretation through the International Labour Organization's International Classification of Radiographs of Pneumoconioses criteria[26] and low radiation dose. Although it is widely used and complies with the Brazilian legislation on occupational safety,[25] chest radiography has lost relevance with the advent of CT, especially with the drastic reduction in ionizing radiation enabled by the new tomography machines.[27]

It is well established that chest CT is more sensitive for the diagnosis of diseases related to asbestos exposure.[9,13] HRCT, including low-dose CT of the chest,[28] provides a more accurate diagnosis of interstitial lung diseases, such as asbestosis, and that of pleural thickening, such as pleural plaques. Furthermore, it is more indicated for the early diagnosis of pulmonary nodules. Between 20% and 50% of pleural abnormalities visualized in autopsies and CT scans are not visualized in radiographs, and 15-30% of individuals with radiographs interpreted as normal present abnormalities suggestive of asbestosis on HRCT. In addition to greater sensitivity and specificity, chest HRCT also presents lower variability between experienced chest radiograph readers compared with radiography.[2,9-13,16,29] The patterns of tomographic images also allow to enhance the differential diagnosis between asbestosis and interstitial lung diseases of other etiologies[30,31] and a greater accuracy in the identification of pulmonary nodules.[32,33]

In the current scenario, most individuals exposed to asbestos have lower exposure doses because they started working in the 1980s, the decade when movements and actions to restrict and eliminate asbestos use began. Even though such movements and actions had a reduced reach, they succeeded in bringing about improved environmental control and prohibiting the use of amphiboles. As a consequence, exposed individuals may present subtle abnormalities, both in the pleura and in the parenchyma. In addition, individuals with a smoking history, emphysema, and/or chronic bronchitis or other tobacco-related lung diseases, advanced age, heart failure, obesity, and other exposures to dust or particles may present radiographic abnormalities that hinder the adequate identification of asbestosis and reduce the accuracy of interpretation.[2,13,30,31,34,35]

Specialty societies in the thoracic area have long been indicating the use of chest HRCT to diagnose interstitial lung diseases.[36] Therefore, there is no justification for indicating HRCT for the diagnosis and monitoring of interstitial diseases in general and restricting it in the case of occupational interstitial diseases like asbestosis.

On the other hand, the identification of nonmalignant abnormalities, especially asbestosis,[21] but also pleural plaques,[37,38] enables to evaluate the inclusion of these individuals in the high-risk group for developing lung cancer and to ensure that they are monitored.

Furthermore, studies carried out in the past 20 years have shown that the sensitivity of low-dose HRCT (LD-HRCT) to detect interstitial lung abnormalities is apparently similar to that of conventional thin-slice tomography (HRCT), and both of them are superior to the older, initial conventional tomography,[38-42] with lower exposure to radiation. A study involving 2,760 nuclear weapons workers potentially exposed to asbestos found that LD-HRCT enabled the detection of 3.7 times more pleural plaques and five times more interstitial lung diseases than chest radiography.[33]

These results stimulated the conduction of studies focusing on long-term screening for the early diagnosis of lung cancer,[25] which demands repeated tests with the use of LD-HRCT and, more recently, ultra-LD-HRCT.[41-44] In the past, the radiation dose from a conventional chest tomography used to be higher than the dose from 100 chest X-rays. Comparative studies have shown that exposure per exam has been reduced with the use of low-dose helical tomography equipped with a higher number of detectors (32 or more) and new algorithms for image reconstruction. Such studies have found radiation exposures, measured in millisieverts (mSv), of 0.16 mSv and 1-2 mSv from ultra-low-dose HRCT and low-dose HRCT, respectively, compared with 0.05 mSv and 0.24 mSv from lateral and posteroanterior chest X-ray, images being acquired with appropriate quality.[43-46] The risk of HRCT is not zero, but it is much lower than the benefits related to the reduction in mortality by lung cancer revealed by many studies conducted with risk populations. Although it is not possible to produce accurate estimates, estimated risk[47] is calculated based on the radiation effects of the exposure to the atomic bombs in Hiroshima and Nagasaki. Thus, the estimated risk is that the annual exposure of an individual from the age of 50 to the age of 75 years to LD-HRCT radiation is 1.8% (95% CI: 0.5-5.5%), much lower than the mortality reduction found in different studies, which ranges between 15% and 30%.[27,48-50]

As studies have shown a favorable inclination towards the utilization of HRCT in lung cancer screening, its use started to be recommended in the USA,[48-50] in European countries,[51] by Collegium Ramazzini,[27] and, recently, by the Brazilian Thoracic Society,[52] for individuals who meet the criteria suggested in the studies, centered on the main risk factor: smoking. One of the concerns in screening studies is the overdiagnosis of non-neoplastic nodules, leading to procedures that have a negative impact on patients. However, analyses of many international and Brazilian studies have shown only a few relevant complications and that the benefits outweigh the risks.[50-52]

The lung cancer risk of individuals with a history of occupational asbestos exposure is comparable to or higher than that of individuals who meet the classic eligibility criteria for lung cancer screening programs with LD-HRCT[49,53,54] even if they have been former smokers for more than 15 years or have smoked less than 20 pack-years. A recent guideline from the American Cancer Society[49,50] recommends, among other updates, that the number of years since smoking cessation should not be one more eligibility criterion for inclusion in screening programs, which is something that other studies, such as those that suggest the use of risk calculators,[55-57] already do.

A model developed in England to assess risk prediction based on a cohort study involving more than 18 million individuals revealed that asbestos exposure is one of the main risk prediction factors for lung cancer.[57]

RECOMMENDATIONS

1. For all individuals with a history of occupational exposure to asbestos for at least one year, or domestic exposure (workers' relatives exposed through clothes that are likely to be contaminated or exposed to asbestos products brought for use inside the domicile) or environmental exposure (individuals living near mining companies or factories involved in the manufacture of asbestos products) for at least five years, with 20 years' latency or over, the recommendation is that, apart from clinical, functional assessment, and the necessary compliance with the labour rules for periodical examination, when needed, they should be submitted to an HRCT of the chest as the first imaging test (Table 1).

Based on the findings obtained through the images and on clinical and functional aspects, the individuals can be followed up through criteria defined according to the potential risk, as follows:

Table 1. Summary of recommendations.

Eligibility criteria	Recommendations
Occupational exposure to asbestos ≥ 1 year, or domestic/environmental exposure to asbestos ≥ 5 years AND Latency period ≥ 20 years	Submit to HRCT as the first imaging test
Age 50-75 years old AND Exposure to asbestos AND Any nonmalignant asbestos-related disease: Pleural plaques, diffuse pleural thickening, round atelectasis, and/or asbestosis	Submit to pulmonary function test with plethysmography and DL_{CO} assessment, if available
Age 50-75 years old AND Exposure to asbestos with or without nonmalignant asbestos-related disease AND Latency period ≥ 20 years AND Lung cancer risk estimate > 1.5%*	Submit to annual lung cancer screening with LD-HRCT Lung-RADS diagnostic criteria are recommended as the main method of assessment of LD-HRCT findings Lung cancer screening programs should have support of smoking cessation programs

LD: low dose; Lung-RADS: Lung Imaging Reporting and Data System.[61] *Estimated by the Liverpool Lung Project (LLP)[55,56] or the CanPredict[57] cancer risk calculators.

1.1. Individuals aged 50 or older up to 75 years of age presenting pleural plaques and/or diffuse pleural thickening, with or without round atelectasis, and/or signs compatible with asbestosis, mainly presence of subpleural dots and lines, interlobular septal thickening, parenchymal bands, ground-glass opacities, mosaic perfusion in early cases, and in more advanced cases, also traction bronchiectasis and honeycombing,[2,58,59] in addition to a previous clinical assessment, should be submitted to an assessment of the respiratory function, which should be thorough whenever possible (not only spirometry), with determination of DL_{CO}. If they meet the inclusion criteria, such as absence of comorbidities that impose limitations on diagnosis and treatment procedures in the case of a cancer diagnosis, they should be followed up according to item 1.2 below.

1.2. Annual lung cancer screening is recommended to the services that meet the requirements suggested in the studies and recommendations.[27,49-52,60] Such services should plan the timely performance of tests, including reassessments in accordance with the indication of the nodules found, and the performance of procedures for diagnosis, follow-up, and treatment with the use of LD-HRCT to minimize the risks of radiation exposure.

2. Individuals aged 50 or older up to 75 years of age with occupational exposure to asbestos for one year or over or domestic and/or environmental exposure for five years or over, with 20 years' latency or over, for any of the exposure conditions, even if they do not present asbestos-related diseases at the moment, should be considered exposed in a significant way and assessed through the use of risk calculators for inclusion in the screening program with the use of LD-HRCT of the chest. If they do not meet such criteria, they can be included in the screening program through the other factors assessed by the calculators.

3. Chest LD-HRCT screening should be performed in individuals with a history of occupational exposure to asbestos who meet the criteria described above if their lung cancer risk estimate is at least 1.5% according to Liverpool Lung Project (https://liverpoollungproject.org.uk/MLRV3/MLRCalculation.html) or CanPredict calculators.[55-57][1]

4. For the assessment of CT scans in the lung cancer screening program, the classification of findings and diagnosis criteria recommended by Lung Imaging Reporting and Data System (Lung-RADS),[61] a tool recommended in lung cancer screening programs,[51,54-57] should be used.

5. All the services involved in lung cancer screening programs should have the support of smoking cessation programs.

FINAL CONSIDERATIONS

The diagnosis and registration of occupational diseases have historically been inadequate and limited for many reasons, such as the deficient education of health professionals and the lack of specialized services in Brazil. Respiratory diseases deriving from asbestos exposure are included in this context. Diagnosing asbestos-related diseases is necessary to enhance the monitoring of patients' health. Furthermore, with such a diagnosis, Brazil can have accurate knowledge of the repercussions of asbestos use, and the victims will have the right to seek compensation if they wish to, either

[1] The risk calculators Liverpool Lung Project (LLP)[54,55] and CanPredict[56] are tools developed to estimate individual risk of lung cancer in a time horizon of five to ten years. They include asbestos exposure and smoking in their mathematical models, as well as clinical and demographic variables.

from the State (social security, environmental care) or from the companies that generated the exposure.

The present document represents the position of the Committee on Environmental and Occupational Diseases of the Brazilian Thoracic Society on screening, diagnosis, and follow-up of asbestos-related diseases with the main objective of improving their recognition and monitoring.

AUTHOR CONTRIBUTIONS

All the authors participated in one or more development stages of these recommendations, and all read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Shukla A, Gulumian M, Hei TK, Kamp D, Rahman Q, Mossman BT. Multiple roles of oxidants in the pathogenesis of asbestos-induced diseases. Free Radic Biol Med. 2003;34(9):1117-1129. https://doi.org/10.1016/S0891-5849(03)00060-1
2. American Thoracic Society. Diagnosis and initial management of nonmalignant diseases related to asbestos. Am J Respir Crit Care Med. 2004;170(6):691-715. https://doi.org/10.1164/rccm.200310-1436ST
3. Wolff H, Vehmas T, Oksa P, Rantanen J, Vainio H. Asbestos, asbestosis, and cancer, the Helsinki criteria for diagnosis and attribution 2014: recommendations. Scand J Work Environ Health. 2015;41(1):5-15. https://doi.org/10.5271/sjweh.3462
4. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1223-1249. https://doi.org/10.1016/S0140-6736(20)30752-2
5. Magnani C, Dalmasso P, Biggeri A, Ivaldi C, Mirabelli D, Terracini B. Increased risk of malignant mesothelioma of the pleura after residential or domestic exposure to asbestos: a case-control study in Casale Monferrato, Italy. Environ Health Perspect. 2001;109(9):915-919. https://doi.org/10.1289/ehp.01109915
6. Kwak K, Kang D, Paek D. Environmental exposure to asbestos and the risk of lung cancer: a systematic review and meta-analysis. Occup Environ Med. 2022;79(3):207-214. https://doi.org/10.1136/oemed-2020-107222
7. Algranti E, Saito CA, Carneiro AP, Moreira B, Mendonça EM, Bussacos MA. The next mesothelioma wave: mortality trends and forecast to 2030 in Brazil. Cancer Epidemiol. 2015;39(5):687-692. https://doi.org/10.1016/j.canep.2015.08.007
8. Park EK, Takahashi K, Hoshuyama T, Cheng TJ, Delgermaa V, Le GV, et al. Global magnitude of reported and unreported mesothelioma. Environ Health Perspect. 2011;119(4):514-518. https://doi.org/10.1289/ehp.1002845
9. Aberle DR, Gamsu G, Ray CS. High-resolution CT of benign asbestos-related diseases: clinical and radiographic correlation. AJR Am J Roentgenol. 1988; 151(5):883-891. https://doi.org/10.2214/ajr.151.5.883
10. Bégin R, Ostiguy G, Filion R, Colman N, Bertrand P. Computed tomography in the early detection of asbestosis. Br J Ind Med. 1993;50(8):689-698. https://doi.org/10.1136/oem.50.8.689
11. Gamsu G, Salmon CJ, Warnock ML, Blanc PD. CT quantification of interstitial fibrosis in patients with asbestosis: a comparison of two methods. AJR Am J Roentgenol. 1995;164(1):63-68. https://doi.org/10.2214/ajr.164.1.7998570
12. Gevenois PA, de Maertelaer V, Madani A, Winant C, Sergent G, De Vuyst P. Asbestosis, pleural plaques and diffuse pleural thickening: three distinct benign responses to asbestos exposure. Eur Respir J. 1998;11(5):1021-1027. https://doi.org/10.1183/09031936.98.11051021
13. Ross RM. The clinical diagnosis of asbestosis in this century requires more than a chest radiograph. Chest. 2003;124(3):1120-1128. https://doi.org/10.1378/chest.124.3.1120
14. Miao X, Yao T, Dong C, Chen Z, Wei W, Shi Z, et al. Global, regional, and national burden of non-communicable diseases attributable to occupational asbestos exposure 1990-2019 and prediction to 2035: worsening or improving? BMC Public Health. 2024; 24(1):832. https://doi.org/10.1186/s12889-024-18099-4
15. Kocarnik JM, Compton K, Dean FE, Fu W, Gaw BL, Harvey JD, et al. Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019. JAMA Oncol. 2022;8(3):420-444. https://doi.org/10.1001/jamaoncol.2021.6987
16. Algranti E, Mendonça EM, DeCapitani EM, Freitas JB, Silva HC, Bussacos MA. Non-malignant asbestos-related diseases in Brazilian asbestos-cement workers. Am J Ind Med. 2001;40(3):240-254. https://doi.org/10.1002/ajim.1095
17. Baur X. Asbestos-Related Disorders in Germany: Background, Politics, Incidence, Diagnostics and Compensation. Int J Environ Res Public Health. 2018;15(1):143. https://doi.org/10.3390/ijerph15010143
18. Sex-Specific Mortality from Asbestos-Related Diseases, Lung and Ovarian Cancer in Municipalities with High Asbestos Consumption, Brazil, 2000-2017 [published correction appears in Int J Environ Res Public Health. 2022 May 31;19(11):6720. doi: 10.3390/ijerph19116720]. Int J Environ Res Public Health. 2022;19(6):3656. https://doi.org/10.3390/ijerph19116720
19. Santana VS, Salvi L, Cavalcante F, Campos F, Algranti E. Underreporting of mesothelioma, asbestosis and pleural plaques in Brazil. Occup Med (Lond). 2021;71(4-5):223-230. https://doi.org/10.1093/occmed/kqab073
20. World Health Organization. International Agency for Research on Cancer (IARC). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Arsenic, metals, fibers and dust, Vol 100C. Lyon, France: IARC; 2012.
21. Markowitz SB, Levin SM, Miller A, Morabia A. Asbestos, asbestosis, smoking, and lung cancer. New findings from the North American insulator cohort. Am J Respir Crit Care Med. 2013;188(1):90-96. https://doi.org/10.1164/rccm.201302-0257OC
22. Malta DC, Gomes CS, Andrade FMD, Prates EJS, Alves FTA, Oliveira PPV, et al. Tobacco use, cessation, secondhand smoke and exposure to media about tobacco in Brazil: results of the National Health Survey 2013 and 2019. Rev Bras Epidemiol. 2021;24(suppl 2):e210006. https://doi.org/10.1590/1980-549720210006.supl.2
23. WHO. WHO global report on trends in prevalence of tobacco use 2000-2025. 4th ed. Geneva: World Health Organization; 2021.
24. Klebe S, Leigh J, Henderson DW, Nurminen M. Asbestos, Smoking and Lung Cancer: An Update. Int J Environ Res Public Health. 2019;17(1):258. https://doi.org/10.3390/ijerph17010258
25. gov.br. Presidência da República. Ministério do Trabalho e Emprego homepage on the Internet]. Brasília: o Ministério; c2023 [updated 2023 Feb 14; cited 2024 Apr 6]. Normas Regulamentadoras - NR. Available from: https://www.gov.br/trabalho-e-emprego/pt-br/assuntos/inspecao-do-trabalho/seguranca-e-saude-no-trabalho/ctpp-nrs/normas-regulamentadoras-nrs
26. International Labour Organization (ILO) [homepage on the Internet]. Geneva: International Labour Office; c2022 [cited 2024 Apr 6]. Guidelines for the use of the ILO International Classification of Radiographs of Pneumoconioses. Revised edition 2022. [Adobe Acrobat document, 45p.]. Available from: https://www.ilo.org/resource/ilo-international-classification-radiographs-pneumoconioses-1
27. Markowitz S, Ringen K, Dement JM, Straif K, Christine Oliver L, Algranti E, et al. Occupational lung cancer screening: A Collegium Ramazzini statement. Am J Ind Med. 2024;67(4):289-303. https://doi.org/10.1002/ajim.23572
28. Nogami S, J-P NA, Nogami M, Matsui T, Ngatu NR, Tamura T, et al. Radiographic diagnosis of Pneumoconioses by AIR Pneumo-trained physicians: Comparison with low-dose thin-slice computed tomography. J Occup Health. 2020;62(1):e12141. https://doi.org/10.1002/1348-9585.12141

29. Bégin R, Ostiguy G, Filion R, Groleau S. Recent advances in the early diagnosis of asbestosis. Semin Roentgenol. 1992;27(2):121-139. https://doi.org/10.1016/0037-198X(92)90054-6
30. Akira M, Yamamoto S, Inoue Y, Sakatani M. High-resolution CT of asbestosis and idiopathic pulmonary fibrosis. AJR Am J Roentgenol. 2003;181(1):163-169. https://doi.org/10.2214/ajr.181.1.1810163
31. Arakawa H, Kishimoto T, Ashizawa K, Kato K, Okamoto K, Honma K, et al. Asbestosis and other pulmonary fibrosis in asbestos-exposed workers: high-resolution CT features with pathological correlations. Eur Radiol. 2016;26(5):1485-1492. https://doi.org/10.1007/s00330-015-3973-z
32. Markowitz SB. Lung Cancer Screening in Asbestos-Exposed Populations. Int J Environ Res Public Health. 2022;19(5):2688. https://doi.org/10.3390/ijerph19052688
33. Miller A, Widman SA, Miller JA, Manowitz A, Markowitz SB. Comparison of x-ray films and low-dose computed tomographic scans: demonstration of asbestos-related changes in 2760 nuclear weapons workers screened for lung cancer. J Occup Environ Med. 2013;55(7):741-745. https://doi.org/10.1097/JOM.0b013e3182954067
34. Nair A, Hansell DM. High-resolution computed tomography features of smoking-related interstitial lung disease. Semin Ultrasound CT MR. 2014;35(1):59-71. https://doi.org/10.1053/j.sult.2013.10.005
35. Vehmas T, Kivisaari L, Huuskonen MS, Jaakkola MS. Scoring CT/HRCT findings among asbestos-exposed workers: effects of patient's age, body mass index and common laboratory test results. Eur Radiol. 2005;15(2):213-219. https://doi.org/10.1007/s00330-004-2552-5
36. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(5):e44-e68. https://doi.org/10.1164/rccm.201807-1255ST
37. Brims FJH, Kong K, Harris EJA, Sodhi-Berry N, Reid A, Murray CP, et al. Pleural Plaques and the Risk of Lung Cancer in Asbestos-exposed Subjects. Am J Respir Crit Care Med. 2020;201(1):57-62. https://doi.org/10.1164/rccm.201901-0096OC
38. Remy-Jardin M, Sobaszek A, Duhamel A, Mastora I, Zanetti C, Remy J. Asbestos-related pleuropulmonary diseases: evaluation with low-dose four-detector row spiral CT. Radiology. 2004;233(1):182-190. https://doi.org/10.1148/radiol.2331031133
39. Carrillo MC, Alturkistany S, Roberts H, Nguyen E, Chung TB, Paul N, et al. Low-dose computed tomography (LDCT) in workers previously exposed to asbestos: detection of parenchymal lung disease. J Comput Assist Tomogr. 2013;37(4):626-630. https://doi.org/10.1097/RCT.0b013e31828e1b8e
40. Harris EJA, Lim KP, Moodley Y, Adler B, Sodhi-Berry N, Reid A, et al. Low dose CT detected interstitial lung abnormalities in a population with low asbestos exposure. Am J Ind Med. 2021;64(7):567-575. https://doi.org/10.1002/ajim.23251
41. Zhu X, Yu J, Huang Z. Low-dose chest CT: optimizing radiation protection for patients. AJR Am J Roentgenol. 2004;183(3):809-816. https://doi.org/10.2214/ajr.183.3.1830809
42. Ludes C, Schaal M, Labani A, Jeung MY, Roy C, Ohana M. Ultra-low dose chest CT: The end of chest radiograph? [Article in French]. Presse Med. 2016;45(3):291-301. https://doi.org/10.1016/j.lpm.2015.12.003
43. Neroladaki A, Botsikas D, Boudabbous S, Becker CD, Montet X. Computed tomography of the chest with model-based iterative reconstruction using a radiation exposure similar to chest X-ray examination: preliminary observations. Eur Radiol. 2013;23(2):360-366. https://doi.org/10.1007/s00330-012-2627-7
44. O'Brien C, Kok HK, Kelly B, Kumamaru K, Sahadevan A, Lane S, et al. To investigate dose reduction and comparability of standard dose CT vs Ultra low dose CT in evaluating pulmonary emphysema. Clin Imaging. 2019;53:115-119. https://doi.org/10.1016/j.clinimag.2018.10.012
45. Markowitz SB, Manowitz A, Miller JA, Frederick JS, Onyekelu-Eze AC, Widman SA, et al. Yield of Low-Dose Computerized Tomography Screening for Lung Cancer in High-Risk Workers: The Case of 7189 US Nuclear Weapons Workers. Am J Public Health. 2018;108(10):1296-1302. https://doi.org/10.2105/AJPH.2018.304518
46. Radiological Society of North America (RSNA) [homepage on the Internet]. Oakbrook, IL: RSNA; c2022 [updated 2022 Nov 1; cited 2024 Apr 25]. Effective radiation dose in adults Available from: https://wwwradiologyinfoorg/en/info/safety-xray
47. Brenner DJ. Radiation risks potentially associated with low-dose CT screening of adult smokers for lung cancer. Radiology. 2004;231(2):440-445. https://doi.org/10.1148/radiol.2312030880
48. Jonas DE, Reuland DS, Reddy SM, Nagle M, Clark SD, Weber RP, et al. Screening for Lung Cancer With Low-Dose Computed Tomography: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2021;325(10):971-987. https://doi.org/10.1001/jama.2021.0377
49. U.S. Preventive Services Task Force (USPSTF) [homepage on the Internet]. Rockville, MD: USPSTF; c2021 [updated 2021 Mar 9; cited 2024 Apr 1]. Final Recommendation Statement. Lung Cancer: Screening. Available from: https://www.uspreventiveservicestaskforce.org/uspstf/document/RecommendationStatementFinal/lung-cancer-screening
50. Wolf AMD, Oeffinger KC, Shih TY-C, Walter LC, Church TR, Fontham ETH, et al. Screening for lung cancer: 2023 guideline update from the American Cancer Society. CA Cancer J Clin. 2024;74(1):50-81. https://doi.org/10.3322/caac.21811
51. Baldwin D, O'Dowd E, Tietzova I, Kerpel-Fronius A, Heuvelmans M, Snoeckx A, et al. Developing a pan-European technical standard for a comprehensive high-quality lung cancer computed tomography screening programme: an ERS technical standard. European Respiratory Journal. 2023;61(6):2300128. https://doi.org/10.1183/13993003.00128-2023
52. Pereira LFF, Santos RSD, Bonomi DO, Franceschini J, Santoro IL, Miotto A, et al. Lung cancer screening in Brazil: recommendations from the Brazilian Society of Thoracic Surgery, Brazilian Thoracic Association, and Brazilian College of Radiology and Diagnostic Imaging. J Bras Pneumol. 2024;50(1):e20230233. https://doi.org/10.36416/1806-3756/e20230233
53. National Lung Screening Trial Research Team; Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409. https://doi.org/10.1056/NEJMoa1102873
54. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. 2020;382(6):503-513. https://doi.org/10.1056/NEJMoa1911793
55. Cassidy A, Myles JP, van Tongeren M, et al. The LLP risk model: an individual risk prediction model for lung cancer. Br J Cancer. 2008;98(2):270-276. https://doi.org/10.1038/sj.bjc.6604158
56. Field JK, Vulkan D, Davies MPA, Duffy SW, Gabe R. Liverpool Lung Project lung cancer risk stratification model: calibration and prospective validation. Thorax. 2021;76(2):161-168. https://doi.org/10.1136/thoraxjnl-2020-215158
57. Liao W, Coupland CAC, Burchardt J, Baldwin DR; DART initiative; Gleeson FV, et al. Predicting the future risk of lung cancer: development, and internal and external validation of the CanPredict (lung) model in 19•67 million people and evaluation of model performance against seven other risk prediction models. Lancet Respir Med. 2023;11(8):685-697. https://doi.org/10.1016/S2213-2600(23)00050-4
58. Akira M, Morinaga K. The comparison of high-resolution computed tomography findings in asbestosis and idiopathic pulmonary fibrosis. Am J Ind Med. 2016;59(4):301-306. https://doi.org/10.1002/ajim.22573
59. Masanori A. Imaging diagnosis of classical and new pneumoconiosis: predominant reticular HRCT pattern. Insights Imaging. 2021;12(1):33. https://doi.org/10.1186/s13244-021-00966-y
60. Mazzone PJ, Silvestri GA, Souter LH, Caverly TJ, Kanne JP, Katki HA, et al. Screening for Lung Cancer: CHEST Guideline and Expert Panel Report. Chest. 2021;160(5):e427-e494. https://doi.org/10.1016/j.chest.2021.06.063
61. American College of Radiology (ACR) [homepage on the Internet]. Philadelphia, PA: ACR; c2022 [cited 2024 Apr 1]. Lung-RADS® v2022. [Adobe Acrobat document, 2p.]. Available from: https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/Lung-RADS-2022.pdf

Talc slurry versus thoracoscopic talc insufflation for malignant pleural effusion: a systematic review and meta-analysis

Anna Luíza Soares de Oliveira Rodrigues[1], Maria Eduarda Cavalcanti Souza[2], Francisco Cezar Aquino de Moraes[3], David Paes de Lima[4], Rafael Lucas Costa de Carvalho[4]

1. Centro Universitário de João Pessoa, João Pessoa (PB) Brasil.
2. Universidade de Pernambuco, Recife (PE) Brasil.
3. Universidade Federal do Pará, Belém (PA) Brasil.
4. Divisão de Cirurgia Torácica, Instituto do Coração - InCor - Universidade de São Paulo (SP) São Paulo.

Submitted: 17 April 2024.
Accepted: 13 May 2024.

ABSTRACT

Objective: Talc pleurodesis is a widely used treatment option for malignant pleural effusion (MPE). However, the optimal form of administration remains controversial. Thus, we performed a systematic review and meta-analysis to assess the effectiveness of talc slurry (TS) in comparison with thoracoscopic talc insufflation/poudrage (TTI) for MPE treatment. **Methods:** We searched PubMed, EMBASE, and Cochrane Library databases for studies that compared TS with TTI in patients with MPE. We used a random-effects model with a 95% CI to pool the data. Heterogeneity was assessed with I^2 statistics. **Results:** We included eight studies involving 1,163 patients, 584 of whom (50.21%) underwent TS. Pleurodesis failure rates were similar between the procedures (OR = 1.07; 95% CI: 0.56-2.06; p = 0.83; I^2 = 62%); and 68% of patients (95% CI: 0.31-1.47; p = 0.33; I^2 = 58%) had postoperative complications, which were lower in patients in the TS group than in the TTI group. In a subgroup analysis considering only randomized clinical trials, the failure rate was significantly lower in the TS treatment group (OR = 0.62; 95% CI: 0.42-0.90; p = 0.01; I^2 = 0%). Similarly, dyspnea was less common in the TS group (OR = 0.74; 95% CI: 0.41-1.34; p = 0.32; I^2 = 55%). Adverse effects were reported in 86 patients, and no significant difference was seen between the TS and TTI groups: empyema (OR = 1.43; 95% CI: 0.36-5.64; p = 0.86; I^2 = 0%), pain (OR = 1.22 (95% CI: 0.67-2.21; p = 0.51; I^2 = 38%), and pneumonia (OR = 1.15; 95% CI: 0.30-4.46; p = 0.86; I^2 = 27%). **Conclusions:** Our findings suggest that TS is an effective treatment for MPE, with no significant increase in adverse events. Results suggest equivalent efficacy and safety for both procedures.

Keywords: Talc; Pleurodesis; Pleural effusion, malignant.

INTRODUCTION

Malignant pleural effusion (MPE) is characterized by the presence of fluid and malignant cells in the pleural cavity.[1,2] MPEs affect approximately up to 15% of all patients with cancer. Meanwhile, lung cancer and breast cancer account for 50-65% of MPEs,[2] and more than 90% of patients with mesothelioma present with MPE.[3,4] The incidence of MPE is likely to rise as the global incidence of cancer increases and overall survival improves.[5] Regardless of the moment of presentation, the presence of MPE usually portends a poor prognosis.[5,6] The clinical manifestation spectrum varies according to the severity of the effusion as well as with individual characteristics.[7,8] The majority of patients with MPE are symptomatic, with debilitating symptoms, such as breathlessness, which is the most common symptom, or chest pain.[4] In the presence of MPE, an intervention is required along with cancer treatment.[9]

Treatment options are determined by the patient's clinical status, the type of tumor itself, the response to systemic therapy, and the degree of lung re-expansion following pleural fluid evacuation. The more traditional and established approach to MPE is pleurodesis.[10-13] Pleurodesis is a procedure that obliterates the pleural space to prevent recurrent pleural effusion. Once the pleural cavity is evacuated, further fluid formation is commonly prevented by stimulating a local inflammatory response, resulting in fibrosis and adhesion, by either instilling a chemical irritant (chemical pleurodesis) or performing mechanical abrasion. According to international guidelines, talc is the preferred agent used for chemical pleurodesis.[6] The primary perceived benefit of this approach is that a single intervention can lead to long-term fluid prevention, and the estimated success rate ranges from 80% to 100%.[12,13]

Talc slurry (TS) via chest tube is the current standard treatment approach for pleurodesis. Usually, TS requires the insertion of a chest tube to administer the chemical substance. An alternative method, known as thoracoscopic talc poudrage or insufflation (TTI), is the application of sterile talc powder under direct visualization during thoracoscopy.[13] Evidence of high quality for the optimal treatment of symptomatic MPE suggests that both talc pleurodesis procedures (via slurry

Correspondence to:
Anna Luíza Soares de Oliveira Rodrigues. Centro Universitário de João Pessoa, Rodovia BR-230, km 22, CEP 58053-000, João Pessoa, PB, Brasil.
Tel.: 55 83 3003-1189. E-mail: annaluizasor@gmail.com
Financial support: None.

◄ Voltar ao sumário
ISSN 1806-3756

or poudrage) are highly effective and significantly improve symptoms.[4] Meanwhile, other studies reported fewer recurrence rates with TTI.[13] However, there is still uncertainty regarding whether TTI is more beneficial when compared with TS. Therefore, we conducted a systematic review and meta-analysis aiming to compare TTI with TS regarding pleurodesis in patients with MPE.

METHODS

Protocol and registration

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42023414497.

Eligibility criteria

Studies that met the following eligibility criteria were included: (1) randomized controlled trials (RCTs) or observational studies; (2) comparing treatment via TS with TTI treatment; (3) in individuals with MPE. We excluded studies (1) with overlapping populations; (2) not reporting outcomes of interest; or (3) unpublished results.

Search strategy and data extraction

PubMed, Cochrane Library, and EMBASE were systematically searched on May 22, 2023. The search strategy included the terms chemical pleurodesis, pleurodesis, talc pleurodesis, surgical pleurodesis, thoracoscopic pleurodesis, thoracoscopic talc pleurodesis, thoracoscopic poudrage, thoracoscopic talc poudrage, talc insufflation, thoracoscopic talc insufflation, medical thoracoscopy, talc poudrage, bedside pleurodesis, medical pleurodesis, talc slurry, tube thoracostomy, chest tube talc slurry, chest tube, malignant pleural effusion, oncological patients. In addition, reference lists of included articles and previous systematic reviews were evaluated for additional eligible studies, and an alert was set for notifications in each database in case a new study correlated to the consultation carried out was eventually published.

All articles obtained from the initial literature search were entered into the reference management software Zotero, version 6 (Digital Scholar, Vienna, VA, USA). Duplicate articles were removed using both automated and manual methods. Subsequently, two authors (ALSOR and MECS) independently analyzed the titles and abstracts for inclusion criteria. Disagreements were resolved by consensus between the two authors and the senior author.

The following baseline characteristics were extracted: (1) ClinicalTrials.gov Identifier and study design; (2) number of patients allocated to each arm; (3) regimen details in experimental and control arms; and (4) main characteristics of patients. The same two authors collected the pre-specified baseline characteristics and outcome data.

Endpoints and subgroup analysis

Outcomes of interest were as follows: (1) pleurodesis failure; (2) postoperative complications; (3) dyspnea; (4) respiratory complications; (5) empyema; (6) pain; (7) pneumonia; (8) postoperative death; (9) pulmonary edema; (10) reexpansion pulmonary edema; (11) fever; and (12) wound infection.

To minimize potential confounding factors due to selection bias or different prognostic factors, a post-hoc subgroup analysis including only RCTs was conducted. Studies reporting the failure rate of the procedure were included, and the criteria for its evaluation varied among the studies. Specifications of the criteria considered by each author are described in Table 1.

Risk of bias assessment

The quality assessment of each RCTs was carried out using the Cochrane Collaboration tool for assessing the risk of bias in randomized trials (RoB 2) and nonrandomized studies were assessed using the Risk of Bias in Nonrandomized studies of intervention (ROBINS I).[14,15] For each randomized trial, a risk of bias score was assigned, indicating whether it was at a high, low, or unclear risk across five domains: randomization process, deviations from intended interventions, missing outcomes, measurement of outcomes, and selection of reported results. To assess publication bias, funnel-plot analyses were employed.[16] In this assessment, each study was categorized as critical, serious, moderate, or low risk in the seven domains: confounding, selection, classification, deviations from intended interventions, missing data, and selection of reported results. Two authors (FCAM and MECS) independently conducted the assessment, and disagreements were resolved by consensus. To quantify publication bias, Begg and Mazumdar rank correlation and Egger's linear regression methods were used.

Statistical analysis

Binary endpoints were evaluated with hazard ratios (HRs) or odds ratios (ORs), with 95% CIs. The Cochran's Q-test and I^2 statistics were used to assess heterogeneity; p values > 0.10 and I^2 values > 25% were considered to indicate significance for heterogeneity.[16] We used DerSimonian and Laird random-effect models for all endpoints.[17,18] Statistical analyses were performed using R statistical software, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study selection and baseline characteristics

As illustrated in Figure 1, the initial search strategy yielded 709 articles, of which 244 were excluded after title and abstract review and removal of duplicate reports. The remaining were fully reviewed, and eight

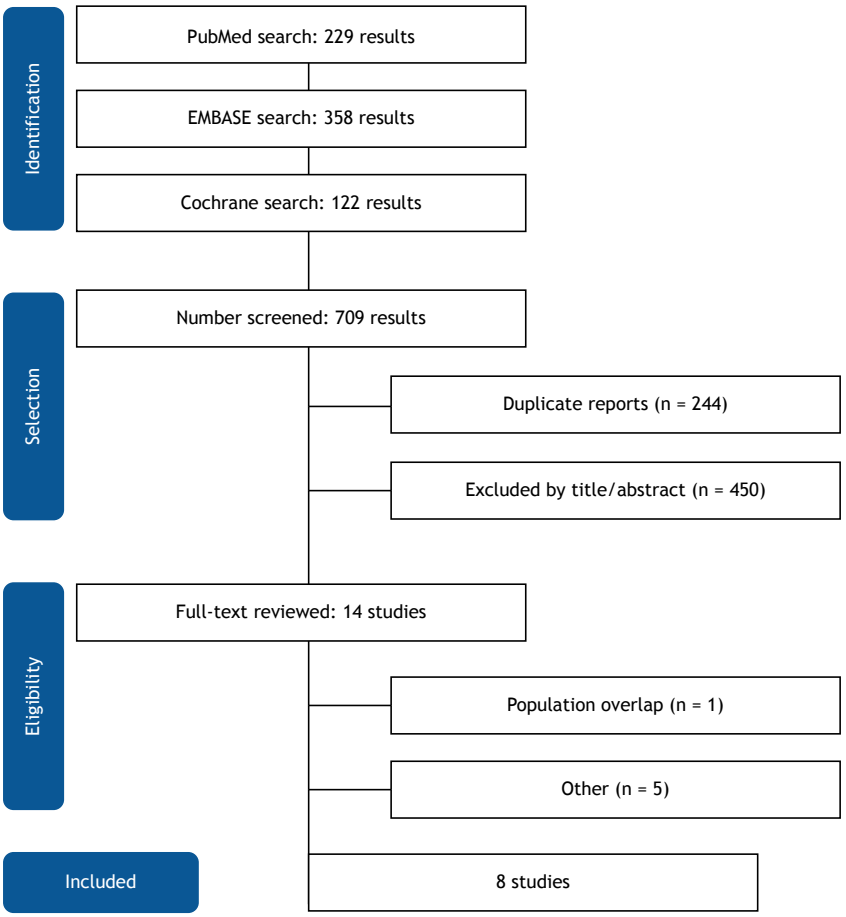

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram of study screening and selection.

studies were included in this meta-analysis.[19-25] The studies included involved 1,163 patients (Figure 1). Among them, 584 (50.21%) underwent TS treatment. Mean follow-up period ranged from 1 to 6 months. Among studies that reported the cancer type, the most prevalent types were lung (n = 410; 33.5%) and breast (n = 379; 31%) cancer, while other types accounted for 33.5%. Study and participant characteristics are summarized in Table 1. The definition of success varied across studies, and specific details regarding success criteria for each study can be found in Table S1 of the supplementary material, and the definition of failure can be found in Table S2.

Pooled analyses of all studies

Regarding pleurodesis failure rate, this analysis showed no significant difference between TS and TTI groups (OR = 1.07; 95% CI: 0.56-2.06; p = 0.83; I^2 = 62%; Figure 2). Likewise, there were no significant differences between the groups in terms of postoperative complications, post-operative death, and pulmonary edema (Table 2). Regarding other adverse events, there were no significant statistical differences between TS and TTI treatment in regard to pneumonia, empyema, dyspnea, pain, fever, reexpansion pulmonary edema, and wound infection (Table 2).

The rate of side effects was comparable in the TS and TTI treatment groups within the trials. Overall, fever was the most prevalent adverse effect, with 193 events (47.67% vs. 52.33%). When analyzing organism system disorders, 2 patients had a cerebrovascular event (100% vs. 0%) as the most frequent nervous disorder, 25 had dysrhythmia or arrhythmia (44% vs. 56%) as a cardiovascular disorder, 77 had pneumonia (38.96% vs. 61.04%) as a respiratory disorder, 4 had nausea or vomiting (50% vs. 50%) as a gastrointestinal disorder, and 18 had emphysema (27.78% vs. 72.22%) as the most prevalent tissue disorder. There were a total of 43 events leading to death (39.53% vs. 60.46%) and 158 post-operative deaths (46.84% vs. 53.16%). The results for adverse events are detailed in Table 2 and in the supplementary material (Figures S1-S10).

Subgroup analysis

In the analysis of only RCTs, which involved 661 patients, the failure rate was significantly lower in

Table 1. Design and characteristics of studies included in this meta-analysis.

Study	Design	Follow-up (median)	Participants IG/CG, n.	Male + female/ male, n.	Cancer type, n (%) IG (TS)	Cancer type, n (%) CG (TTI)	Successful pleurodesis in TS n/N, (%)	Successful pleurodesis in TTI n/N, (%)
Bhatnagar et al.[2]	RCT	1-6 months	164/166	181/149	Lung - 54 (33) Breast - 49 (30) Other* - 57 (34.76) Unknown - 4 (2)	Lung - 59 (36) Breast - 50 (30) Other* - 54 (32.53) Unknown - 3 (2)	121/159 (76.10)	125/161 (77.64)
Dresler et al.[21]	RCT	1-6 months	240/242	269/213	Lung - 13 (26.5) Breast - 9 (18.5) Mesothelioma - 8 (16.5) Other* - 8 (16.5) Unknown - 11 (22)	Lung - 1 (4.5) Mesothelioma - 16 (73) Other* - 4 (18.19) Unknown - 2 (9)	80 (77.67)	38/49 (78.00)
Terra et al.[24]	RCT	1-6 months followed by every 3 months or if symptoms arose	30/30	45/15	Lung - 6 (20) Breast - 19 (63.34) Other* - 4 (13.34) Unknown - 1 (3.34)	Lung - 11 (36.67) Breast - 15 (50) Other* - 3 (10) Unknown - 1 (3.34)	26/30 (86.6)	25/30 (83.3)
Yim et al.[25]	RCT	6 weeks from 1-4.5 months, then every 3 months	29/28	37/20	Lung - 15 (53.57) Breast - 9 (32.14) Gastrointestinal - 4 (14.29) Other* - 1 (3.57)	Lung - 18 (62.07) Breast - 6 (20.69) Gastrointestinal - 2 (6.90) Other* - 2 (6.90)	27/28 (96.48)	26/29 (89.65)
Alihodzic-Pasalic et al.[8]	Retrospective	2.6 months	30/30	16/44	N/A	N/A	13/24 (54.16)	14/16 (87.50)
Debeljak et al.[20]	Retrospective	1 month	49/22	N/A	Lung - 13 (26.5) Breast - 9 (18.5) Mesothelioma - 8 (16.5) Other* - 8 (16.5) Unknown - 11 (22)	Lung - 1 (4.5) Mesothelioma - 16 (73) Other* - 4 (18.19) Unknown - 2 (9)	38/41 (92.68)	17/21 (80.95)
Inoue et al.[22]	Prospective	1-6 months	49/8	39/18	Lung - 28 (49.12) Breast - 15 (26.32) Ovarian - 4 (7.02) Others* - 10 (17.54)		40/45 (88.89%)	8/8 (100.0)
Stefani et al.[23]	Prospective	1, 3, and 6 months; monthly for 3 months	37/72	58/51	Lung - 21 (56.76) Breast - 7 (18.92) Other* - 9 (24.32)	Lung - 28 (38.89) Breast - 21 (29.17) Other* - 23 (31.95)	23/37 (62.16)	59/72 (81.95)

IG: intervention group; CG: control group; TS: talc slurry; TTI: thoracoscopic talc insufflation; RCT: randomized controlled trial. *Other: mesothelioma, lower gastrointestinal tract, kidney, upper gastrointestinal tract, lymphoma, osteosarcoma (tibia), pancreatic adenocarcinoma, adenocarcinoma of unknown origin, genitourinary, gynecologic, sarcoma, head and neck, and melanoma.

the TS treatment group (OR = 0.62; 95% CI: 0.42-0.90; p = 0.01; I^2 = 0%; Figure 2). Additionally, dyspnea was less common in the TS group (OR = 0.74; 95% CI: 0.41-1.34; p = 0.32; I^2 = 55%; Table 2). Furthermore, 86 patients reported other adverse events, but there were no significant differences between the TS and TTI groups in terms of empyema, pain, and pneumonia (Table 2).

Quality assessment

Our meta-analysis included 4 RCTs and 4 observational studies. The assessment of the RCTs demonstrated a low risk across all studies (Figures 3A and 3B). Among the included nonrandomized studies, two presented one domain with a moderate risk of bias, while other domains were labeled as with a low risk. The funnel plot analysis showed an asymmetry in the distribution of studies according to the failure rate (Figure 3C), although no significant publication bias was detected by Egger's (p = 0.1471) and Begg and Mazumdar tests (p = 0.3272).

DISCUSSION

In this systematic review and meta-analysis of eight studies including 1,163 patients, we compared TS pleurodesis with TTI in patients with MPE. The main finding from the analysis is that there was no significant difference between treatments regarding failure rates when analyzing randomized and nonrandomized studies. Similarly, Bhatnagar et al.[19] and Dresler et al.[21] concluded that both approaches are effective. However, when pooling subgroup data only from RCTs to minimize selection bias, the results indicated that TS was associated with a lower failure rate.

In clinical practice, the treatment of choice is based on several factors, including whether a chest tube has already been inserted; the infrastructure of the

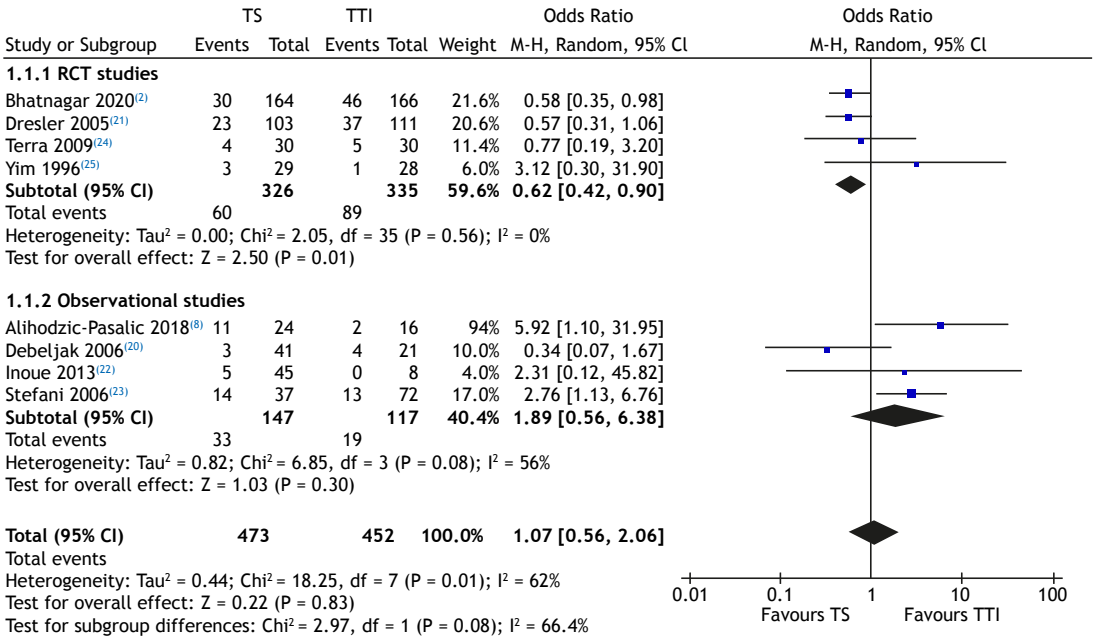

Figure 2. Treatment failure rate (pleurodesis) using talc slurry versus thoracoscopic talc insufflation, also known as thoracoscopic talc poudrage, in patients with malignant pleural effusion.

Table 2. Statistical analysis of the adverse events of interest.

Adverse events	Study, n	Patients, n	OR	95% CI	p	Heterogeneity			
						T^2	df	p	I^2 (%)
Dyspnea	3	809	0.74	0.41-1.34	0.32	0.15	2	0.11	55
Empyema	4	659	1.43	0.36-5.64	0.97	0.00	3	0.86	0
Fever	4	445	1.13	0.73-1.75	0.59	0.00	3	0.45	0
Pain	4	929	1.22	0.67-2.21	0.18	0.14	3	0.18	38
Pneumonia	3	499	1.15	0.30-4.46	0.84	0.48	2	0.26	27
Postoperative complications	3	461	0.68	0.31-1.47	0.33	0.28	2	0.09	58
Postoperative death	7	1,103	0.87	0.60-1.27	0.48	0.00	2	0.62	0
Pulmonary edema	4	297	0.35	0.08-1.63	0.18	0.00	3	0.84	0
Reexpansion pulmonary edema	3	226	1.51	0.42-5.39	0.52	0.00	2	0.86	0
Wound infection	4	440	1.29	0.26-6.48	0.76	0.00	2	0.93	0

df: degrees of freedom.

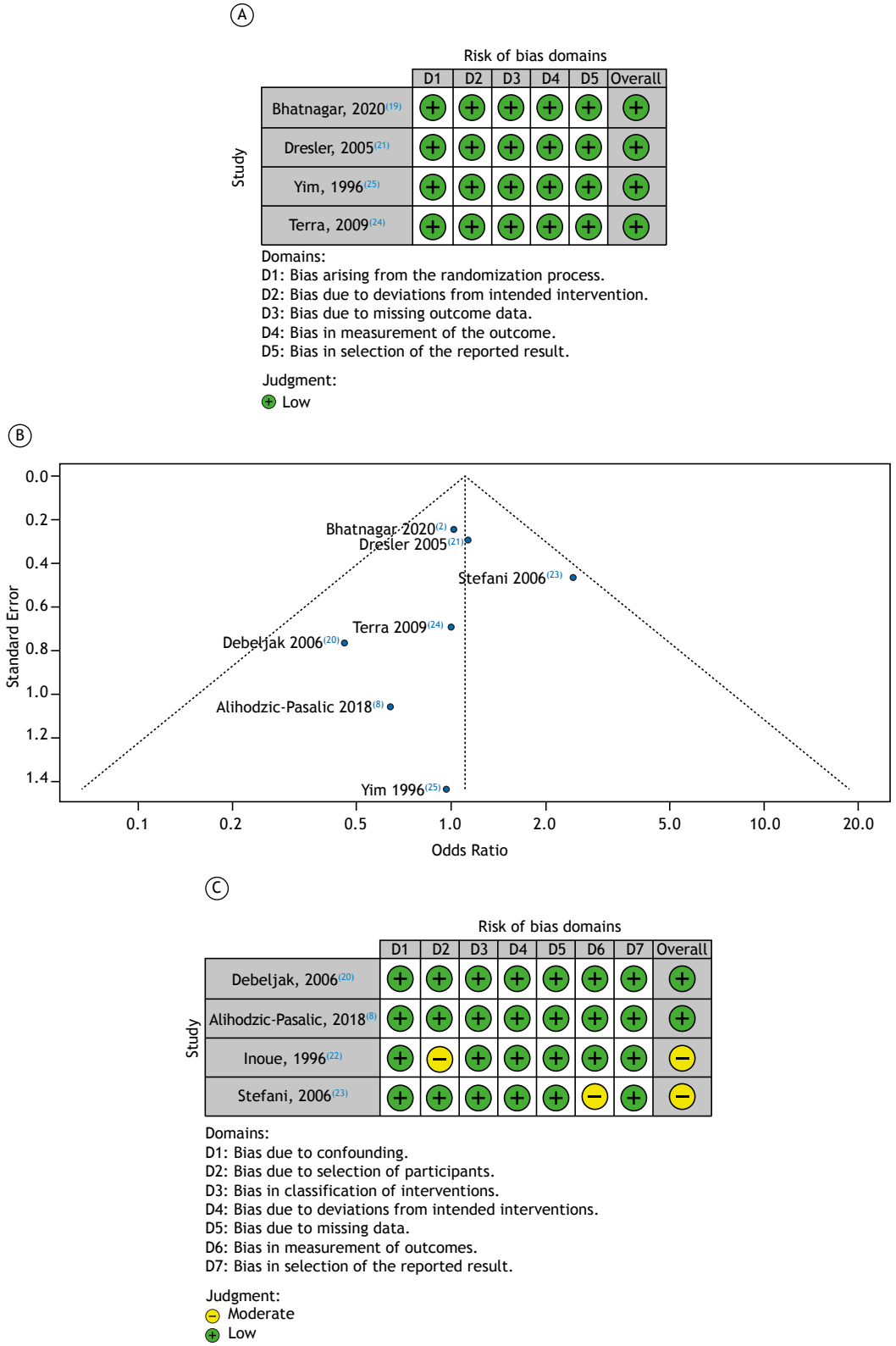

Figure 3. In A, critical appraisal of randomized controlled trials according to the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (RoB 2). In B, results of the Risk Of Bias in Nonrandomised Studies of Interventions (ROBINS-I) regarding the observational studies included in the analysis. In C, funnel plot analysis of treatment failure rate (pleurodesis) using talc slurry versus thoracoscopic talc insufflation in patients with malignant pleural effusion. There is no evidence of publication bias.

local facility where the treatment will take place; staff experience and training; and patient phenotype regarding fluid production and accessibility.[4,5,8,26] Only one observational study explained the characteristics of the patients that were used in order to select the groups.[8] Alihodzic-Pasalic et al. selected those patients at high risk for general anesthesia into the TS group.[8

The benefits of performing thoracoscopy are that it allows the surgeon to examine the pleural cavity and perform a pleural biopsy or adhesiolysis,[9] and it is most often the preferred choice of physicians.[27-30] Additionally, TS offers additional advantages, such as the possibility of administration in patients who are not candidates for surgery, but still allows diagnostic procedures such as pleural biopsy needle biopsy. This flexibility is crucial, especially in cases in which surgery is not a viable option, but therapeutic or diagnostic interventions in the pleural cavity are necessary.[6,7] However, previous observational studies addressing the ideal method for administering talc diverged in their results and were considered inconclusive, resulting in inconsistency in both clinical practice and recommendations.[19,27]

This meta-analysis showed lower failure rates in the TS group, when compared with the TTI group, when only RCT data were pooled, which supports that talc pleurodesis performed at the bedside through a chest tube is more effective than TTI. Our results differ from previous meta-analyses. Mummadi et al. suggest that there is no difference between the techniques.[27] Beltsios et al. compared talc pleurodesis with other approaches, and a statistically significant superiority was seen when compared with control methods, especially when compared with bleomycin.[29]

Adverse effects may occur due to inflammation of the pleura by the agent chosen for pleurodesis. In our analysis, there was no statistical difference in the occurrence of adverse effects, such as dyspnea, respiratory complications, empyema, pain, pneumonia, postoperative death, pulmonary edema, reexpansion pulmonary edema, fever, and wound infection. Likewise, the occurrence of postoperative complications was statistically similar in both treatment groups.

This study has some limitations. Firstly, we included both RCT and observational study data, which can introduce bias. However, the implementation of a subgroup analysis of only RCTs was possible. This approach was aimed at mitigating potential confounding factors. Secondly, different criteria were used for evaluating success and failure rates among the studies. Thirdly, the type of cancer varied among the study populations, and, in some studies, certain details of population characteristics, such as the size of the effusion, were not provided. Fourth, not all observational studies characterized the conditions of patients and whether these were choice points for selection between intervention and control groups. Although the heterogeneity was high for the main outcome in the analysis of all included studies, that was not significant, and when pooling data only from RCTs, the heterogeneity was low.

FINAL CONSIDERATIONS

In this meta-analysis, the use of TS for MPE treatment demonstrated comparable failure rates to the use of TTI without a significant increase in adverse events. These results suggest that both interventions are equally effective and safe for managing MPE, aligning with the overall findings of the primary analysis.

AUTHOR CONTRIBUTION

ALSOR and MECS: project conception, material preparation, and data collection and analysis. ALSOR, MECS, and FCAM: figures and tables. All authors contributed to study conception and design, drafting, editing, and reviewing of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Desai NR, Lee HJ. Diagnosis and management of malignant pleural effusions: state of the art in 2017. J Thorac Dis. 2017;9(Suppl 10):S1111-S1122. https://doi.org/10.21037/jtd.2017.07.79
2. Bhatnagar R, Laskawiec-Szkonter M, Piotrowska HE, Kahan BC, Hooper CE, Davies HE, et al. Evaluating the efficacy of thoracoscopy and talc poudrage versus pleurodesis using talc slurry (TAPPS trial): protocol of an open-label randomised controlled trial. BMJ Open. 2014;4(11):e007045. https://doi.org/10.1136/bmjopen-2014-007045
3. Psallidas I, Kalomenidis I, Porcel JM, Robinson BW, Stathopoulos GT. Malignant pleural effusion: from bench to bedside. Eur Respir Rev. 2016 Jun;25(140):189-98. https://doi.org/10.1183/16000617.0019-2016
4. Bibby AC, Dorn P, Psallidas I, Porcel JM, Janssen J, Froudarakis M, et al. ERS/EACTS statement on the management of malignant pleural effusions. Eur Respir J. 2018;52(1):1800349. https://doi.org/10.1183/13993003.00349-2018
5. Feller-Kopman DJ, Reddy CB, DeCamp MM, Diekemper RL, Gould MK, Henry T, et al. Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(7):839-849. https://doi.org/10.1164/rccm.201807-1415ST
6. Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ; BTS Pleural Disease Guideline Group. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii32-ii40. https://doi.org/10.1136/thx.2010.136994
7. Skok K, Hladnik G, Grm A, Crnjac A. Malignant Pleural Effusion and Its Current Management: A Review. Medicina (Kaunas). 2019;55(8):490. https://doi.org/10.3390/medicina55080490
8. Alihodzic-Pasalic A, Maric V, Hadzismailovic A, Pilav A, Grbic K. Comparison of Efficiency of Pleurodesis Between Video Assisted Thoracoscopic Surgery (VATS) and Standard Thoracostomy. Acta Inform Med. 2018;26(3):185-189. https://doi.org/10.5455/aim.2018.26.185-189
9. Rahman NM, Ali NJ, Brown G, Chapman SJ, Davies RJ, Downer NJ, et al. Local anaesthetic thoracoscopy: British Thoracic Society Pleural

Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii54-ii60. https://doi.org/10.1136/thx.2010.137018

10. Basso SM, Mazza F, Marzano B, Santeufemia DA, Chiara GB, Lumachi F. Improved quality of life in patients with malignant pleural effusion following videoassisted thoracoscopic talc pleurodesis. Preliminary results. Anticancer Res. 2012;32(11):5131-5134.
11. Davies HE, Lee YC. Management of malignant pleural effusions: questions that need answers. Curr Opin Pulm Med. 2013;19(4):374-379. https://doi.org/10.1097/MCP.0b013e3283615b67
12. Lumachi F, Mazza F, Ermani M, Chiara GB, Basso SM. Talc pleurodesis as surgical palliation of patients with malignant pleural effusion. Analysis of factors affecting survival. Anticancer Res. 2012;32(11):5071-5074.
13. Heffner JE, Klein JS. Recent advances in the diagnosis and management of malignant pleural effusions [published correction appears in Mayo Clin Proc. 2009 Sep;84(9):847]. Mayo Clin Proc. 2008;83(2):235-250. https://doi.org/10.1016/S0025-6196(11)60848-3
14. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
15. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. https://doi.org/10.1136/bmj.i4919
16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-634. https://doi.org/10.1136/bmj.315.7109.629
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-188. https://doi.org/10.1016/0197-2456(86)90046-2
18. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol. 2014;14:25. https://doi.org/10.1186/1471-2288-14-25
19. Bhatnagar R, Piotrowska HEG, Laskawiec-Szkonter M, Kahan BC, Luengo-Fernandez R, Pepperell JCT, et al. Effect of Thoracoscopic Talc Poudrage vs Talc Slurry via Chest Tube on Pleurodesis Failure Rate Among Patients With Malignant Pleural Effusions: A Randomized Clinical Trial. JAMA. 2020;323(1):60-69. https://doi.org/10.1001/jama.2019.19997
20. Debeljak A, Kecelj P, Triller N, et al. Talc pleurodesis: comparison of talc slurry instillation with thoracoscopic talc insufflation for malignant pleural effusions. J BUON. 2006;11(4):463-467.
21. Dresler CM, Olak J, Herndon JE 2nd, Richards WG, Scalzetti E, Fleishman SB, et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. Chest. 2005;127(3):909-915. https://doi.org/10.1378/chest.127.3.909
22. Inoue T, Ishida A, Nakamura M, Nishine H, Mineshita M, Miyazawa T. Talc pleurodesis for the management of malignant pleural effusions in Japan. Intern Med. 2013;52(11):1173-1176. https://doi.org/10.2169/internalmedicine.52.9281
23. Stefani A, Natali P, Casali C, Morandi U. Talc poudrage versus talc slurry in the treatment of malignant pleural effusion. A prospective comparative study. Eur J Cardiothorac Surg. 2006;30(6):827-832 https://doi.org/10.1016/j.ejcts.2006.10.002
24. Terra RM, Junqueira JJM, Teixeira LR, Vargas FS, Pêgo-Fernandes PM, Jatene FB. Is full postpleurodesis lung expansion a determinant of a successful outcome after talc pleurodesis?. Chest. 2009;136(2):361-368. https://doi.org/10.1378/chest.08-2448
25. Yim AP, Chan AT, Lee TW, Wan IY, Ho JK. Thoracoscopic talc insufflation versus talc slurry for symptomatic malignant pleural effusion. Ann Thorac Surg. 1996;62(6):1655-1658. https://doi.org/10.1016/S0003-4975(96)00808-9
26. Davies HE, Mishra EK, Kahan BC, Wrightson JM, Stanton AE, Guhan A, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA. 2012;307(22):2383-2389. https://doi.org/10.1001/jama.2012.5535
27. Mummadi S, Kumbam A, Hahn PY. Malignant pleural effusions and the role of talc poudrage and talc slurry: a systematic review and meta-analysis. F1000Res. 2014;3:254. https://doi.org/10.12688/f1000research.5538.1
28. Light RW. Counterpoint: should thoracoscopic talc pleurodesis be the first choice management for malignant pleural effusion? No. Chest. 2012;142(1):17-19. https://doi.org/10.1378/chest.12-1087
29. Beltsios ET, Mavrovounis G, Adamou A, Panagiotopoulos N. Talc pleurodesis in malignant pleural effusion: a systematic review and meta-analysis. Gen Thorac Cardiovasc Surg. 2021;69(5):832-842. https://doi.org/10.1007/s11748-020-01549-2
30. Lee P. Point: Should thoracoscopic talc pleurodesis be the first choice management for malignant effusion? Yes. Chest. 2012;142(1):15-17. https://doi.org/10.1378/chest.12-1085

Respiratory amyloidosis: a case series from a Brazilian referral center

Philippe de Figueiredo Braga Colares[1,2], Alfredo Nicodemos Cruz Santana[3], Rodrigo Abensur Athanazio[1], Ronaldo Adib Kairalla[1], Bruno Guedes Baldi[1]

TO THE EDITOR:

Amyloidosis is characterized by abnormal extracellular protein aggregation and deposition, which may occur associated with inflammatory, hereditary, or neoplastic conditions and may involve a single organ or be multisystemic.[1-3] Consequently, these patients may present with various clinical manifestations involving different organs. The International Classification of Amyloidosis[4] recognizes 30 types of human amyloids and their precursors. Amyloidosis can be classified according to the type of amyloid, extent (local or systemic), nature of the disease (acquired or inherited), and organs involved.

Amyloidosis occurs in approximately 60% of patients with immunoglobulin light-chain amyloidosis (AL), 10% of those with serum amyloid A amyloidosis (AA) due to chronic inflammatory diseases, 10% of those with transthyretin amyloidosis (ATTR) from variations (mutations) in the transthyretin gene (mut-ATTR), 8% of those with wild-type ATTR (wt-ATTR) amyloidosis, and 10% of those with localized amyloidosis.[3-5] Histologically, amyloid deposits appear as apple-green birefringence under polarized light with Congo red dye staining.[1-3]

Although the actual incidence of amyloidosis is unclear, it is estimated to be 10-14 cases per million person-years.[6] Based on histopathological studies, the prevalence of pulmonary deposition in AL patients ranges from 36% to 90%.[3]

Respiratory amyloidosis may be localized or be part of systemic amyloidosis, and it may be categorized as tracheobronchial, nodular, or interstitial.[1-3,5] Furthermore, there may be mediastinal or hilar lymphadenopathy and pleural effusion. Cystic lung disease associated with pulmonary amyloidosis is another uncommon presentation that has been described to be associated with collagen vascular diseases, mainly Sjögren's syndrome and lymphoproliferative disease.[7] Factors potentially related to the pattern of pulmonary deposition in amyloidosis remain unclear.

This retrospective study aimed to describe all patients with respiratory amyloidosis who were followed at the Pulmonary Division of the University of Sao Paulo, located in the city of São Paulo, Brazil, between 2010 and 2022.[1-3] Data were collected by reviewing the medical records of patients. We evaluated demographic and clinical characteristics, comorbidities, laboratory examinations, pulmonary function tests, imaging records, histopathological characteristics, treatments, and outcomes, including survival and complications. The study protocol was approved by the local research ethics committee (CAAE no. 76830724.9.0000.0068).

Pulmonary function tests (PFTs) were performed with a calibrated pneumotachograph (Koko PFT; nSpire Health Inc., Longmont, CO, USA). The following variables were collected: FEV_1, FVC, FEV_1/FVC ratio, RV, TLC, RV/TLC ratio, and DL_{CO}. Predicted values were derived from a Brazilian population.[8] We also evaluated pulse oximetry at room air.

HRCT was performed in all patients, and results were classified into three patterns: nodular pulmonary, diffuse alveolar-septal, or tracheobronchial amyloidosis. All tissue biopsies were reviewed by pulmonary pathologists at the University of São Paulo. Congo red dye stained samples under polarized light showing apple-green birefringence is the gold standard for the diagnosis of amyloidosis.[1-3] Tissue samples were obtained through bronchoscopy (n = 10), surgical biopsy (n = 5), or transthoracic biopsy (n = 5), depending on the lung pattern, after multidisciplinary discussion.

Continuous variables with normal distribution were expressed as means and standard deviations. Categorical variables were described as absolute and relative frequencies. One-way ANOVA was used to compare functional data at diagnosis with the latest available functional data, and the Tukey's test was used when multiple comparisons were necessary. Statistical significance was set at $p < 0.05$. Survival was estimated using the Kaplan-Meier method. Data were analyzed using the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA).

Twenty patients with respiratory amyloidosis were assessed and diagnosed as having tracheobronchial amyloidosis, in 9; nodular amyloidosis, in 8; and amyloidosis with interstitial patterns, in 3. Patient characteristics are presented in Table 1. The mean age at diagnosis was 56 years, and patients with interstitial patterns were younger; 55% of the patients were women, and dyspnea was the most common symptom (80%). PFTs were available for 12/20 of the patients (60%): 6 patients (30%) presented with an obstructive pattern, 2 (10%) showed a restrictive pattern, and 4 (20%) had normal PFTs.

By definition, systemic amyloidosis is characterized by deposits of AL, AA, ATTR, and mut-ATTR proteins.[1-5] Considering only the involvement of multiple organs, without immunohistochemistry confirmation, 1 patient had cutaneous involvement and another 1 had renal involvement. Hematological disease and Sjögren's

1. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Hospital de Base de São José do Rio Preto, Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto (SP) Brasil.
3. Hospital Regional da Asa Norte – HRAN – Curso de Medicina e Enfermagem, Escola Superior de Ciências da Saúde, Brasília (DF) Brasil.

◄ Voltar ao sumário
ISSN 1806-3756

syndrome were present in 15% of the patients. Four patients with tracheobronchial amyloidosis underwent an endoscopic procedure, with endobronchial dilation or placement of a prosthesis (tracheostomy or T-tube). One patient with interstitial amyloidosis underwent kidney transplantation. The median survival time was 6 ± 5 years (range: 0.5-19; p = 0.209). One patient with interstitial amyloidosis died of pulmonary sepsis, and another 8 patients were lost to outpatient follow-up; therefore, their outcomes are unknown.

There were no statistically significant differences among the three groups regarding functional features and survival, and patients with nodular and tracheobronchial patterns tended to have a long evolution. Among those with autoimmune features, Sjögren's syndrome and lymphocytic bronchiolitis were the most common. Patients with tracheobronchial or nodular amyloidosis had normal or obstructive PFT pattern more often. Furthermore, although cardiac involvement is the most common immediate cause of death in patients with pulmonary amyloidosis, only 25% of the patients reported previous cardiac impairment.

Here, we present a case series of patients with different manifestations of respiratory amyloidosis and clinical and functional impairments regardless of the type of disease. Additionally, our study did not demonstrate mediastinal lymph node or pleural amyloidosis, which differs from other studies.[8-10] However, the survival rates of our patients were similar to those in previous studies.[1,5] There is no definitive treatment for respiratory amyloidosis, and supportive care is the main target in the management of the disease to decrease symptoms and improve quality of life.

Table 1. Demographics, clinical characteristics, functional features, and survival of patients with respiratory amyloidosis.[a]

Variable	Group				p
	Tracheobronchial (n = 9)	Nodular (n = 8)	Interstitial (n = 3)	Total (N = 20)	
Diagnosis delay, years	3.7 ± 3.9	3.3 ± 2.9	4.2 ± 3.3	3.6 ± 3.3	0.933
Clinical characteristics					
Age at onset of symptoms, years	50.2 ± 12.5	59.8 ± 9.9	39.7 ± 16.0	52.5 ± 13.4	0.060
Age at diagnosis, years	54.0 ± 9.91	63.3 ± 8.70	44.0 ± 18.2	56.2 ± 12.3	0.043
Sex, female	3 (33.3)	5 (62.5)	3 (100)	11 (55.0)	0.064
Race or ethnicity, White	8 (88.9)	6 (75.0)	3 (100)	17 (85.0)	0.442
Smoker (current or former smoker)	4 (44.4)	4 (50.0)	0 (0.00)	8 (40.0)	0.177
Peripheral oximetry, %	96.0 ± 1.2	95.0 ± 2.2	97.0 ± 2.3	96.0 ± 1.9	0.226
Presence of symptoms	8 (88.9)	5 (62.5)	3 (100)	16 (80.0)	0.207
Weight loss	0 (0.0)	1 (12.5)	0 (0.0)	1 (5.0)	0.384
Dyspnea	8 (88.9)	5 (62.5)	3 (100)	16 (80.0)	0.207
Cough	3 (33.3)	3 (37.5)	3 (100)	9 (45.0)	0.064
Hemoptysis	1 (11.1)	1 (12.5)	0 (0.0)	2 (10.0)	0.706
Comorbidities	6 (66.7)	8 (100)	3 (100)	17 (85.0)	0.066
Systemic hypertension	3 (33.3)	6 (75.0)	0 (0.0)	9 (45.0)	0.029
Diabetes mellitus/dyslipidemia	2 (22.2)	3 (37.5)	0 (0.0)	5 (25.0)	0.305
Hypothyroidism	0 (0.0)	2 (25.0)	1 (33.3)	3 (15.0)	0.129
Heart failure/ischemic heart disease	3 (33.3)	2 (25.0)	0 (0.0)	5 (25.5)	0.361
Kidney disease	0 (0.0)	0 (0.0)	1 (33.3)	1 (5.0)	0.127
Depression/anxiety	1 (11.1)	0 (0.0)	1 (33.3)	2 (10.0)	0.234
Hematological disease	0 (0.0)	1 (12.5)	2 (66.7)	3 (15.0)	0.029
Sjögren's syndrome/lymphocytic bronchiolitis	0 (0.0)	2 (25.0)	1 (33.3)	3 (15.0)	0.129
COPD	1 (11.1)	1 (12.5)	0 (0.0)	2 (10.0)	0.706
Protein electrophoresis, abnormal	2 (22.2)	3 (37.5)	2 (66.7)	7 (35.0)	0.375
Autoimmune features	1 (11.1)	2 (25.0)	1 (33.3)	4 (20.0)	0.631
Exposure to	1 (11.1)	2 (25.0)	0 (0.0)	3 (15.0)	0.442
Birds or feather/down-containing items	1 (11.1)	2 (25.0)	0 (0.0)	3 (15.0)	0.442
Mold or mildew	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Pulmonary function tests	4 (44.4)	6 (75.0)	2 (66.7)	12 (60.0)	0.419
Obstructive pattern	3 (33.3)	2 (25.0)	0 (0.0)	5 (25.0)	0.361
FEV_1, % of predicted	80.3 ± 11.1	51.0 ± 29.7	-	68.6 ± 23.2	0.382
Restrictive pattern	0 (0.0)	1 (12.5)	1 (33.3)	2 (10.0)	0.206
FVC, % of predicted	-	54	77	64 [52-77]	-
Survival, years	6.6 ± 4.7	7.8 ± 5.7	1.7 ± 1.2	6.3 ± 5.1	0.209

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

The major limitations of our study were its retrospective nature and the small number of patients included. However, amyloidosis is a rare disease; therefore, we believe that we have a relevant number of patients in our study. Another limitation was that the analysis of amyloidotic material with the proteomic method of mass spectrometry (the new gold standard for fibril typing) was not performed.

In conclusion, respiratory amyloidosis may have different manifestations and should be considered in the differential diagnosis of patients with tracheobronchial involvement, pulmonary nodules, or interstitial lung abnormalities. Furthermore, most patients with respiratory amyloidosis are asymptomatic and require careful follow-up.

AUTHOR CONTRIBUTIONS

PFBC: study design; data collection; and writing and reviewing of the manuscript. ANCS: study design; and writing and reviewing of the manuscript. RAA: study design; data collection; and manuscript review. RAK: study design; and manuscript review. BGB: study design; and writing and reviewing of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Rech JS, Arnulf B, de Margerie-Mellon C, Talbot A, Malphettes M, Vignon M, et al. Lower respiratory tract amyloidosis: Presentation, survival and prognostic factors. A multicenter consecutive case series. Am J Hematol. 2019;94(11):1214-1226. https://doi.org/10.1002/ajh.25608
2. de Almeida RR, Zanetti G, Pereira E Silva JL, Neto CA, Gomes AC, Meirelles GS, et al. Respiratory Tract Amyloidosis. State-of-the-Art Review with a Focus on Pulmonary Involvement. Lung. 2015;193(6):875-883. https://doi.org/10.1007/s00408-015-9791-x
3. Ussavarungsi K, Yi ES, Maleszewski JJ, Kurtin PJ, Dasari S, Theis JD, et al. Clinical relevance of pulmonary amyloidosis: an analysis of 76 autopsy-derived cases. Eur Respir J. 2017;49(2):1602313. https://doi.org/10.1183/13993003.02313-2016
4. Sipe JD, Benson MD, Buxbaum JN, Ikeda S, Merlini G, Saraiva MJ, et al. Amyloid fibril protein nomenclature: 2012 recommendations from the Nomenclature Committee of the International Society of Amyloidosis. Amyloid. 2012;19(4):167-170. https://doi.org/10.3109/13506129.2012.734345
5. Yamada M, Takayanagi N, Yamakawa H, Ishiguro T, Baba T, Shimizu Y, et al. Amyloidosis of the respiratory system: 16 patients with amyloidosis initially diagnosed ante mortem by pulmonologists. ERJ Open Res. 2020;6(3):00313-2019. https://doi.org/10.1183/23120541.00313-2019
6. Magy-Bertrand N, Dupond JL, Mauny F, Dupond AS, Duchene F, Gil H, et al. Incidence of amyloidosis over 3 years: the AMYPRO study. Clin Exp Rheumatol. 2008;26(6):1074-1078.
7. Zamora AC, White DB, Sykes AMG, Hoskote SS, Moua T, Yi ES, Ryu JH, Amyloid-associated Cystic Lung Disease. Chest. 2016;149(5):1223-1233. https://doi.org/10.1378/chest.15-1539
8. Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. J Bras Pneumol. 2007;33(4):397-406. https://doi.org/10.1590/S1806-37132007000400008
9. Eggleston RH, Hartman TE, Walkoff LA, Yi ES, Ryu JH, Baqir M. Clinical, radiologic, and pathologic features and outcomes of pulmonary transthyretin amyloidosis. Respir Med. 2022;194:106761. https://doi.org/10.1016/j.rmed.2022.106761
10. Brandelik SC, Heussel CP, Kauczor HU, Röcken C, Huber L, Basset M, et al. CT features in amyloidosis of the respiratory system - Comprehensive analysis in a tertiary referral center cohort. Eur J Radiol. 2020;129:109123. https://doi.org/10.1016/j.ejrad.2020.109123

Pulmonary embolization with cyanoacrylate after obliteration of gastric varicose veins

Camila Alcantara Quidigno[1], Daniela de Lima Guerra[1], Paulo Henrique Ramos Feitosa[1]

A 46-year-old woman with a history of portal vein and bile duct injury during cholecystectomy reported hematemesis, melena, and syncope. A previous endoscopy showed fine and medium esophageal varices. She was hospitalized with massive melena. A new endoscopy was performed, and hemostasis of bleeding was carried out using cyanoacrylate. The patient achieved clinical stability. Subsequently, the patient developed dyspnea and desaturation. A chest CT showed hyperdense material in structures, such as the gastric fundus, which is compatible with hemostasis material. Chest CT angiography showed hyperdense material in the segmental branch of the middle lobe and in the medial basal subsegmental branch of the right lower lobe, leading to partial filling failure, which is compatible with cyanoacrylate embolization.

Treatment of variceal bleeding with cyanoacrylate in endoscopy is effective in patients with liver disease and can reduce the size of varices on the first application.[1] However, this procedure can be complicated by embolization of the resulting polymer in some vessels, such as pulmonary arteries,[1] especially in patients with large varicose veins that require larger volumes of sclerosing agent.[2] Embolization appears to be more common in patients who received a greater volume of this agent.[3] Treatment for cyanoacrylate pulmonary embolism is mainly supportive.[2]

AUTHOR CONTRIBUTIONS

CAQ: data collection, writing, descriptive analysis, and translation. PHRF: data collection, writing, descriptive analysis, and translation. DLG: data collection. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

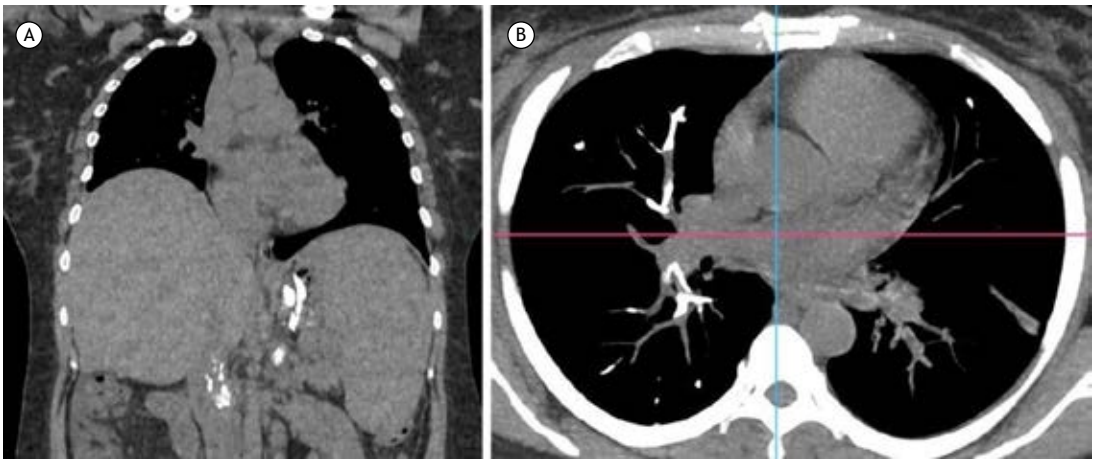

Figure 1. In A, a coronal section of chest CT showing hyperdense material in the topography of the gastric fundus, splenic hilum, left renal vein, and inferior vena cava, which is compatible with hemostasis material. In B, the axial section also showed hyperdense material in the segmental branch of the middle lobe and in the medial basal subsegmental branch of the right lower lobe, leading to partial filling failure, which is compatible with cyanoacrylate pulmonary embolization.

REFERENCES

1. Frassei JDS, Franco CS, Brambilla VR, Loureiro BMC, Kiebert CDS, Fonseca EKUN, et al. Cyanoacrylate pulmonary embolism after endoscopic sclerotherapy of gastric varices. Einstein (Sao Paulo). 2021;19:eAI5778. https://doi.org/10.31744/einstein_journal/2021AI5778
2. Michael PG, Antoniades G, Staicu A, Seedat S. Pulmonary Glue Embolism: An unusual complication following endoscopic sclerotherapy for gastric varices. Sultan Qaboos Univ Med J. 2018;18(2):e231-e235. https://doi.org/10.18295/squmj.2018.18.02.020
3. Habib SF, Muhammad R, Koulaouzidis A, Gasem J. Pulmonary embolism after sclerotherapy treatment of bleeding varices. Ann Hepatol. 2008;7(1):91-93.

1. Hospital Regional da Asa Norte – HRAN – Brasília (DF) Brasil.

Impact of COVID-19 on diagnosis of tuberculosis and tuberculosis infection in South America, Asia, and Africa

Denise Rossato Silva[1], Rosella Centis[2], Lia D'Ambrosio[3], Fernanda Carvalho de Queiroz Mello[4], Giovana Rodrigues Pereira[5], Sarita Aguirre[6], Seif Al-Abri[7], Khalsa Al-Thohli[7], Fatma Al Yaquobi[8], Marianne Calnan[9], Rosarito Coronel Teixeira[10], Sandra Inwentarz[11], Domingo Juan Palmero[11], Alberto Piubello[12], Samridhi Sharma[13], Mahamadou Bassirou Souleymane[14], Alphazazi Soumana[15], Sai Meng Tham[16], Pei Min Thong[17], Zarir F Udwadia[13], Martin van den Boom[18], Giovanni Sotgiu[19], Giovanni Battista Migliori[2]

TO THE EDITOR:

During the COVID-19 pandemic, most countries implemented public health measures intended to contain the spread of SARS-CoV-2, such as travel restrictions, stay-at-home measures, use of face masks, among others.[1] Because of the pandemic, several disruptions occurred in healthcare services. tuberculosis-related services were severely affected, with closing of health care units or limited patient access, reduction of the number of healthcare professionals due to relocation to COVID-19 care, and decreased healthcare demand by patients due to fear of exposure to SARS-CoV-2, with a consequent decrease in diagnosed cases due to diagnostic delay.[1-4]

The WHO reported that tuberculosis notifications dropped 18% from 2019 to 2020 (from 7.1 to 5.8 million cases), with a partial recovery in 2021, but still without reaching pre-pandemic values.[5] A global study,[2] coordinated by the Global Tuberculosis Network and involving 43 centers from 19 countries, demonstrated that newly diagnosed tuberculosis disease, drug-resistant tuberculosis (DR-TB), tuberculosis deaths, outpatient clinic visits, and newly diagnosed tuberculosis infection were reduced.

Information on the effects of COVID-19 on tuberculosis, specifically in South America, Asia, and Africa, is very limited. Therefore, the aim of this study was to compare the prevalence of tuberculosis disease (new or retreatment cases), newly diagnosed tuberculosis infection, and DR-TB between the years 2020 and 2019 in eight countries located in South America (Argentina, Brazil, Paraguay), Asia (India, Oman, the Philippines, Singapore), and Africa (Niger).

Data previously collected by the Global Tuberculosis Network were used.[2] The following variables were collected monthly: total number of tuberculosis cases, including new diagnoses and recurrences; number of DR-TB; and number of tuberculosis deaths. The coordinating and the participating centers had ethics clearance in accordance with their institutional regulations. Data were collected from January 01, 2019, to December 31, 2020. Statistical analysis was performed using IBM SPSS Statistics, version 22.0 (IBM Corporation, Armonk, NY, USA). Data were presented as medians and interquartile ranges. Variables were compared using the Wilcoxon test. A two-sided $p < 0.05$ was considered significant.

The median number of tuberculosis disease cases decreased in 2020 (33.0 [19.3-105.8] vs. 41.0 [25.0-114.0], $p = 0.029$). Newly diagnosed tuberculosis infections did not significantly decrease from 2019 to 2020 (7.0 [3.3-28.0] vs. 6.0 [2.0-23.0]; $p = 0.470$). No differences were found in the number of DR-TB cases and tuberculosis deaths ($p = 0.293$ and $p = 0.433$, respectively). In India, the number of DR-TB cases was significantly lower in 2020 (86.0 [60.3-106.3] vs. 323.5 [308.3-354.5]; $p < 0.0001$). Tuberculosis deaths

1. Faculdade de Medicina, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
2. Servizio di Epidemiologia Clinica delle Malattie Respiratorie, Istituti Clinici Scientifici Maugeri – IRCCS – Tradate, Italia.
3. Public Health Consulting Group, Lugano, Switzerland.
4. Instituto de Doenças do Tórax – IDT – Faculdade de Medicina, Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ) Brasil.
5. Ambulatório de Tuberculose de Alvorada, Alvorada (RS) Brasil.
6. Ministerio de Salud Pública y Bienestar Social, Asunción, Paraguay.
7. Royal Hospital, Ministry of Health, Muscat, Sultanate of Oman.
8. TB and Acute Respiratory Diseases Section, Department of Communicable Diseases, Directorate General of Disease Surveillance and Control, Ministry of Health, Sultanate of Oman.
9. University Research Co. LLC, Manila, Philippines.
10. National Institute of Respiratory Diseases and the Environment – INERAM – Asunción, Paraguay.
11. Instituto Vaccarezza – UBA – Buenos Aires, Argentina.
12. Damien Foundation, Brussels, Belgium.
13. P.D. Hinduja National Hospital and Medical Research Centre, Mumbai, India.
14. Damien Foundation, Niamey, Niger.
15. National Tuberculosis Programme, Niamey, Niger.
16. Division of Infectious Diseases, Department of Medicine, National University Hospital, Singapore.
17. Department of Medicine, Infectious Disease Translational Research Programme, National University of Singapore, Yong Loo Lin School of Medicine, Singapore.
18. World Health Organization, Regional Office for the Eastern Mediterranean Region, Cairo, Egypt.
19. Clinical Epidemiology and Medical Statistics Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy.

◄ Voltar ao sumário
ISSN 1806-3756

in Paraguay decreased in 2020 (16.5 [12.5-19.8] vs. 26.5 [22.3-27.0]; p < 0.0001; Figure 1).

Our findings are similar to those described in previous studies.[6,7] demonstrating a reduced number of tuberculosis notifications during the first year of the COVID-19 pandemic. Morena et al.[7] evaluated the impact of the COVID-19 pandemic on pulmonary tuberculosis using artificial intelligence in the region of Castilla-La Mancha in Spain: a significant decrease in the incidence of pulmonary tuberculosis at the start of the COVID-19 outbreak was found. In another study,[6] changes of reported tuberculosis incidence and mortality before and during the pandemic were described in China from January of 2015 to January of 2023. In the present study, we found no differences in the number of tuberculosis deaths when comparing 2019 with 2020, except in Paraguay where the number of deaths decreased in 2020.

In summary, a decrease in the number of tuberculosis disease cases notified in South America, Asia, and Africa was proven in 2020 if compared with that notified in 2019. Tuberculosis infection decreased from 2019 to 2020 without any statistical significance. Further monitoring will be necessary, as an increase of several indicators of tuberculosis disease and infection may be expected in future years.

ACKNOWLEDGEMENTS

This study was conducted under the auspices of the Global Tuberculosis Network, hosted by the World Association for Infectious Diseases and Immunological Disorders.

AUTHOR CONTRIBUTIONS

DRS, GBM, LD, and RC: conceptualization, methodology, project administration, and drafting of the manuscript. FCQM, GRP, SA, SA-A, KA-T, FA-Y, MC, RCT, SI, DJP, AP, SS, MBS, AS, SMT, PMT, ZFU, MvdB, and GS: conceptualization, methodology and revision of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared

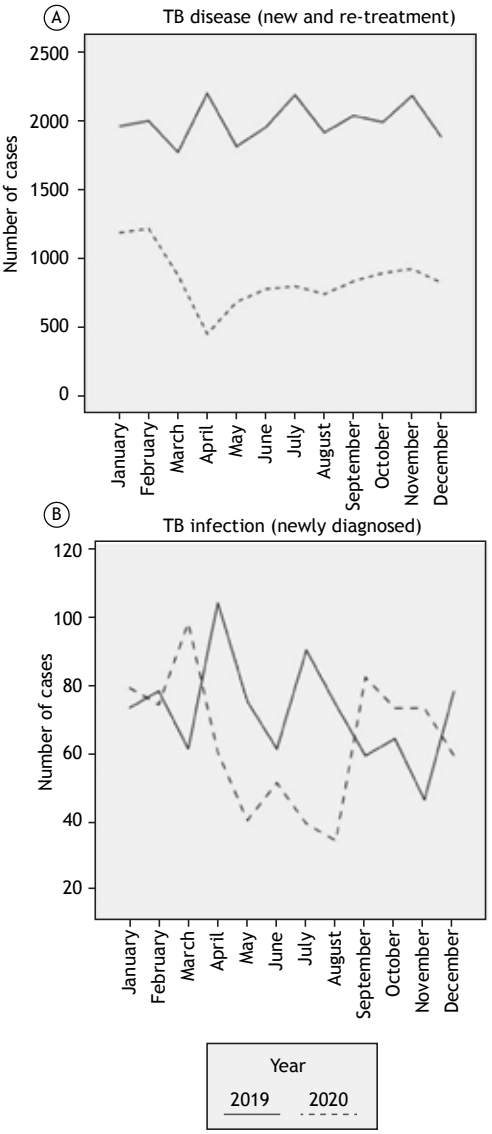

Figure 1. Number of tuberculosis (TB) disease cases (new and retreatment; in A) and of TB infection cases (in B) in 2019 and 2020, by month, in eight South American, Asian, and African countries.

REFERENCES

1. Migliori GB, Thong PM, Alffenaar JW, Denholm J, Tadolini M, Alyaquobi F, et al. Country-specific lockdown measures in response to the COVID-19 pandemic and its impact on tuberculosis control: a global study. J Bras Pneumol. 2022;48(2):e20220087. https://doi.org/10.36416/1806-3756/e20220087
2. Migliori GB, Thong PM, Alffenaar JW, Denholm J, Tadolini M, Alyaquobi F, et al. Gauging the impact of the COVID-19 pandemic on tuberculosis services: a global study. Eur Respir J. 2021;58(5):2101786. https://doi.org/10.1183/13993003.01786-2021
3. García-García JM, Blanc FX, Buonsenso D, Centis R, Codecasa LR, D'Ambrosio L, et al. COVID-19 Hampered Diagnosis of TB Infection in France, Italy, Spain and the United Kingdom. Arch Bronconeumol. 2022;58(11):783-785. https://doi.org/10.1016/j.arbres.2022.07.013
4. Nalunjogi J, Mucching-Toscano S, Sibomana JP, Centis R, D'Ambrosio L, Alffenaar JW, et al. Impact of COVID-19 on diagnosis of tuberculosis, multidrug-resistant tuberculosis, and on mortality in 11 countries in Europe, Northern America, and Australia. A Global Tuberculosis Network study. Int J Infect Dis. 2023;130 Suppl 1:S25-S29. https://doi.org/10.1016/j.ijid.2023.02.025
5. World Health Organization [homepage on the Internet]. Geneva: WHO; c2021. Global Tuberculosis Report 2021. [Adobe Acrobat document, 57p.]. Available from: https://apps.who.int/iris/rest/bitstreams/1379788/retrieve
6. Zhang Y, Zhang L, Gao W, Li M, Luo Q, Xiang Y, et al. The impact of COVID-19 pandemic on reported tuberculosis incidence and mortality in China: An interrupted time series analysis. J Glob Health. 2023;13:06043. https://doi.org/10.7189/jogh.13.06043
7. Morena D, Campos C, Castillo M, Alonso M, Benavent M, Izquierdo JL. Impact of the COVID-19 Pandemic on the Epidemiological Situation of Pulmonary Tuberculosis-Using Natural Language Processing. J Pers Med. 2023;13(12):1629. https://doi.org/10.3390/jpm13121629

Lung cancer screening eligibility and recruitment during routine care by pulmonologists: barriers and new opportunities in the Brazilian public healthcare system

Fábio Munhoz Svartman[1,2], Marina Ilha de Azambuja[1], Eduarda de Albuquerque Palma[1], Ana Paula Garcia Sartori[1], Maurício Mello Roux Leite[3]

TO THE EDITOR:

Lung cancer screening (LCS) with low-dose CT (LDCT) reduces mortality in high-risk patients and its practice is now widely recommended.[1-3] However, large-scale implementation and adherence to screening remain low,[4] and difficulties in screening implementation may be greater in low- and middle-income countries such as Brazil.[3]

Organized, population-based programs are the preferable approach for cancer screening, due to their greater scope and impact.[5] However, initiatives with features of opportunistic screening (i.e., offering screening during a medical visit for another reason) have demonstrated positive outcomes across diverse real-world scenarios.[6,7]

Our group performs LCS with LDCT in patients with chronic, stable lung diseases (mostly COPD) who are regularly followed by pulmonologists in a Brazilian public hospital.[8] Data from the program implementation demonstrated adequate rates of early-stage diagnoses and treatments with curative intent.[8] However, little is known about the effective recruitment potential of LCS programs for patients with respiratory diseases. The present study aimed to identify the number of patients who are truly eligible for screening in this context, as well as physicians' adherence to recruiting eligible patients. Secondarily, we aimed to identify factors that hinder a greater volume of LCS program recruitment.

This was a cross-sectional study involving all patients seen in November of 2022 at the institution's pulmonology outpatient clinic. Demographic data and presence of the screening inclusion criteria in accordance with the institutional program were retrospectively reviewed. Inclusion criteria for our LCS program are: 1) being between 55 and 80 years of age; 2) being a current smoker or a former smoker for less than 15 years; and 3) having a smoking history of 30 pack-years or more. Reasons for not requesting LDCT were actively sought by reviewing the data recorded by the attending physicians, and exam requests were searched in the hospital's radiology system. The month of November of 2022 was used for index consultations, the following period of one year being evaluated to detect LDCT screening. This was a convenience sample, and all individual outpatient appointments in the specified month were analyzed. The program's exclusion criteria are: current suspicion of cancer, personal history of lung cancer, and presence of comorbidities that, in the judgment of the attending physician, limit the patient's life expectancy and/or clinical performance for curative treatment. Descriptive statistics were used for main results, and the chi-square and the Fisher's exact tests were used for exploratory comparisons between the group of patients effectively screened and those in which screening was not performed despite confirmed eligibility. This study is the initial stage of a project that proposes evaluating future educational interventions to increase enrollment in screening. The project was approved by the institution in its ethical and methodological aspects (CAAE no. 77187623.1.0000.5530).

Figure 1 presents the flowchart of evaluated patients and the causes identified for non-enrollment in the program. Of the 805 patients seen during the study period, 532 (66.2%) were in the target age range for screening, and 267 (33.1%) met all inclusion criteria. In 40% of these (n = 107; 13.3% of the total) absence of exclusion criteria could be verified (i.e., eligibility confirmed). The most common medical reasons for exclusion were current suspicion of cancer and/or active investigation of another medical condition and poor lung function. There were insufficient data in the medical records of 90 patients (11% of the total sample) to determine eligibility. Table 1 presents the demographic data of patients who met all inclusion criteria and of the subgroup with confirmed eligibility.

Of the 107 patients with confirmed eligibility, LDCT was requested and not requested in 46 (43%) and 61 (57%) cases, respectively. The comparison between these two groups revealed a statistically significant difference in the proportion of women, who constituted 60.9% of the screened group and 80.3% of the non-screened group ($p = 0.027$). In other words, of the 77 women with confirmed eligibility, 28 (36.3%) were screened, in contrast to 18 of the 30 men (60%) in the same situation. There was no difference regarding age between the groups ($p = 0.738$).

1. Hospital Nossa Senhora da Conceição, Porto Alegre (RS) Brasil.
2. Hospital de Clínicas de Porto Alegre, Porto Alegre (RS) Brasil.
3. Hospital Ernesto Dornelles, Porto Alegre (RS) Brasil.

  ◄ Voltar ao sumário ISSN 1806-3756

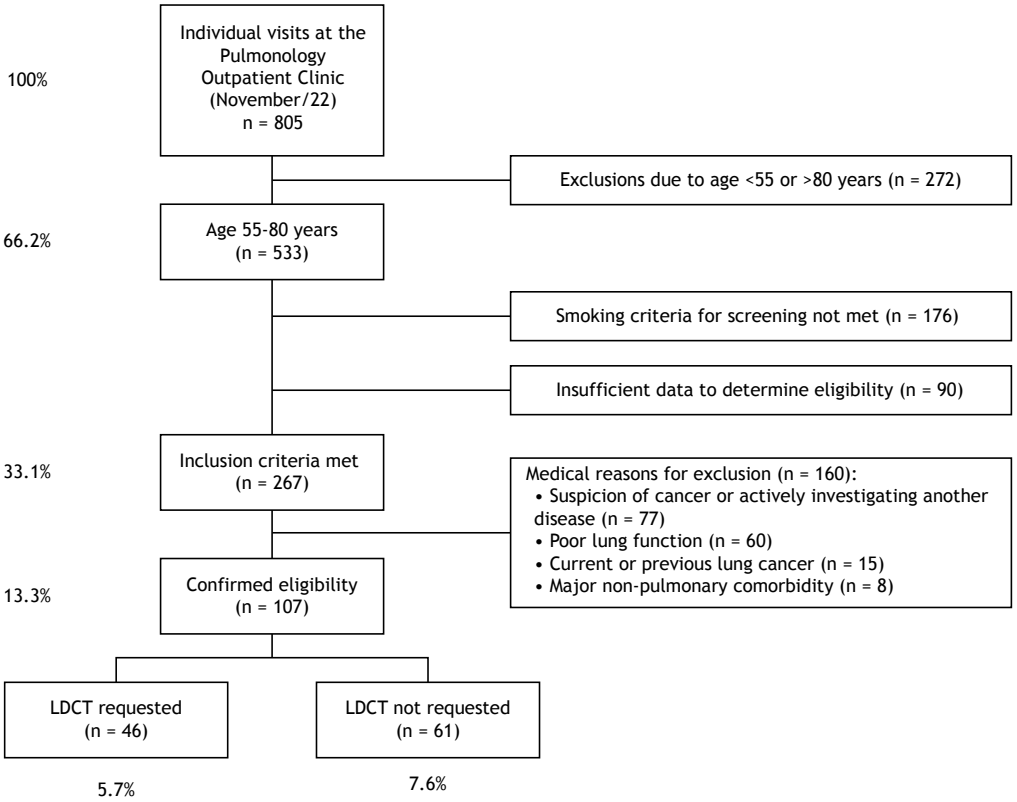

Figure 1. Flow chart of the patient selection process. Criteria used by the program: current smoking or smoking cessation less than 15 years ago; and smoking history of 30 pack-years or more.

Table 1. In A, demographic profile, age range, and confirmed eligibility for lung cancer in the patients who met all inclusion criteria (N = 267). In B, association between demographic variables and low-dose CT performance of patients with confirmed eligibility.[a]

A		B			
Variable	Result	Variable	LDCT (n = 46)	No LDCT (n = 61)	p
Gender		Gender			
Female	170 (63.7)	Female	28 (60.9)	49 (80.3)	0.027*
Male	97 (36.3)	Male	18 (39.1)	12 (19.7)	
Age, years	66.9 ± 6.5				
Age range, years		Age range, years			
55-60	55 (20.6)	55-60	15 (32.6)	13 (21.3)	0.738**
61-64	43 (16.1)	61-64	9 (19.6)	12 (19.7)	
65-67	54 (20.2)	65-67	8 (17.4)	16 (26.2)	
68-71	46 (17.2)	68-71	6 (130)	11 (18.0)	
72-75	37 (13.9)	72-75	3 (6.5)	3 (4.9)	
76-80	32 (12.0)	76-80	5 (10,9)	6 (9,8)	
Confirmed eligibility					
Yes	107 (40.1)				
No	160 (59.9)				

LDCT: low-dose computed tomography. [a]Values expressed as n (%) or mean ± SD. *Chi-square test. **Fisher's exact test.

These results point to four main conclusions: 1) at least one third of patients in this context met the inclusion criteria for screening, although only 13% had confirmed eligibility; 2) underreporting of clinical data was significant, pointing to a potential greater number of eligible patients; 3) even in patients with confirmed eligibility, the effective inclusion rate was low (43%); 4) patient characteristics, such as gender, might have an impact on the decision to request LDCT.

This study has several limitations, including its retrospective single-center nature and the small number of participants. However, it was possible to quantify

and detail barriers, some of which were inherent to the nature of our program, such as the number of patients with medical contraindications. On the other hand, barriers with the possibility of intervention for improvement include underreporting and, in particular, the low inclusion rate of patients with confirmed eligibility. Our study does not allow us to conclude whether this low inclusion rate was due exclusively to physician nonadherence or to patient factors (such as possible refusals to undergo screening). A finding that deserves further investigation is the lower rate of LDCT requests for women, raising awareness of possible gender inequalities. The small sample size and the absence of analysis of potentially confounding factors limit conclusions about this finding. Unfortunately, ethnicity and socioeconomic data were unavailable, precluding inferences about possible inequities in these aspects as well. Efforts to reduce inequities in LCS have recently led to important advancements,[9,10] and we believe that such programs should have a special focus on systematically monitoring this issue.

In conclusion, the number of patients with chronic respiratory diseases and confirmed eligibility for LCS appears significant, although effective inclusion remains low. We believe that educational interventions and periodic reminders to physicians are necessary in such scenarios. Pulmonologists' expertise in order to select and conduct screenings carefully in a setting with the necessary resources is crucial for this high-risk subgroup of patients.

AUTHOR CONTRIBUTIONS

FMS, MIA, EAP, APGS, and MMRL: conceptualization. FMS, MIA, and EAP: data curation. FMS, MIA, and EAP: formal analysis. MIA, EAP: investigation. FMS: methodology and supervision. FMS, MIA, and EAP: original drafting. All of the authors edited, reviewed, and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. US Preventive Services Task Force, Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, et al. Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2021;325(10):962-970. https://doi.org/10.1001/jama.2021.1117
2. Wolf AMD, Oeffinger KC, Shih TY, Walter LC, Church TR, Fontham ETH, et al. Screening for lung cancer: 2023 guideline update from the American Cancer Society. CA Cancer J Clin. 2024; 74(1): 50-81. https://doi.org/10.3322/caac.21811
3. Pereira LFF, Santos RSD, Bonomi DO, Franceschini J, Santoro IL, Miotto A, et al. Lung cancer screening in Brazil: recommendations from the Brazilian Society of Thoracic Surgery, Brazilian Thoracic Association, and Brazilian College of Radiology and Diagnostic Imaging. J Bras Pneumol. 2024;50(1):e20230233. https://doi.org/10.36416/1806-3756/e20230233
4. Maki KG, Tan NQP, Toumazis I, Volk RJ. Prevalence of Lung Cancer Screening Among Eligible Adults in 4 US States in 2021. JAMA Netw Open. 2023;6(6):e2319172. https://doi.org/10.1001/jamanetworkopen.2023.19172
5. World Health Organization (WHO) [homepage on the Internet]. Geneva: WHO; c2020 [updated 2020 Feb 3; cited 2024 Jan 2]. WHO report on cancer: setting priorities, investing wisely and providing care for all. Geneva: WHO, 2020. Available in: https://www.who.int/publications/i/item/9789240001299
6. Wang L, Qi Y, Liu A, Guo X, Sun S, Zhang L, et al. Opportunistic Screening With Low-Dose Computed Tomography and Lung Cancer Mortality in China. JAMA Netw Open. 2023;6(12):e2347176. https://doi.org/10.1001/jamanetworkopen.2023.47176
7. Grover H, Ross T, Fuller E. Implementation of targeted screening for lung cancer in a high-risk population within routine NHS practice using low-dose computed tomography. Thorax. 2020;75(4):348-350. https://doi.org/10.1136/thoraxjnl-2019-214303
8. Svartman FM, Leite MMR, Sartori APG, Gutierrez RS, Cadore AC, Oliveira CTM, et al. Lung cancer screening with low-dose CT integrated with pulmonary care in a public hospital in southern Brazil: results from the first 712 patients. J Bras Pneumol. 2022;48(5):e20220146. https://doi.org/10.36416/1806-3756/e20220146
9. Pinheiro LC, Groner L, Soroka O, Prosper AE, Jack K, Tamimi RM, et al. Analysis of Eligibility for Lung Cancer Screening by Race After 2021 Changes to US Preventive Services Task Force Screening Guidelines. JAMA Netw Open. 2022;5(9):e2229741. https://doi.org/10.1001/jamanetworkopen.2022.29741
10. Sears CR, Rivera MP. Age, Sex, Smoking, and Race: Is Progress Being Made in Lung Cancer Screening Eligibility? Chest. 2021;160(1):31-33. https://doi.org/10.1016/j.chest.2021.03.043

Intrapericardial fibrinolysis and video-assisted thoracoscopic surgery in managing severe pediatric *Streptococcus pneumoniae* purulent complications

Jinghui Jiang[1], Qianqian Du[2], Jun Liang[1], Kaihu Yao[2]

DEAR EDITOR:

Confirmed *Streptococcus pneumoniae* infections in sterile body cavities, such as pediatric purulent pericarditis and typical pleural empyema, were relatively rare in the post-antibiotic and post-vaccine era.[1-3] Inappropriate treatment selection could leave constrictive pericarditis or constrictive pleurisy, which have a considerable bearing on the long-term prognosis of affected children.[4] We herein reported two cases featuring definitive etiological evidence and characteristic clinical presentations, with distinct therapeutic approaches employed to address the purulent effusions; both yielded favorable outcomes.

The first case (a 2-year-old female) was admitted under the primary diagnosis of pericardial effusion and sepsis. CT imaging disclosed the presence of pneumonia, bilateral pleural effusions, and a substantial pericardial effusion (Figure A1). *S. pneumoniae* was isolated from the patient's blood and pericardial effusion cultures, which was subsequently identified as serotype 6A (ST9789) at Beijing Children's Hospital. Unfortunately, cardiac ultrasound showed cellulose-like material in the pericardium (Figure A2). The patient underwent a series of eight intrapericardial fibrinolysis procedures. Urokinase was administered daily at a dose of 8 mL containing 40,000 units, which was directly infused into the pericardial cavity. A cumulative volume of 510 mL of pericardial fluid was drained throughout treatment. Echocardiography demonstrated a marked reduction in pericardial effusion volume, with only a negligible amount remaining (Figure A3).

On admission with severe dyspnea, the second child (1 year old) had a white blood cell count of 35.9 × 10^9/L, accompanied by a C-reactive protein level exceeding 200 mg/L. CT revealed consolidation in the left lung, atelectasis areas, and pleural effusion (Figures B1 and B3, left). Microbiological analyses confirmed the presence of *S. pneumoniae* in blood, sputum, and pleural fluid cultures. Despite receiving intravenous antibiotics (azithromycin and cephalosporin) for a cumulative duration of 10 days, the patient's clinical symptoms and blood biomarkers failed to demonstrate adequate improvement. Ultrasound examination of the chest revealed a substantial left-sided pleural effusion characterized by a profuse, grid-like septation pattern. The drainage volume was small and contained flocs or cord-like material, which prevented continuous drainage of the effusion. VATS was performed on the left side on the fifth day of admission, and the abscess and effusion in the left pleural cavity were carefully removed. The pleural cavity's fibrous purulent material and pus could be cleared under direct vision (Figure B2). VATS removed the thick fiber separation that hindered the sufficient drainage of pleural effusion by the thoracic duct. A CT scan conducted four months later confirmed the child's complete recovery to normalcy, with no discernible sequelae (Figure B3, right).

The British Thoracic Society and the American Pediatric Surgical Association guidelines[5,6] suggested a trial of fibrinolytic therapy as the initial treatment of choice, followed by VATS for those failing pleural drainage with a fibrinolytic. This recommendation was founded on a lack of empirical data, yet we acknowledge the appropriateness of either therapeutic strategy in our two cases. Institutional expertise, economic constraints, and patient preferences may sway the ultimate decision.

Fibrin deposition, triggered by *S. pneumoniae*, seems pivotal in progressing towards constrictive pericarditis/pleuritis and perpetuating the disease state. The effectiveness of fibrinolytic agents (streptokinase and urokinase) in degrading extravascular fibrin has been well-established. Upon administering intrapericardial urokinase in the first case, the drainage volume of the patient escalated from 15 mL to 135 mL on the initial post-treatment day. Given the inherent risks of morbidity associated with pericardiectomy, intrapericardial fibrinolysis during pericardiocentesis emerges as a potentially less invasive alternative for averting the persistence of purulent pericarditis and the development of constrictive pericarditis.[7] Minimally invasive treatment modalities are crucial in pediatric populations, as they typically offer superior safety profiles and enhanced feasibility. Urokinase has undergone a placebo-controlled investigation in pediatric populations; 40,000 units in 40 mL 0.9% saline in children aged one year and older was recommended by the British Thoracic Society[5] and the Pediatric Infectious Diseases Society.[8] It appeared to be safe and effective in preventing the development of pericardial constriction.

Surgical intervention may be employed as a first-line treatment modality for patients presenting with loculated pleural effusions/empyema or as a secondary therapeutic option for those who fail to respond satisfactorily to fibrinolytic therapy. Early engagement of a surgeon in the clinical decision-making process was instrumental

1. Liaocheng People's Hospital, Shandong 252000, China.
2. Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, 100045, China.

ISSN 1806-3756

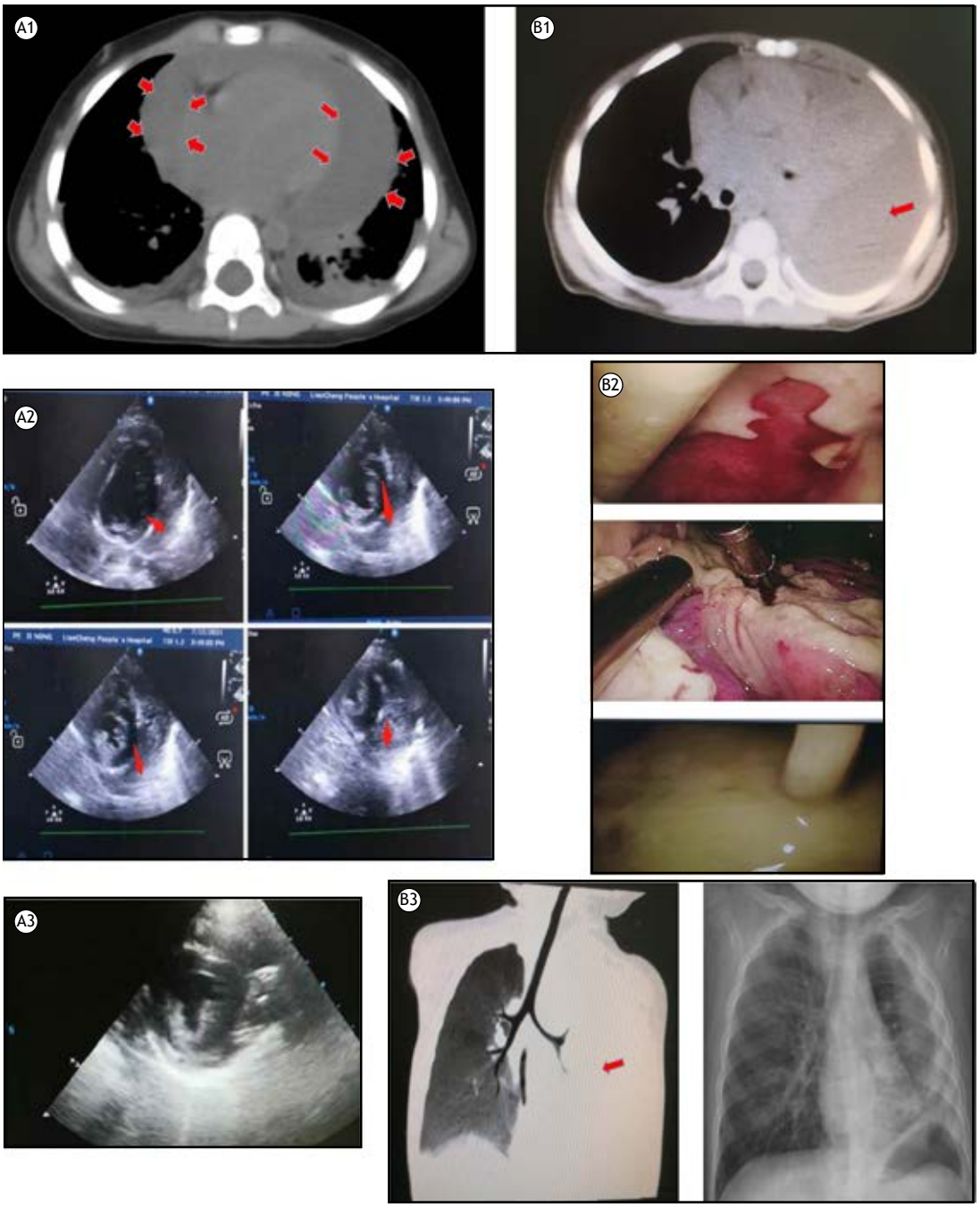

Figure 1. In A1, a chest CT scan showed the presence of pneumonia, bilateral pleural effusions, and substantial pericardial effusion (red arrow). In A2, cardiac ultrasound showed cellulose-like material in the pericardium. In A3, an echocardiography image showing the negligible amount of pericardial effusion remaining. In B1, a CT scan showing consolidation in the left lung, atelectasis areas, and pleural effusion (red arrow); In B2, the pleural cavity's fibrous purulent material and pus could be cleared under direct vision. In B3, the left picture was a CT scan at admission, and the right picture was a CT scan conducted four months later confirming the child's complete recovery.

in ensuring that any necessary surgical intervention could be promptly executed should the circumstances dictate. When surgical decortication was required, maximizing the benefits while minimizing physiological impact was more feasible through early intervention, swift progression to advanced treatment modalities, and management at a facility proficient in performing VATS.[9] VATS may be indicated in loculated empyema.

Upon the child's admission, we promptly solicited the expert opinion of a pediatric surgeon, who advised that surgical intervention should be pursued if the conservative treatment proved ineffective. Relative to

the first case, this second patient received long-term intravenous antibiotics treatment and exhibited a more protracted clinical course and more pronounced symptomatology. According to the Pediatric Infectious Diseases Society recommendations,[8] VATS should be selected directly if closed drainage is ineffective. The child recovered and was discharged 14 days after the operation and recovered well during the follow-up for the next 4 months. The second case aligned with the understanding that VATS was suitable for localized empyema.[10] There was no recurrence and no constrictive pleurisy, indicating that timely treatment can help shorten the course of the patient's illness and reduce costs.

AUTHOR CONTRIBUTIONS

JJ and QD (equal contribution): conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; and software. JL (support): conceptualization; data curation; formal analysis; methodology; project administration; and resources. KY (lead): conceptualization; data curation; formal analysis; methodology; visualization; writing original draft; and writing (review & editing).

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Cillóniz C, Rangel E, Barlascini C, Piroddi IM, Torres A, Nicolini A. Streptococcus pneumoniae-associated pneumonia complicated by purulent pericarditis: case series. J Bras Pneumol. 2015;41(4):389-394. http://dx.doi.org/10.1590/S1806-37132015000000010
2. Madhi F, Levy C, Morin L, Minodier P, Dubos F, Zenkhri F, et al. Change in Bacterial Causes of Community-Acquired Parapneumonic Effusion and Pleural Empyema in Children 6 Years After 13-Valent Pneumococcal Conjugate Vaccine Implementation. J Pediatr Infect Dis Soc. 2019;8(5):474-477. http://dx.doi.org/10.1093/jpids/piy103
3. Wiese AD, Griffin MR, Zhu Y, Mitchel EF Jr, Grijalva CG. Changes in empyema among U.S. children in the pneumococcal conjugate vaccine era. Vaccine. 2016;34(50):6243-6249. http://dx.doi.org/10.1016/j.vaccine.2016.10.062
4. Allen JL. Airway function throughout the lifespan: Pediatric origins of adult respiratory disease. Pediatr Investig. 2019;3(4):236-244. http://dx.doi.org/10.1002/ped4.12165
5. Balfour-Lynn IM, Abrahamson E, Cohen G, Hartley J, King S, Parikh D, et al. BTS guidelines for the management of pleural infection in children. Thorax. 2005;60 Suppl 1(Suppl 1):i1-i21. http://dx.doi.org/10.1136/thx.2004.030676
6. Islam S, Calkins CM, Goldin AB, Chen C, Downard CD, Huang EY, et al. The diagnosis and management of empyema in children: a comprehensive review from the APSA Outcomes and Clinical Trials Committee. J Pediatr Surg. 2012;47(11):2101-2110. http://dx.doi.org/10.1016/j.jpedsurg.2012.07.047
7. Abdelnabi M, Almaghraby A, Saleh Y, El Sayed A, Rizk J. Acute purulent pericarditis treated conservatively with intrapericardial fibrinolysis and intrapericardial and systemic antibiotics. Proc (Bayl Univ Med Cent). 2021;34(4):498-499. http://dx.doi.org/10.1080/08998280.2021.1889297
8. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin infect Dis. 2011;53(7):e25-e76. http://dx.doi.org/10.1093/cid/cir531
9. Godfrey MS, Bramley KT, Detterbeck F. Medical and Surgical Management of Empyema. Semin Respir Crit Care Med. 2019;40(3):361-374. http://dx.doi.org/ 10.1055/s-0039-1694699
10. Prestes LM, Castro MÂUL, Souza GAB, Barros LGB, Scotta MC, Pinto LA. Management of pneumonia and pleural effusion in children. J Bras Pneumol. 2023;49(6):e20230370. http://dx.doi.org/10.36416/1806-3756/e20230370

Sarcoidosis-lymphoma syndrome: a diagnostic dilemma

Clara Perini Fiorot[1], Rosana Souza Rodrigues[1,2], Edson Marchiori[1]

A 57-year-old patient who had been diagnosed with pulmonary sarcoidosis 10 years prior and had received irregular corticosteroid treatment was admitted for investigation due to dyspnea on minimal effort, dry cough, dysphagia, and a 12-kg weight loss over 8 months. Physical examination revealed collateral circulation in the anterior thoracic region. Laboratory tests performed at admission showed only thrombocytopenia. Chest CT revealed a bulky lobulated mass in the anterior mediastinum (Figure 1A), calcified "eggshell" lymph nodes in various mediastinal chains, and fibrotic interstitial changes consistent with chronic sarcoidosis (Figures 1B and C). PET/CT demonstrated glycolytic hypermetabolism suggesting the presence of neoplastic tissue within the mass (Figure 1D). Biopsy of the mediastinal mass with immunohistochemical analysis led to the diagnosis of B-cell lymphoma. The patient underwent a 1-year regimen of chemotherapy combined with corticosteroid treatment, which resulted in marked reduction in mediastinal mass volume and glycolytic metabolism (Figure 1E).

The diagnosis of sarcoidosis is based on clinical presentation, complementary examination findings, and biopsy. Sarcoidosis increases the risk of lymphoma development, possibly via lymphocytic proliferation associated with high mitotic activity in the active chronic form, ultimately leading to the rare sarcoidosis-lymphoma syndrome.[1-4] The understanding of this relationship remains limited, and the condition is documented sparsely in the medical literature.

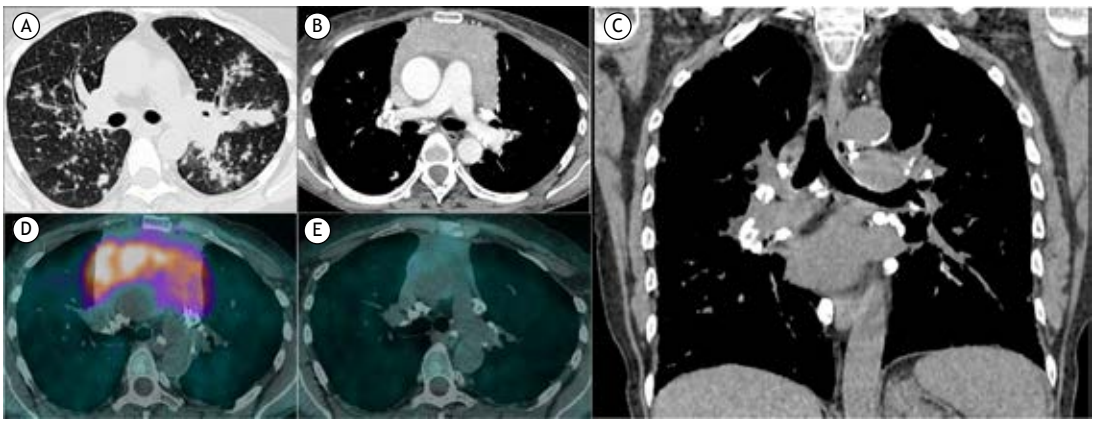

Figure 1. In A, an axial CT image of the chest (lung window) showing small nodules with peribronchovascular infiltrations. Mediastinal lymph node enlargement was also observed (not shown). In B, axial CT image (mediastinal window) showing a large mass with soft-tissue density in the anterior mediastinum. In C, a coronal reconstruction image (mediastinal window) showing the mediastinal mass and lymph node calcifications in multiple hilar and mediastinal chains. In D, axial PET/CT fusion image showing diffusely high ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake of the mass. In E, PET/CT image acquired 10 months after treatment initiation showing marked reduction of the mass volume and absence of ^{18}F- FDG uptake. Note also mediastinal lymph node calcifications.

REFERENCES

1. Alzghoul BN, Zayed Y, Obeidat A, Alzghoul B, Naser A, Shilbayeh AR, et al. Clinical Characteristics of Sarcoidosis Patients with Self-Reported Lymphoma: A US Nationwide Registry Study. Lung. 2021;199(6):611-618. https://doi.org/10.1007/s00408-021-00485-z
2. Faurschou M, Omland LH, Obel N, Lindhardsen J, Baslund B. Risk of Cancer Among Sarcoidosis Patients With Biopsy-verified Nonnecrotizing Granulomatous Inflammation: Population-based Cohort Study. J Rheumatol. 2022;49(2):186-191. https://doi.org/10.3899/jrheum.210588
3. Brincker H. The sarcoidosis-lymphoma syndrome. Br J Cancer. 1986;54(3):467-473. https://doi.org/10.1038/bjc.1986.199
4. Papanikolaou IC, Sharma OP. The relationship between sarcoidosis and lymphoma. Eur Respir J. 2010;36(5):1207-1209. https://doi.org/10.1183/09031936.00043010

1. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
2. Instituto D'Or de Pesquisa e Ensino – IDOR – Rio de Janeiro (RJ) Brasil.

◄ Voltar ao sumário
ISSN 1806-3756

Fat embolism: a rare cause of pulmonary infarction

Cyro Antonio Fonseca Jr[1], Gláucia Zanetti[2], Edson Marchiori[2]

A 68-year-old woman was admitted to the emergency department with sudden dyspnea and chest pain of 3 days' duration. She had had a domestic accident resulting in closed tibial and fibular fractures 5 days prior. Chest CT showed a filling defect in the left lower-lobe pulmonary artery with fatty attenuation, and a ground-glass opacity in this lobe, compatible with pulmonary infarction (Figure 1). The final diagnosis was pulmonary infarction due to macroscopic fat embolism.

Fat embolism syndrome, defined as the release of fat into the systemic or pulmonary circulation, is rare. It usually occurs after long bone fracture, orthopedic surgery, or cosmetic procedures.[1] The majority of fat embolism cases are microscopic, presenting on CT as bilateral patchy or diffuse ground-glass opacities. Macroscopic fat embolism is a rare presentation of the disease in which macroscopic fat deposits are present in the pulmonary arteries. Its diagnosis is based on the demonstration of fat-attenuation filling defects in these arteries. Fat typically has negative attenuation values, enabling the distinction of fat embolism from pulmonary thromboembolism, characterized by positive attenuation values. This differentiation can have important implications for patient management.[1-3]

AUTHOR CONTRIBUTIONS

The authors equally contributed to this work.

CONFLICTS OF INTEREST

None declared.

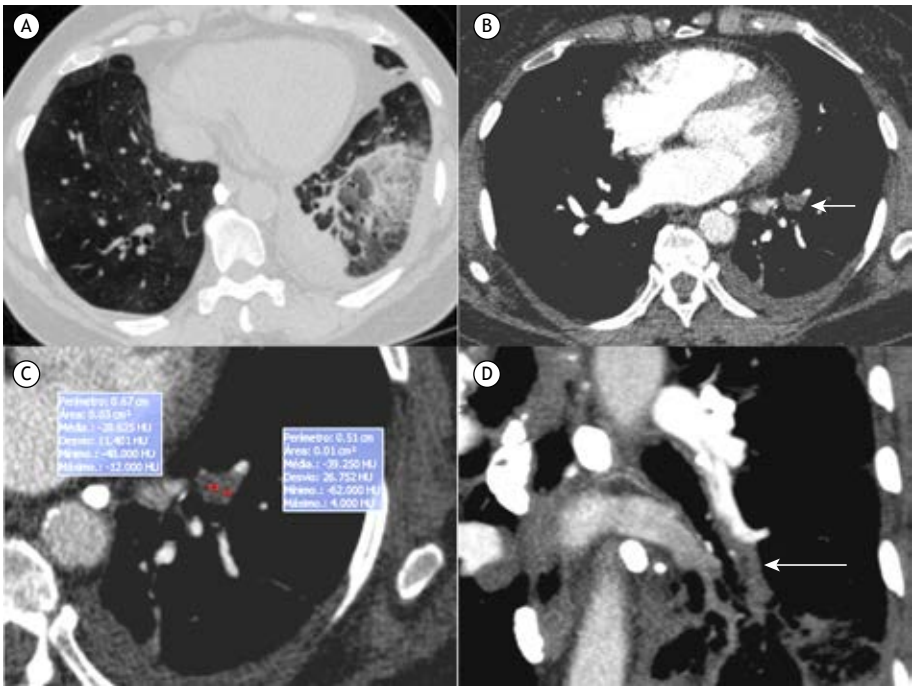

Figure 1. In A, unenhanced chest CT image (lung window) showing heterogeneous ground-glass opacities in the left lower lobe, with internal reticulation, compatible with pulmonary infarction. Note also the pleural reaction. In B, enhanced axial CT image showing a heterogeneous filling defect in the left lower-lobe artery (arrow). In C, magnified image of the emboli in B showing internal fatty density (−29 to −39 Hounsfield units). In D, coronal oblique reconstruction showing the heterogeneous emboli (arrow).

REFERENCES

1. Kaiser Ururahy Nunes Fonseca E, Chate RC. Macroscopic Fat Embolism after Cosmetic Surgery. Radiol Cardiothorac Imaging. 2022;4(2):e210316. https://doi.org/10.1148/ryct.210316
2. Newbigin K, Souza CA, Torres C, Marchiori E, Gupta A, Inacio J, et al. Fat embolism syndrome: State-of-the-art review focused on pulmonary imaging findings. Respir Med. 2016;113:93-100. https://doi.org/10.1016/j.rmed.2016.01.018
3. Murphy R, Murray RA, O'hEireamhoin S, Murray JG. CT pulmonary arteriogram diagnosis of macroscopic fat embolism to the lung. Radiol Case Rep. 2024;19(5):2062-2066. https://doi.org/10.1016/j.radcr.2024.02.062

1. Hospital Unimed Rio, Rio de Janeiro (RJ) Brasil.
2. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.

EDITAL DE SELEÇÃO

Brasília, 25 de junho de 2024

No período entre 01 de julho e 15 de setembro de 2024 estarão abertas as inscrições para candidatos ao cargo de Vice-Editor do Jornal Brasileiro de Pneumologia, com atuação no biênio 2025-2026. O Vice-Editor eleito assumirá a posição de Editor-Chefe em 2027, permanecendo na função por quatro anos (2027-2030) e, no biênio seguinte (2031-2032), assume novamente a função de Vice-Editor para auxiliar o novo Editor-Chefe.

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.

Dra. Margareth Maria Pretti Dalcolmo
Presidente da SBPT

Dra. Marcia Margaret Menezes Pizzichini
Editora-Chefe do Jornal Brasileiro de Pneumologia

◄ Voltar ao sumário

The Jornal Brasileiro de Pneumologia (J Bras Pneumol, Brazilian Journal of Pulmonology) ISSN-1806-3756, 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

CONHEÇA O NOVO APLICATIVO DA BAYER!

O aplicativo **Risco na HP** facilita a utilização das estratégias para estratificação de risco do seu paciente, de acordo com as diretrizes do **Registro Francês**[1, 2], **Registro COMPERA**[3,4], **REVEAL 2.0 e REVEAL Lite 2**

O aplicativo Risco na HP está disponível para download gratuito nas principais lojas de aplicativo.

Baixar na App Store

DISPONÍVEL NO Google Play

O aplicativo Risco na HP foi desenvolvido com base em publicações científicas1-6 para realizar uma estimativa na estratificação de risco da Hipertensão Pulmonar.

A responsabilidade pela determinação da conduta terapêutica para cada paciente é do médico e sua equipe. O aplicativo apenas facilita a utilização das estratégias de avaliação de risco. As informações apresentadas pelo aplicativo não devem ser utilizadas isoladamente.

Referências:

1. Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J. 2017 Aug 3;50(2):1700889. 2. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016 Jan 1;37(1):67-119. 3. Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J. 2017 Aug 3;50(2):1700740. 4. Delcroix M, et al. Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients. Eur Respir J. 2018 Nov 8;52(5):1800248. 5. Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, McGoon MD, Pasta DJ, Selej M, Burger CD, Frantz RP. Predicting Survival in Patients With Pulmonary Arterial Hypertension: The REVEAL Risk Score Calculator 2.0 and Comparison With ESC/ERS-Based Risk Assessment Strategies. Chest. 2019 Aug;156(2):323-337. 6. Benza RL, Kanwar MK, Raina A, Scott JV, Zhao CL, Selej M, Elliott CG, Farber HW. Development and Validation of an Abridged Version of the REVEAL 2.0 Risk Score Calculator, REVEAL Lite 2, for Use in Patients With Pulmonary Arterial Hypertension. Chest. 2021 Jan;159(1):337-346.

PP-VEN-BR-0037-1 | Fevereiro 2022

Chegou: EGURINEL® (pirfenidona)

O primeiro similar de pirfenidona do Brasil!

Egurinel® (pirfenidona) é bioequivalente ao medicamento referência![1]

Referência: 1. Vespasiano CFP, Accennato VAC, Costa F, Riccio MF, Bernasconi G, et al. (2020) Bioequivalence between Two Capsules of Pirfenidona in Healthy Subjects under Fed Condition. J Bioeq Stud 6(1): 101.

EGURINEL® (pirfenidona) é apresentado em embalagem contendo 270 cápsulas. **Indicações**: EGURINEL® (pirfenidona) está indicado para tratamento de fibrose pulmonar idiopática (FPI). **Posologia**: Adultos: Ao iniciar o tratamento, a dose deve ser escalonada em um período de 14 dias até a dose diária recomendada de nove cápsulas por dia, como se segue: **Dias 1 a 7**: uma cápsula, três vezes por dia (801 mg/dia). **Dias 8 a 14**: duas cápsulas, três vezes por dia (1602 mg/dia). **Dias 15 em diante**: três cápsulas, três vezes por dia (2403 mg/dia). A dose diária recomendada de EGURINEL® para pacientes com FPI é de três cápsulas de 267 mg três vezes por dia com alimentos até um total de 2403 mg/dia. **Contraindicações**: EGURINEL® (pirfenidona) está contraindicado nos casos de hipersensibilidade à substância ativa ou qualquer um de seus componentes; histórico de angioedema devido ao uso de pirfenidona; insuficiência hepática grave ou doença hepática terminal; insuficiência renal grave (CrCl < 30mL/min) ou doença renal terminal com necessidade de diálise. O uso concomitante de fluvoxamina e EGURINEL® está contraindicado. **Precauções e Advertências**: Função Hepática: lesão hepática induzida por medicamento (DILI) na forma de elevação transitória e clinicamente silenciosa de transaminases tem sido continuamente reportada em pacientes tratados com EGURINEL® (pirfenidona). Em casos raros, estas elevações foram associadas com elevação concomitante da bilirrubina e consequências clínicas sérias, incluindo casos isolados com desfecho fatal reportados pós-comercialização. Provas de função hepática (ALT, AST e bilirrubinas) devem ser realizadas antes do início do tratamento com EGURINEL® e subsequentemente em intervalos mensais nos 6 primeiros meses e depois a cada 3 meses a partir de então. Reação de hipersensibilidade e erupção cutânea: a exposição direta à luz solar (incluindo bronzeamento artificial) deve ser evitada ou reduzida durante o tratamento com pirfenidona. Os pacientes devem ser orientados a usar bloqueador solar eficaz diariamente, usar roupas que protejam contra a exposição solar e evitar outros medicamentos que reconhecidamente provoquem fotossensibilidade. Os pacientes devem ser orientados a reportar sintomas de fotossensibilidade ou erupção cutânea ao seu médico. Ajustes de dose ou descontinuação temporária de tratamento podem ser necessários no caso de reação de fotossensibilidade ou erupção. Tontura: tonturas têm sido relatadas em pacientes tomando pirfenidona. Portanto, os pacientes devem saber como eles reagem a este medicamento antes de se envolver em atividades que exigem prontidão ou coordenação mentais. Em estudos clínicos, a maioria dos pacientes que apresentaram tontura tinham um único evento, e a maioria dos eventos resolvidos, com uma duração média de 22 dias. Se a tontura não melhorar ou se agravar, pode ser necessário um ajuste da dose ou até mesmo a interrupção de pirfenidona. Fadiga: Fadiga tem sido relatada em pacientes tomando pirfenidona. Portanto, os pacientes devem saber como eles reagem a este medicamento antes de se envolver em atividades que exigem prontidão ou coordenação mental. Perda de peso: a perda de peso tem sido relatada em pacientes tratados com pirfenidona. Os médicos devem monitorar o peso dos pacientes, e, quando necessário, incentivar o desenvolvimento do consumo de calorias se a perda de peso for considerada de importância clínica. Distúrbios gastrintestinais: nos estudos clínicos, os eventos adversos gastrointestinais como náuseas, diarreia, dispepsia, vômitos, doença do refluxo gastresofágico e dor abdominal foram mais frequentemente relatados pelos pacientes nos grupos de tratamento com pirfenidona do que naqueles que receberam o placebo. **Interações**: EGURINEL® é contraindicado para pacientes em uso concomitante de fluvoxamina. A coadministração de EGURINEL® e ciprofloxacino 750 mg (inibidor moderado e seletivo de CYP1A2) aumentou a exposição a pirfenidona em 81%. Se o uso de ciprofloxacino 750 mg duas vezes por dia não puder ser evitado, a dose de EGURINEL® deve ser reduzida para 1602 mg por dia (duas cápsulas, três vezes por dia). EGURINEL® deve ser usado com cautela quando o ciprofloxacino for utilizado em dose de 250 mg ou 500 mg, uma ou duas vezes por dia. No caso de indutores moderados de CYP1A2 (p.ex., omeprazol), o uso concomitante pode teoricamente resultar em redução dos níveis plasmáticos de pirfenidona. A coadministração de medicamentos que atuem como indutores potenciais tanto de CYP1A2 quanto de outras isoenzimas CYP envolvidas no metabolismo da pirfenidona (p.ex., rifampicina) pode resultar em redução significativa dos níveis plasmáticos de pirfenidona. Esses medicamentos devem ser evitados sempre que possível. O tabagismo tem o potencial para induzir a produção de enzimas hepáticas e por isso aumenta a depuração e reduz a exposição ao EGURINEL®. O uso concomitante de indutores potentes de CYP1A2, incluindo o fumo, deve ser evitado durante a terapia com EGURINEL® **Reações Adversas**: as reações adversas mais comuns, obtidas dos estudos pivotais foram: náuseas (36%); erupção cutânea (30,3%); tosse (27,8%); infecção do trato respiratório superior (26,8%) e diarréia (25,8%). VENDA SOB PRESCRIÇÃO MÉDICA. **Reg. MS- 1.2214.0114. SAC: 08000 016 6575 "Informações adicionais disponíveis aos profissionais de saúde mediante solicitação a Zodiac Produtos Farmacêuticos S.A – www.zodiac.com.br - Para informações completas, consultar a instrução de uso do produto. Contraindicação**: EGURINEL® (pirfenidona) está contraindicado nos casos de hipersensibilidade à substância ativa ou qualquer um de seus componentes; histórico de angioedema devido ao uso de pirfenidona; insuficiência hepática grave ou doença hepática terminal; insuficiência renal grave (CrCl < 30mL/min) ou doença renal terminal com necessidade de diálise. O uso concomitante de fluvoxamina e EGURINEL® está contraindicado. **Interação:** EGURINEL® é contraindicado para pacientes em uso concomitante de fluvoxamina. A coadministração de EGURINEL® e ciprofloxacino 750 mg (inibidor moderado e seletivo de CYP1A2) aumentou a exposição a pirfenidona em 81%. Se o uso de ciprofloxacino 750 mg duas vezes por dia não puder ser evitado, a dose de EGURINEL® deve ser reduzida para 1602 mg por dia (duas cápsulas, três vezes por dia). EGURINEL® deve ser usado com cautela quando o ciprofloxacino for utilizado em dose de 250 mg ou 500 mg, uma ou duas vezes por dia. No caso de indutores moderados de CYP1A2 (p.ex., omeprazol), o uso concomitante pode teoricamente resultar em redução dos níveis plasmáticos de pirfenidona. A coadministração de medicamentos que atuem como indutores potenciais tanto de CYP1A2 quanto de outras isoenzimas CYP envolvidas no metabolismo da pirfenidona (p.ex., rifampicina) pode resultar em redução significativa dos níveis plasmáticos de pirfenidona. Esses medicamentos devem ser evitados sempre que possível. O tabagismo tem o potencial para induzir a produção de enzimas hepáticas e por isso aumenta a depuração e reduz a exposição ao EGURINEL®. O uso concomitante de indutores potentes de CYP1A2, incluindo o fumo, deve ser evitado durante a terapia com EGURINEL® .

Egurinel® é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas.

SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.

30 ANOS Zodiac Produtos Farmacêuticos | ZODIAC